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Emerging MRI Methods in Translational Cardiovascular Research

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Abstract

Cardiac magnetic resonance imaging (CMR) has become a reference standard modality for imaging of left ventricular (LV) structure and function, and, using late gadolinium enhancement, for imaging myocardial infarction. Emerging CMR techniques enable a more comprehensive examination of the heart, making CMR an excellent tool for use in translational cardiovascular research. Specifically, emerging CMR methods have been developed to measure the extent of myocardial edema, changes in ventricular mechanics, changes in tissue composition as a result of fibrosis, and changes in myocardial perfusion as a function of both disease and infarct healing. New CMR techniques also enable the tracking of labeled cells, molecular imaging of biomarkers of disease, and changes in calcium flux in cardiomyocytes. In addition, MRI can quantify blood flow velocity and wall shear stress in large blood vessels. Almost all of these techniques can be applied in both pre-clinical and clinical settings, enabling both the techniques themselves and the knowledge gained using such techniques in pre-clinical research to be translated from the lab bench to the patient bedside.

Keywords

MRI; Myocardial Infarction; Perfusion; Fibrosis; Molecular Imaging; Calcium

Introduction

Diseases of the heart, including myocardial infarction (MI) and heart failure, continue to be a leading cause of morbidity and mortality in the western world. In the United States alone, over 5 million people receive medical care for heart failure each year, at a cost of tens of billions of dollars[1]. Research into the mechanisms of and potential therapies for cardiovascular disease has increasingly relied upon the use of animal models, with the ultimate goal of translating discoveries from the lab bench to the clinic. Similarities between mice and humans in terms of cardiovascular structure and function, physiology, and healing and remodeling of the left ventricle (LV) after MI coupled with both the ability to manipulate the mouse genome and the relatively low cost of mouse research underlie the extensive use of mouse models in cardiovascular translational research. Current efforts to develop novel therapies for patient treatment, including cell[2, 3], gene[4], biomaterial [5], and micro RNA[6] based therapies, will be evaluated extensively in small animal models prior to translation to human use.

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Traditionally, preclinical cardiovascular research has relied upon *in vitro* techniques such as immunohistochemistry of isolated tissue sections and examination of individual cells for assessment of diseases and treatments. In addition, invasive *in vivo* techniques, such as the use of LV pressure catheters, have been used to study LV function. While these techniques are very useful for multi-scale characterization of the heart, they have limitations such as being poorly suited for sequential measurements. To complement conventional methods, a variety of non-invasive and minimally invasive *in vivo* imaging methods have been investigated for small animals. For example, echocardiography using high-frequency transducers has been used to measure LV structure and function. Also, PET imaging is useful for assessment of metabolism and targeted molecular imaging [7], and *in vivo* bioluminescence imaging has become a standard by which to image changes in gene expression using conditional expression of reporter genes.

For the evaluation of cardiac structure and function MRI has become a reference standard modality for essentially all species ranging from mice to humans[8–10]. Cardiac MRI (CMR) offers a combination of high spatial resolution and high soft tissue contrast. As a result, CMR has been used extensively to image the heart in terms of LV structure and function, and also to identify the extent of MI [11, 12], and to measure myocardial perfusion [9]. In addition, newer CMR methods can assess fibrosis, myocardial edema, certain cells, and calcium channel function in preclinical and/or clinical research. This review will focus on current and emerging CMR methods for translational cardiovascular research. Specifically, this review will discuss CMR of LV structure and contractile function, contrast-enhanced CMR of MI and fibrosis, CMR of myocardial edema, CMR of myocardial perfusion, MRI of cell tracking and targeted molecular imaging, manganese-enhanced (Mn-enhanced) MRI of calcium (Ca^{2+}) channel function, and finally MRI of blood flow and wall shear stress in large blood vessels.

I. MRI of Left Ventricular Structure and Function

Changes in the structure and function of the heart, which typically manifest as increases in LV volume, thinning or thickening of the LV wall, regional wall motion abnormalities, and decreases in LV ejection fraction (EF) are typical of the diseased heart [9]. Due to its superb image quality in terms of spatial and temporal resolution, image contrast, and lack of artifacts, cine CMR is well established for the measurement of LV volumes, wall thickness, and ejection fraction (EF) [8, 9, 13, 14]. Example end-diastolic and end-systolic CMR images acquired after MI in a patient and a mouse are shown in Figure 1, and illustrate the ability to visualize changes in wall thickness and LV function in both clinical and preclinical settings. Clinically, cine CMR is routinely used to identify ischemic [9] and non-ischemic cardiomyopathy[15].

Over the past 20 years, several MRI techniques which enable measurement of regional myocardial displacement and strain have been developed, including myocardial tagging[16, 17], and more recently displacement encoding with stimulated echoes (DENSE)[18–24]. In the mammalian heart, mid-wall cardiac myofibers are circumferentially oriented[25, 26]. As such, measurements of mid-wall circumferential shortening (E_{cc}) and rate of circumferential shortening (dE_{cc}/dt) provide *in vivo* measurements that reflect cardiomyocyte shortening and shortening velocity, respectively[27]. Myocardial tagging is a well established technique [16, 17, 28], and has been used extensively in studies ranging from small animals[21, 27, 29, 30] to patients [28, 31]. For example, we recently used myocardial tagging in mice to quantify regional contractile function after MI[17, 21, 32], as well as to elucidate the roles of individual genes in modulating contractile function in transgenic[32] and knock-out mice [21, 27]. Myocardial tagging has also been used to assess mesenchymal stem cell (MSC) therapy in porcine models of acute and chronic MI[33, 34], as well as changes in regional

E_{cc} after MI in humans [28, 35]. A recent myocardial tagging study demonstrated similar patterns of circumferential and radial strain in rodents and humans, with the magnitude of strain increasing with the size of the heart, as well as a consistent transmural E_{cc} gradient across species [36]. Such findings both illustrate the translational capacity of myocardial tagging, and demonstrate the utility that measurement of myocardial strain can play in determining the translational potential of novel therapies.

Cine DENSE MRI, which is an emerging technique that builds on some of the concepts that underlie myocardial tagging, has been used to measure myocardial displacement and strain with higher spatial resolution in mice [19, 20], and humans [18, 22–24, 37]. In this technique, tissue displacement is encoded into the phase of the stimulated echo, and phase images essentially directly record tissue motion at high spatial resolution. Using multiple orthogonal measurements, both two and three dimensional myocardial mechanics can be measured, as demonstrated recently in humans [24, 38]. Sample images from cine-DENSE acquisitions in a human and a mouse, both after MI, are shown in Figure 2. In both humans and mice, reduced displacement and circumferential strain in infarct zone myocardium were measured using cine DENSE. An immediate clinical application of 3D cine DENSE may be the measurement of LV torsion in patients with diastolic dysfunction [39], a condition in which systolic function is preserved but diastole and untwisting of the LV is impaired [40]. Compared to other aspects of heart failure, diastolic dysfunction is less well understood [40]. A better understanding of the causes and characteristics of diastolic dysfunction may help to both improve diagnosis of affