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MR fluoroscopy in vascular and cardiac interventions (review)

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Abstract Vascular and cardiac disease remains a leading cause of morbidity and mortality in developed and emerging countries. Vascular and cardiac interventions require extensive fluoroscopic guidance to navigate endovascular catheters. X-ray fluoroscopy is considered the current modality for real time imaging. It provides excellent spatial and temporal resolution, but is limited by exposure of patients and staff to ionizing radiation, poor soft tissue characterization and lack of quantitative physiologic information. MR fluoroscopy has been introduced with substantial progress during the last decade. Clinical and experimental studies performed under MR fluoroscopy have indicated the suitability of this modality for: delivery of ASD closure, aortic valves, and endovascular stents (aortic, carotid, iliac, renal arteries, inferior vena cava). It aids in performing ablation, creation of hepatic shunts and local delivery of therapies. Development of more MR compatible equipment and devices will widen the applications of MR-guided procedures. At post-intervention, MR imaging aids in assessing the efficacy of therapies, success of interventions. It also provides information on vascular flow and cardiac morphology, function, perfusion and viability. MR

fluoroscopy has the potential to form the basis for minimally invasive image-guided surgeries that offer improved patient management and cost effectiveness.

Keywords Cardiac imaging · Magnetic resonance imaging · Vascular imaging

Introduction

The rapid evolution of minimally invasive vascular and cardiac interventions is shaping the demand for high temporal and spatial resolution imaging that offers safety, accuracy, flexibility and functionality. Recent improvements in signal processing, tissue characterization and angiographic integration allowed MR-guidance in complex interventional procedures, which require optimal spatial resolution and orientation [1, 2]. MR fluoroscopy offers rapid acquisition, reconstruction and display of 3D images. Therefore, it has been used in biopsies [3–7], brachytherapy [8, 9], focused ultrasound [10–13], thermometry [10, 14–17], functional imaging integrated into MR guided neurosurgical interventions [18, 19], local drug delivery [20, 21], endoscopy [22], intravascular interventions [23–34] and intra-operative imaging [19, 35–40].

X-ray fluoroscopy

X-ray fluoroscopy is routinely used in patients to guide vascular and cardiac interventions, because of

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its ability for real-time imaging and easy access to patients during interventions [41–43]. X-ray fluoroscopy, however, is limited for defining soft tissue and obtaining functional information. The poor contrast between pathologic and healthy surrounding tissue hinders X-ray fluoroscopy in defining targets [44], which subsequently leads to blind delivery of therapies to the targets [20, 45]. Furthermore, there is a growing body of evidence that exposure to ionizing radiation from X-ray procedures is associated with an increased risk of cancer [46–50].

Interventional MR magnets

Different MR magnet designs have been developed, namely open and hybrid, for MR guided vascular and cardiac interventions [51]. Open magnets were designed to ease patient access. Both open and double donut XMR hybrid magnets use 0.2T and 0.5T fields and have low gradient strength. These low field magnets offer suboptimal image quality and slow switching speeds that do not meet the need of cardiovascular interventions. For example, Wacker et al. [52] found that 1.0T closed-bore halved the procedure time during stent deployment compared to 0.2T open-bore magnet. Another hybrid XMR system consists of an angiographic laboratory adjacent to closed-bore 1.5T MR magnet, wherein an on-track patient table could be moved rapidly between the two imaging modalities (Fig. 1a) [53, 54]. More recently, another XMR hybrid system has been developed that has a side-by-side 1.5T magnet and C-arm X-ray

system (Personal communication) (Fig. 1b). The in-suite operation consoles and display monitors are of great help in instant imaging acquisition and monitoring.

The advantages of hybrid XMR systems are: (1) intermodal movement is minimized because a patient will remain on a sliding table throughout the imaging session; (2) unlike single system, the XMR hybrid system permits evaluation of the impact of interventional procedures via MR monitoring; (3) it permits rapid deployment of catheters, and efficient execution of desired interventions without the obligation of using MR compatible devices; (4) it reduces radiation exposure [55] and (5) offers the convenience of a single visit. However, currently XMR systems are available only in few medical centers.

Devices for MR interventions

Unfortunately, endovascular catheters and devices are optimized for their mechanical properties and visibility under projection X-ray imaging. There are, therefore, substantial metallic components within the plastic sheath that may be ferrous in nature. Visualization of these commercial endovascular catheters and devices has been difficult on MR imaging due to the susceptibility artifacts derived from the ferromagnetic material, geometry and design [56, 57]. Unlike ferromagnetic material, nickel-titanium alloy (nitinol), platinum, gold, copper, nonbraided or plastic catheters cause substantially less susceptibility artifacts [57–59] and produce less radiofrequency

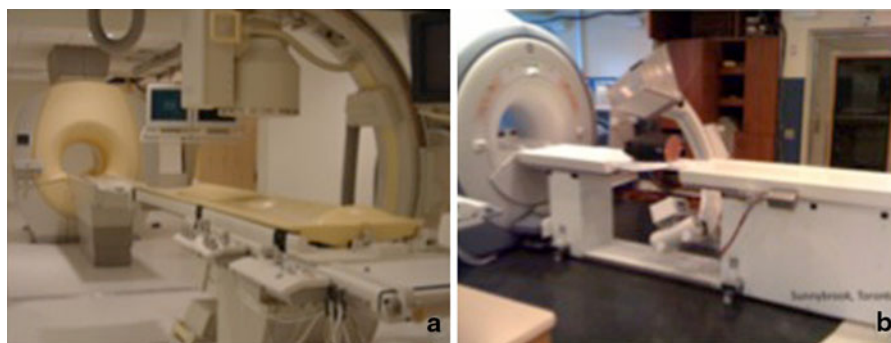


Fig. 1 Two types of hybrid XMR suites equipped with a closed bore 1.5T MR magnet and C-arm X-ray fluoroscopy. The **a** suite consists of 2 rooms separated by a sliding door (Phillips Medical Systems). The recently developed hybrid system **b** is an example of a more advanced facility, where both

C-arm X-ray fluoroscopy and 1.5T MR systems are in the same room, thereby making interventional procedures shorter and more efficient (courtesy of Dr. Graham Wright, Sunnybrook, Toronto)

heating *in vivo* [60, 61]. Nitinol stents and guide-wires are currently used for revascularization of stenosed blood vessels. Mekle et al. [62, 63] used a synthetic MR friendly polymer-based guide-wire for dilatation of an artificial stenosis in phantoms and in the carotid artery, aorta, and iliac arteries of swine [63]. More recently, investigators manufactured a guide wire based on micropultruded fiber-reinforced material doped with iron particles to improve visibility. At the distal part of the guide-wire a nitinol wire was attached to provide flexibility to the tip [64].

In vitro studies showed that MR fluoroscopy can track and navigate nitinol catheters (Fig. 2). At the present time, few prototype catheters have been designed [21, 65–67], but require further investigation. The catheters used for local drug delivery under MR fluoroscopy contain a steering device and needle-adjusting scale pistol at one end and a nitinol needle, which is a part of a thin nitinol catheter runs inside the catheter at the other end.

Investigators used three approaches for endovascular catheter tracking and navigation, namely passive tracking (Fig. 3), active tracking (Figs. 2, 3) and magnetic catheter steering (Fig. 4). Investigators also used dysprosium markers mounted on 3F non-braided catheters for tracking and visualizing the catheters. The contrast between the catheter and background blood can be improved by injecting MR contrast media, which prevents flow artifacts because the steady state is reached earlier [54, 68]. Bakker et al. [24] were the first to use the passive tracking approach for steering basilica veins of healthy volunteers. Later, this passive approach was adapted

by Manke et al. [69] and Razavi et al. in patients [70]. The advantage of this technique is that it requires no hardware or instrument modifications and, thus, appears to be particularly promising in terms of potential clinical applications. The disadvantage is that the catheter disappears when it is out of the image plane due to the motion.

Active tracking is another approach for tracking endovascular catheters (Figs. 2, 3). This technique relies on specially designed micro-coils, electrified wire loop and self-resonant radiofrequency circuits. The coils pick up signal during slice excitation and generate a frequency-encoded recall echo, which can be detected in 3D at a spatial resolution of approximately 1 mm. The micro coils provide robust tracking of the catheter shaft and tip that allows the user to identify its position and target (Fig. 3) [71–74]. Quick et al. [75] used antennas for active catheter tracking and imaging of the abdominal aorta, superior mesenteric artery, renal arteries, hepatic artery and celiac trunk. In another study, they were able to simultaneously visualize vascular tree, catheter shaft and tip [76]. The advantage of this technique is that it allows for visualization of longer portion of the catheter or guidewire when a loopless antenna is placed. On the other hand, the disadvantage includes the need for special hardware and software. Furthermore, the support patient systems, interventional devices and surgical instruments must be MR-compatible. MR-compatible equipment for anesthesia, assessment of physiologic parameters and contrast media injection are currently offered by multiple vendors.

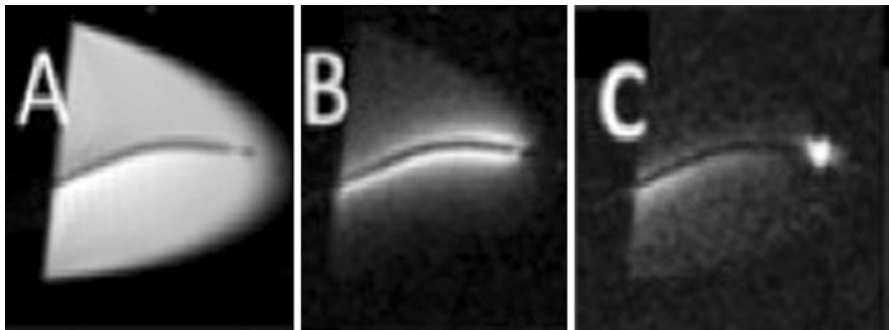


Fig. 2 MR images show the activated coils in a water bath. **a** Shows the external surface coil elements, **b** a coil placed on the shaft of the catheter and **c** a coil placed at the catheter tip.

This type of active catheter has been frequently used for transcatheter delivery of stem cells and angiogenic genes

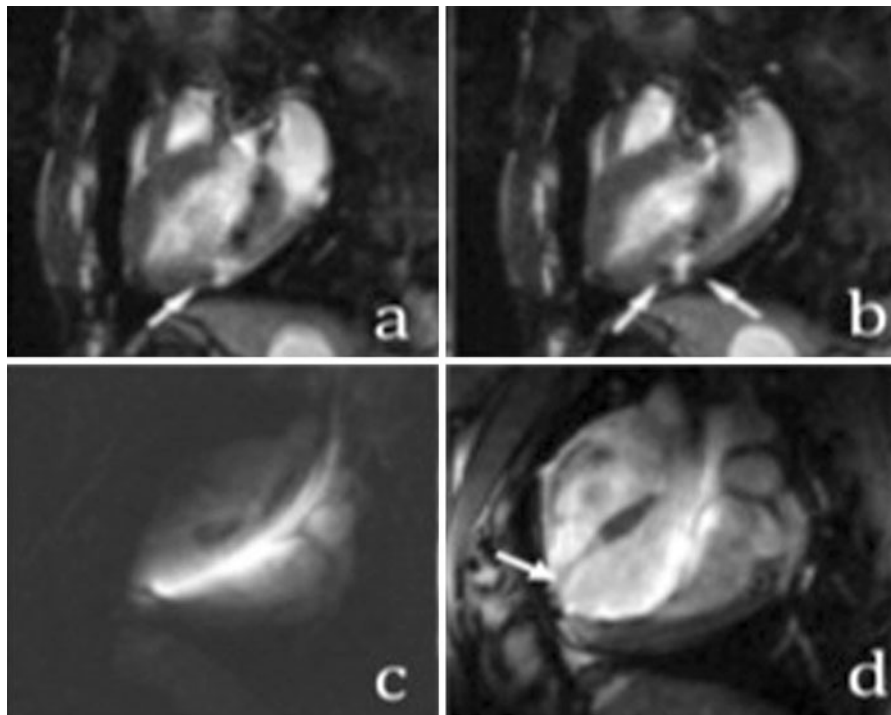


Fig. 3 Selected MR fluoroscopic images show the passive **a, b** and active **c, d** catheters in the left ventricle hitting myocardial targets (*arrows*). The passive catheter is labeled with MR contrast media, while the active catheter wrapped

with coil. Note that the background anatomy of the heart and great vessels can be clearly visualized using both the active catheter and active body coil (**d**)

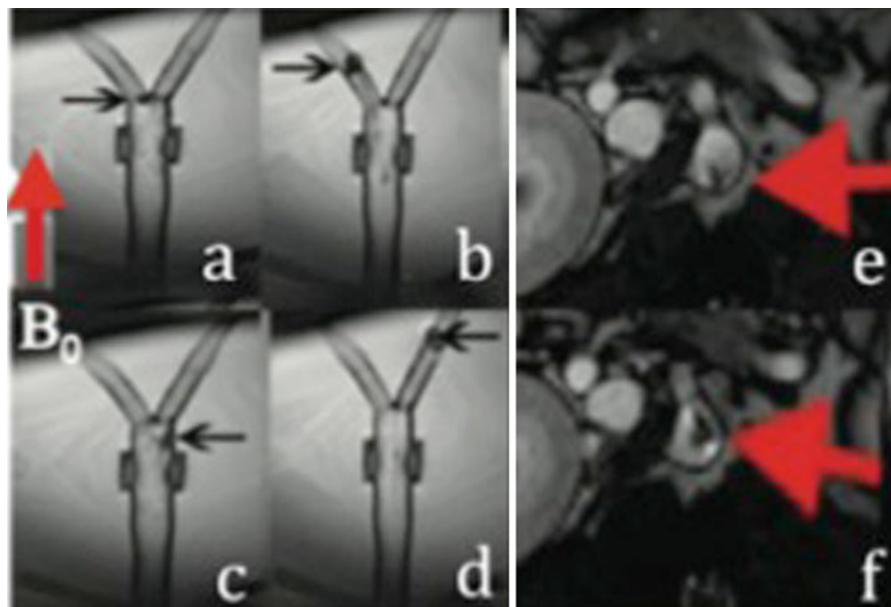


Fig. 4 Dynamic coronal MR images of a 2.5F two axis (*saddle* and *helical*) coil-tipped catheter deflected and advanced up the *left* (**a, b**) and *right* **c, d** of a phantom (B0-

Bore of magnet). The in vivo study shows the catheter in the superior mesenteric artery (*red arrows, e, f*)

The safety of active endovascular devices is still a major concern. The conductive nature of the long metallic braid creates a safety hazard in the MR environment, as the braided shaft can interact with incident RF energy and the electric field transmitted from the RF coil [60, 61, 77]. The heat created by the active coils causes necrosis of the tissue adjacent to the catheter and blood clotting, which may lead to vascular embolization. The methods for mitigating the potential for heating include using unbraided catheters, insulating the conductive structure, limiting the RF power to which it is exposed, or altering its interaction with the RF energy source [78]. The FDA limits the allowable power deposition via MR imaging to 8 W/kg and temperature change to 2°C. Patients with internalized devices containing long conductive structures, such as deep brain stimulators [79] and cardiac pacemakers [80–82], are presently scanned with MR imaging provided additional safety steps are taken. These typically include heightened patient monitoring, lower permissible specific absorption rate levels, and the use of local transmit RF coils.

Magnetic catheter steering is a new approach for tracking endovascular catheters using remote control [83]. It relies on a small magnetic moment created by application of an electrical current to copper coils on the catheter tip, which results in alignment of the catheter in the direction of the B_0 field (Fig. 4) [84, 85]. Magnetic catheter steering approach allows for more efficiency in navigating small, tortuous blood vessels, which are currently difficult to catheterize due to build-up of friction at vascular bends. In addition to improved visualization of the endovascular catheter at low power levels, this technology permits deposition of thermal energy for ablation of tissues at higher power levels. This technology is under active investigation [86, 87].

MR contrast media

MR fluoroscopy and catheter tracking can be expanded using a variety of MR contrast media with high safety profiles [88–90]. Investigators used extracellular and intravascular MR contrast media with T_1 -enhancing or T_2 -enhancing capabilities for labeling different types of cells [91, 92]. Extracellular MR contrast media have small molecular weights (<1 kDa), brief plasma half-life and are clinically used in vascular angiography and in assessing

myocardial viability. On the other hand, intravascular (blood pool) MR contrast media have high molecular weights (>50 kDa), mass and T_1 relaxivity with prolonged plasma half-life. Preclinical experiments showed that intravascular contrast media provide better vascular angiograms. Moreover, contrast media have been used on MR fluoroscopy to improve visualization of endovascular devices [20], in road mapping blood vessels [93, 94] and defining pathologic targets [95]. Investigators also used MR contrast media for labeling different types of cells [91, 92], which assist in monitoring the distribution of the injected cells in vivo [96–98].

A study showed that high dose or repeated administration of gadolinium might be a concern, especially in patients with impaired renal function [99]. This problem can be reduced by paying attention to a glomerular filtration rate of >30 ml/min/1.73 m² and contrast agents with high molecular stability [100].

MR fluoroscopy sequences

MR fluoroscopy became possible because of the major advancements in the speed of data acquisition, data transfer, and interactive control and display. Other factors include highly uniform magnetic fields, rapidly changeable magnetic field gradients, multi-channel receivers and computing systems. MR fluoroscopy sequences achieve their high speeds by maximizing the switching rates of gradients and RF pulses. The temporal and spatial resolution in MR fluoroscopy are often complementary factors. The speed of imaging is determined by how quickly spatial encoding can be performed and how fast k-space data can be acquired. Actively shielded, strong, fast-switching gradients and fast electronics have allowed data acquisition intervals to be reduced.

Fast MR imaging techniques have been developed in recent years, allowing frame rates almost comparable to those achieved with X-ray fluoroscopy. Most modern real-time MR implementations employ balanced steady state free precession techniques because of efficient use of magnetization, high SNR, and short repetition times [101–103]. The performance of these sequences is currently in the range needed to perform MR guided procedures at >5 fps [104]. The SSFP acquisitions have been performed using radial [105], and spiral [106] k-space trajectories. These acquisition techniques in conjunction with spiral or radial filling of

the k-space are considered very reliable for high spatial and temporal resolutions. These imaging sequences also benefit from the use of multiple receiver coil elements [107–109]. Parallel imaging accelerates acquisition by using the different spatial sensitivities of the coils to correct for under-sampling of image data [110]. Other sequences that can improve imaging speed while simultaneously balancing imaging quality include non-Cartesian k-space sampling, temporal data sharing between images, and adjusting the tradeoff between temporal and spatial resolution [102]. The use of 32 channel receiver arrays that will perform rapid 3D cardiac imaging and parallel transmission techniques to permit more efficient parallel data collection are also under active investigation [111]. It should be noted that MR fluoroscopy is not free of limitations. For example, the closed configuration of MR magnets $>1.5T$ limit access to the patient and RF pulses induce heating when conductive material is applied in devices; MR imaging has relatively low spatial and temporal resolution compared with X-ray fluoroscopy; and is sensitive to magnetic field inhomogeneity, pulsatility and motion of spins and chemical shift.

In pre and post-intervention the following MR sequences were used: (a) balanced fast field echo CINE images for measuring LV volumes, ejection fraction, cardiac output, stroke volume, LV mass, wall thickness and radial strain [90, 112–114], (b) tagged gradient echo planar imaging for measuring circumferential strain and LV rotation [115, 116], (c) phase-contrast velocity-encoded gradient echo planar imaging for measuring longitudinal strain [117], (d) T_2 -weighted turbo spin echo sequence for measuring interstitial edema after ablation, (e) T_2^* multi-echo gradient echo sequence for measuring vascular and myocardial hemorrhage after intervention [118], (f) T_1 -weighted gradient echo (radiofrequency spoiled) perfusion imaging sequence for measuring myocardial perfusion changes after delivery of therapy, and (g) delayed contrast enhanced 3D T_1 -weighted gradient echo sequence for assessing tissue viability.

Applications of MR fluoroscopy

Vascular interventions

MR imaging provides detailed information on vascular layers and is able to differentiate between

plaque components, such as fibrous, lipid rich and calcified tissue [119, 120]. In the last decade MR imaging has been extended from a diagnostic to a dynamic modality, which can be used to guide intravascular guidewires and catheters and to assess the success of endovascular procedures. In 1997 the first human MR-guided study was performed and showed excellent visualization of an endovascular catheter labeled with dysprosium ring markers [24]. In this study, investigators did not use guide wires during the movement of the catheter in the cephalic vein of healthy volunteers. Later, MR-guided percutaneous transluminal angioplasty has been conducted without complications in 13 patients with iliac stenosis [121] and in 15 patients with femoral and popliteal artery stenosis [122].

MR-guided procedures (stenting and/or angioplasty) have been performed for dilatation of the aorta, pulmonary, coronary, renal iliac and femoral arteries [45, 57, 121–124]. MR-guided imaging has been used for delivery of stents in major and minor blood vessels [45, 52, 57, 125–131]. Vascular stents, vena cava filters, cardioseptal occluders or prosthetic heart valves require, however, post-interventional follow-up, which are usually made under X-ray or CT. MR imaging, with its superior soft-tissue contrast, arbitrary slice orientation and flow measurement would be the preferred imaging technique; however, most conventional vascular implants made of metal create image artifacts and masked visualization of the lumen. The three main types of MR artifacts associated with metallic vascular implants are susceptibility artifacts, flow-related artifacts and RF artifacts. Active MR resonant stents provide non-invasive visualization of instant thrombosis and restenosis without the need for MR contrast media. Visualization of the lumen of vascular implants is important for a safe and reliable examination on MR-guided procedures.

Mahnken et al. used MR-guided procedures for placement of aortic stents grafts [132]. More recently, Kos et al. used a polyetheretherketone-based MR imaging-compatible guidewire in swine for aortic stenting and vena cava filter placement [133]. Several groups have successfully used MR-guidance for placement of vena cava filters [134, 135]. Pulmonary artery stents have also been accurately implanted across the pulmonary valve [57, 58, 136]. It should be noted that only a few investigators have performed

vascular stenting in patients under MR guidance [121, 122]. Manke et al. [121] successfully deployed stents under MR-guidance in iliac arterial stenosis in patients. Post-interventional MR imaging showed the localization and function of the stents. MR fluoroscopy has been recently used for assessment of the pulmonary arterial pressure in pediatric and adult patients with congenital heart disease [70, 137]. A variety of MR-guided interventions have been performed in patients with congenital heart diseases including; placing transjugular, intrahepatic porto-systemic stents, radiofrequency ablation, aortic coarctation, atrio-septal defect (Fig. 5) and cardiac catheterization. In 2006, Krueger et al. performed the first MR-guided study using balloon angioplasty for treating aortic coarctation in 5 patients. This was an important step toward MR-guided treatment of this congenital disease [138].

Kuehne et al. [139] demonstrated successful implant of a self-expanding stent valve in the aorta via percutaneous access under MR fluoroscopy. Transcatheter aortic valve implantation, either retrograde through a transfemoral approach or antegrade through a transapical approach, has become a clinical reality in the treatment of critical aortic stenosis in high-risk patients. MR fluoroscopy plays an important role in transcatheter aortic valve implantation and replacement of insufficient aortic or pulmonic valves [57, 58, 136]. MR imaging enables accurate and reproducible quantifications of regurgitate

fraction before and after valve placement. Under MR fluoroscopy, McVeigh et al. [140] used apical access to guide the placement of a prosthetic aortic valve in beating heart. MR imaging offered the visualization of both coronary ostium during stent implantation and allowed aortic flow assessment.

Cardiac interventions

Percutaneous closure of atrio-septal defects and ventriculo-septal defects is increasingly performed under X-ray, which brings the disadvantages of ionizing radiation and lack of soft-tissue contrast. MR imaging is a technique that provides high-resolution 3D images of the heart. Three-dimensional MR imaging before intervention is particularly important because it improves our understanding of the anatomic basis of complex arrhythmias. Closure of such congenital defects under MR-guidance has been proved in animals [141], but is hampered by image artifacts produced by the materials of the closure devices and the use of fast sequences for cardiac imaging [142]. Few studies showed that MR imaging is useful for arrhythmic substrate identification [143, 144].

MR-guided procedures have been successfully used in thermal ablation and after intervention to assess the success of ablation [145–150]. Clinical studies showed atrial scar on contrast enhanced MR imaging that results from RF ablation [151–153]. Other studies have demonstrated the association

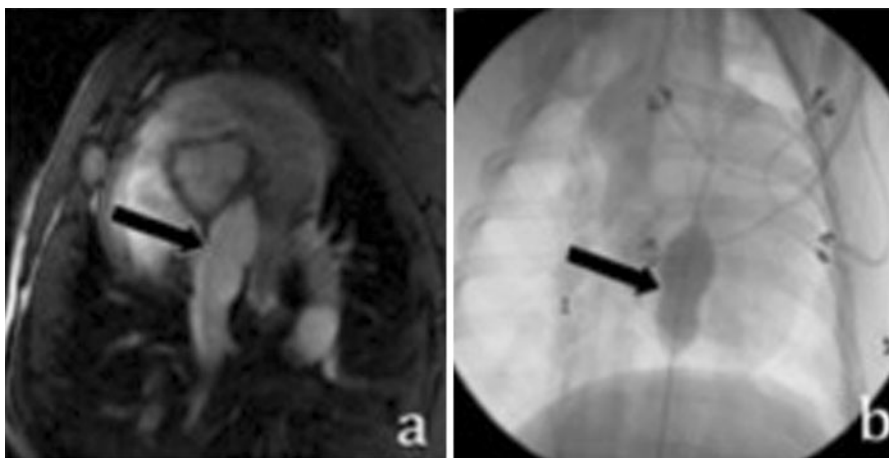


Fig. 5 A balloon at the tip of endovascular catheter (*arrow*) filled with MR contrast medium (**a**), and CT contrast medium (**b**), used for sizing ASD under MR (**a**), and X-ray fluoroscopy

(**b**). Note the close estimate of the waist (*arrows*), representing the ASD diameter

between infarct scar, border-zone and the risk of monomorphic ventricular tachycardia [144, 154, 155]. Dong et al. found that 3D MR imaging is helpful for tailoring ablations to the variant pulmonary vein anatomy in 47% of patients with atrial fibrillation [156]. They also noted that 3D images of the atria helped in localizing areas along the tissue ridge separating the left atrium from the pulmonary vein [156, 157]. The ability of MR fluoroscopy to visualize the needle tip in the inferior vena cava, atria, fossa ovalis, and surrounding vasculature during transseptal cardiac punctures has also been demonstrated [158–161].

Atrial septal defect (ASD) is another congenital defect common in children, leading to heart failure and pulmonary hypertension. Percutaneous transcatheter delivery of an ASD occluder has been performed on X-ray fluoroscopy [162]. A recent study showed that MR imaging provides reliable diagnosis of ASD [163]. Substantial experience has been obtained in animal models where MR fluoroscopy was used for

delivery of ASD closure [164, 165] and sizing of the ASD (Fig. 6) [166]. The ASD occluders, delivered on MR fluoroscopy, are made of a nitenol mesh to reduce the artifacts [161]. Others used a commercial nitinol snare coaxial catheter system for delivering septal occluders [166]. Schalla et al. [161] simulated clinical-grade pediatric diagnostic catheterization in an animal model of ASD. The advancement of the delivery system through the IVC to the right atrium was monitored under MR fluoroscopy (Fig. 7). In another study, they advanced an active catheter, under MR fluoroscopy, to right and left sides of the heart and invasively measured pressure and oxygen in both right and left sides of the heart [70, 161] (Figs. 7, 8). Measurements of flow from velocity encoded MR imaging and blood pressure from the catheter were used to calculate pulmonary resistance. The flow and resistance data obtained from Fick and MR cardiac catheterization methods were in agreement [70, 161], suggesting accurate physiologic data can be obtained on MR imaging.

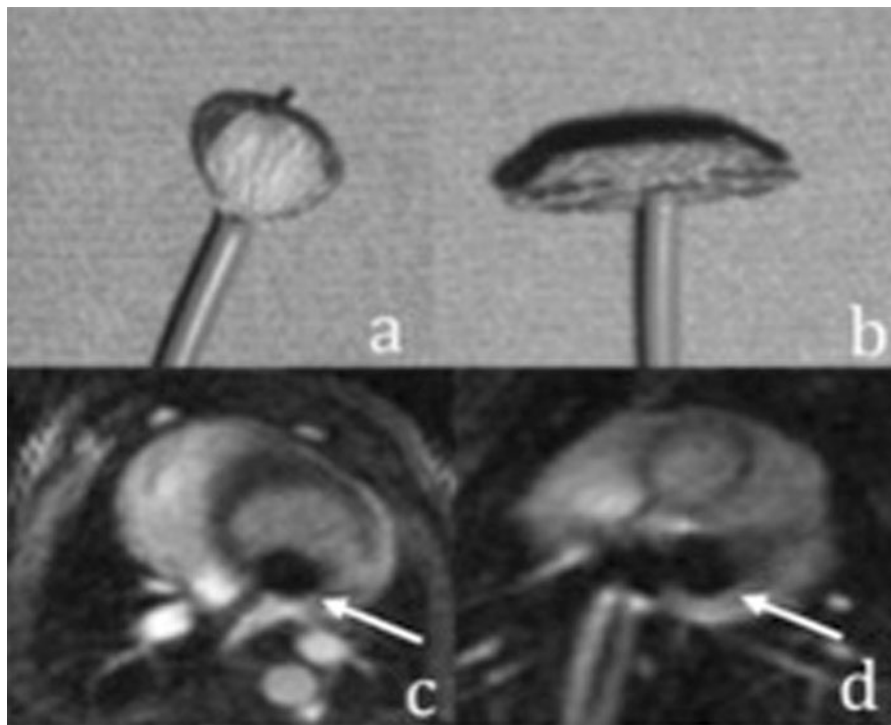


Fig. 6 Simulation of deployment of the septal occluder device in vitro (**a**, **b**), and corresponding selected real-time MR images in vivo (**c**, **d**). The device was easily detected as a signal void on real time MR images. The closure device was

advanced inside the delivery sheath until the folded first disk appeared (**c**) followed by the release of the second disk in the right atrium (**d**)

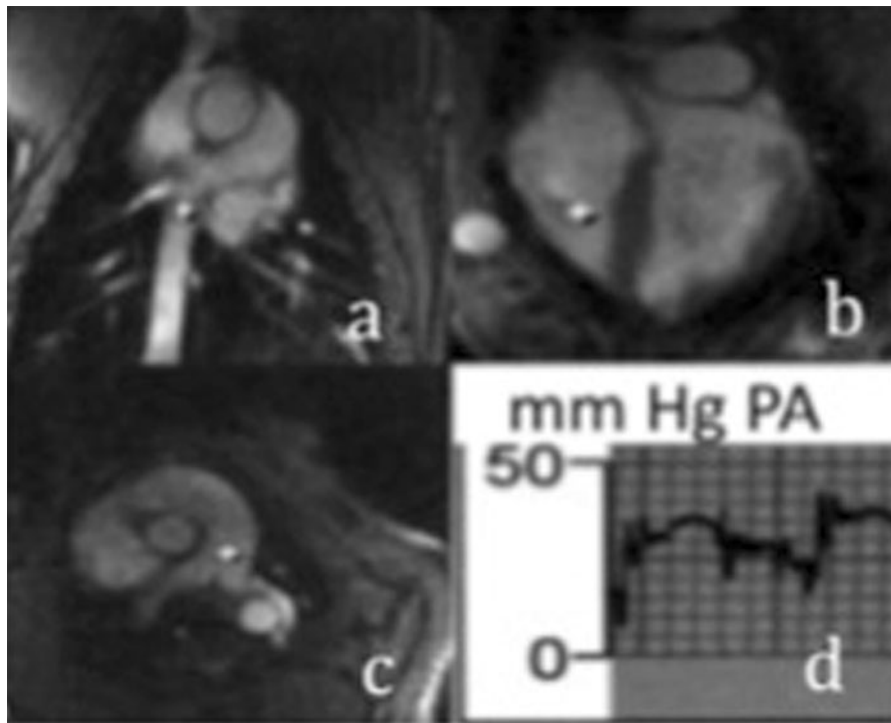


Fig. 7 Catheterization of main pulmonary artery under MR-guidance. Image planes: inferior vena cava (a), right ventricular outflow tract (b), and outflow-tract–pulmonary artery (c) and a pulmonary artery pressure curve in mm Hg (d)

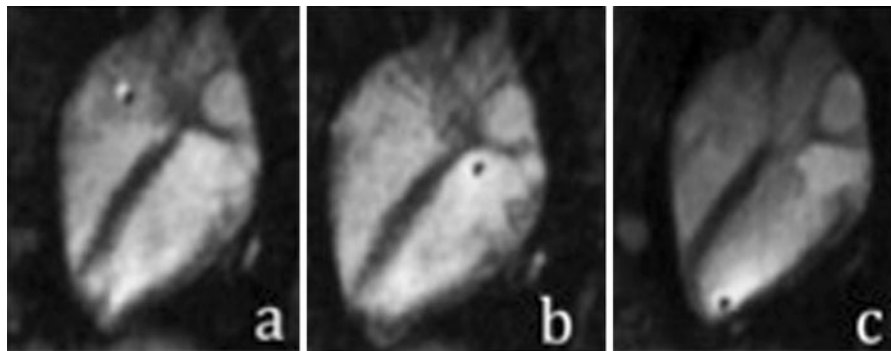


Fig. 8 Selected MR fluoroscopy images show antegrade catheterization of LV (femoral venous/transseptal access). The images show advancement of tracking catheter from RA (a), transseptally into LA (b), and LV (c). Catheter tip is detected as a cross

A recent study in 10 patients and 5 volunteers showed that MR fluoroscopy is suited to guide flow directed catheters for measurement of invasive pulmonary artery pressures [167]. Pulmonary vascular flow was noninvasively measured using velocity-encoded cine MR imaging, while pulmonary pressure was measured invasively through a catheter guided into the pulmonary artery under MR-guidance. The results indicate that MR imaging is a

promising tool for measurement of pulmonary vascular resistance in patients with different degrees and forms of pulmonary hypertension. MR fluoroscopy has also been used in connecting cardiac chambers and blood vessels in a swine model, where Arepally et al. connected the right and left atrium by puncturing the interatrial septum using an active Brockenbrough-style needle [168]. In a clinical study in seven patients, Dick et al. conducted

trans-septal puncture and balloon septostomy under MR fluoroscopy [169].

MR guided delivery of genes and stem cells

Vascular and cardiac disease is a major public and economic health problem leading to more than 7 million deaths world wide each year. Current treatments of this disease include pharmaceutical drugs, deployment of devices and interventional therapies. These method, however were unable to replace necrotic, apoptotic cells and damaged vessels by new cardiomyocytes or blood vessels. Clinical studies confirmed that there are an increasing number of patients who have persistent chronic angina, despite having multiple coronary revascularization procedures. Heart transplantation is the definitive therapy for these patients, but this option is limited to ~2,000 donor hearts annually. Thus, there is a mandate for alternative treatment and minimally invasive approaches, such as endovascular catheter-based techniques, for local delivery of new therapies to restore cardiomyocytes and blood vessels. Angiogenic growth factor, gene and stem cell therapy have been recently used as an alternative treatment to restore cardiomyocytes and blood vessels in end stage patients, in combination with coronary artery bypass grafting [170–175]. Recent preclinical and clinical studies showed that percutaneous intramyocardial and intraarterial delivery of therapies is possible [176–180], but Hou et al. found that 11, 2.6 and 3.2% of the delivered cells are retained in the myocardium after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery [181].

Local delivery approaches include surgical and catheter-based delivery of various types of angiogenic proteins, genes and stem cells. Open-chest surgery, however, is impractical in end-stage patients because this strategy increases morbidity and mortality as well as limiting the feasibility of repeat administration [182]. The advantages of catheter-based local delivery of therapies are: (1) targeting only the diseased region, (2) delivering a high local dose, (3) eliminating a high systemic dose and side effects and (4) reducing the chance of angiogenesis in hidden tumor sites especially in elderly patients [170–175, 183].

Gene therapy is a new approach for treating ischemic heart disease and it is an exciting area of

modern medicine. Recent MR-guided studies demonstrated the success of catheter-based transendocardial delivery of genes (Fig. 2). Preclinical studies have indicated that MR imaging provides quantitative data on infarct size, infarct transmural, microvascular obstruction and hemorrhage). These capabilities have positioned MR imaging as an important approach to pursue for assessing the benefits of locally delivered genes [20]. The MR-guided approach for delivering plasmid-VEGF gene has been validated using histopathology as a gold standard, which ensured the efficacy of delivered therapy into infarcted myocardium by demonstrating the formation of new blood vessels in treated animals (Fig. 9). Another MR study showed the increase in collateral blood flow of infarcted myocardium after delivering vascular endothelial growth factor [184]. Post et al. [185] demonstrated an improvement in regional radial strain after intramyocardial injection of adenovirus coding for P39 gene. Furthermore, Liu et al. found a significant improvement in LV ejection fraction and smaller number of segments with wall motion abnormality after intramyocardial injection of fibroblast growth factor [186].

Stem cell transplantation is another approach for treating ischemic heart disease as it improves cardiac function and revascularizes ischemic myocardium. The therapeutic effect of stem cells seems to be related to the release of angiogenic factors rather than trans-differentiation of delivered stem cells. Two predominant routes for stem cell delivery to infarcted myocardium are intracoronary infusion and direct intramyocardial injection. Each of these delivery routes attempts to maximize the retention of delivered cells to infarcted myocardium namely. Early clinical studies indicated that cell transplantation, delivered under MR fluoroscopy, is safe and feasible [97, 187–189]. MR imaging has been used not only to track stem cells in the myocardium, but also to non-invasively evaluate ventricular function, perfusion and viability [190]. Cell tracking on MR imaging is based on labeling injected cells with US FDA approved super paramagnetic iron oxide particles [189, 191]. It has been shown that iron labeled cells maintain their viability, proliferation and differentiation [97]. The cluster of iron labeled cells appear dark on T_2^* and T_2 MR images [189, 191, 192]. Several factors affect the detection of labeled cells, which include the (1) magnetic field, (2) labeling

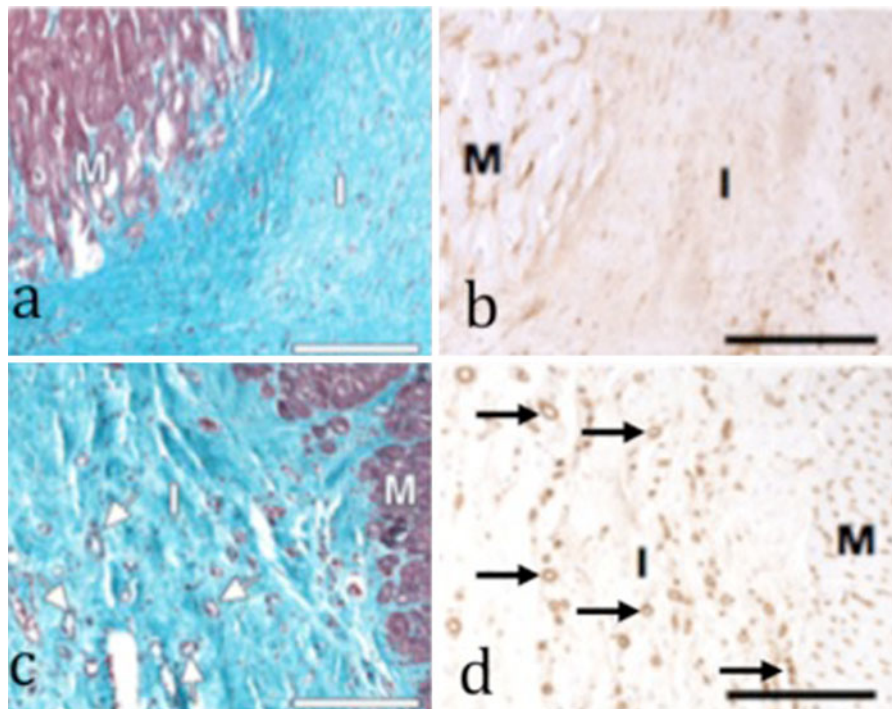


Fig. 9 Photomicrographs of representative infarctions in control (**a, b**) and VEGF gene-treated animals (**c, d**). Sections **a** and **c** were stained with Masson trichrome stain, while **b** and **d** were stained with biotinylated isolectin B4. Sections **a** and **c** show chronic infarction (*I*) in both groups which is comprised of homogeneous replacement fibrosis with a distinct boundary at the interface between scar and viable myocardium (*M*).

Treated animal contained numerous vessels **c, d** (*arrows*), while control infarction contained very few vessels. Biotinylated isolectin B4 localized vessels with brown reaction product, accentuating the neovascularity in VEGF gene-treated infarct (**d**) as compared with infarct in control animal (**b**). Calibration bars = 80 μ m

efficiency, (3) type of cells and (4) time of imaging after delivery. Investigators found that the duration of MR detection varies between cells; up to 5 weeks for embolic stem cells [193] and up to 16 weeks for skeletal myoblasts [194]. Investigators also found hypo-intense tiny regions far from the site of injection, indicative of migration of stem cells within the infarction several weeks after delivery. MR imaging was used to evaluate changes in LV remodeling following the delivery of cellular therapy [98, 195–199]. Amado et al. [200] were able to identify a time-dependent recovery of local contractility associated with the appearance of new tissue resulting from transplantation of allogeneic stem cells in a pig model of myocardial infarct.

Recent randomized clinical trials demonstrated the safety of bone marrow mononuclear treatment after intracoronary injection [201, 202]. Promising clinical results from intracoronary delivery of autologous bone marrow derived stem cells and progenitor cells

showed improved myocardial function [201, 203–206]. The proposed mechanisms of protection by stem cells include angiogenesis via the release of angiogenic factors, myogenesis, cytoprotection via the release of paracrine factors, recruitment of stem cells and suppression of inflammation [207]. More recent 5 year follow-up studies showed that cell therapy causes no significant improvement in LV ejection fraction compared to placebo [208, 209]. Major limitations of intracoronary delivery include: (1) no delivery access to infarct related to permanent coronary artery occlusion; (2) inadequate cellular migration into the interstitial space during the first pass transit; (3) microembolization [210]; (4) systemic delivery to non-cardiac tissue [211] and (5) possibility of intimal dissection [212]. It has been shown that approximately 2% of intracoronary delivered bone marrow mononuclear cells were retained by infarcted myocardium in humans, but when the investigators used enriched bone marrow

mononuclear cells the retention increased to 14–39% [213].

Ripa et al. [214] used MR imaging to monitor the changes in LV function after subcutaneous granulocyte colony stimulating factor (G-CSF) injection in patients with ST-elevated infarct. They found that G-CSF caused no improvement in LV function. Investigators used different types of cells, such as progenitor cells, myocytes, adipocytes, fibroblasts, and smooth muscle cells, in patients with ischemic heart disease [202, 203, 214–223]. Three randomized controlled studies have been published using bone marrow cells for promoting angiogenesis [202, 203, 218]. In the BOOST study 60 patients were enrolled to evaluate the effect of intracoronary autologous bone marrow cells after myocardial infarction [203]. MR imaging showed a significant increase in ejection fraction from 50 to 57% in treated patients versus 51–52% in untreated patients [203]. A more recent update from the BOOST study found the beneficial effects of bone marrow cells were sustained at 18 months [219]. Several complications have been reported after local delivery of growth factor and cell therapies including hemangioma [224], in-stent stenosis and hyperplasia [225] as well as arrhythmia [226].

Summary

During the last decade medical imaging and minimally invasive cardiovascular interventions have made substantial progress. Improvements in temporal resolution, tissue component characterization and angiographic integration have allowed guidance in complex interventional procedures. MR imaging provides 3D datasets, excellent soft-tissue contrast, multi-planar views, dynamic imaging in a single imaging session and guidance of interventional vascular and cardiac procedures. MR imaging allows monitoring of treatment success after intervention that is not available on X-ray fluoroscopy. These advantages of MR imaging are complementary to its potential advantage against the harmful effects of X-ray guided procedures. In recent studies, balloon dilation, stent placement, valvar replacement, atrial septal defect closure, radiofrequency ablation and local gene and cell delivery have been shown to be feasible. In addition, MR-guided procedures involving gene or stem cell therapy represent a new discipline whose systematic development will foster minimally

invasive interventional procedures and will hasten the identification and deployment of effective new therapies for revascularization and myogenesis.

At present, cardiovascular interventions are addressed by multimodality imaging using computed tomography, invasive angiography and transesophageal echocardiography. Whether MR is suited to obviate the need for multimodality imaging is currently unclear and needs to be further evaluated. Furthermore, the availability of safe MR compatible devices will guide future minimally invasive cardiovascular procedures. MR-guided percutaneous transluminal angioplasty and vascular implants placements (such as stents, vena cava filters, heart valves) are examples of future clinical applications.

Catheter-based MR guidance enables a substantially reduced level of invasiveness compared with open-chest surgery, potentially resulting in treatment on an outpatient basis, rapid patient recovery, eliminate radiation exposure and cost savings to the health care system. It should be noted, however, that translation of MR-guided interventions to clinical use has been very slow due to limited availability of MR-friendly catheters, wires, devices and financial funding by National Institute of Health and vendors.

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Conflict of interest None.

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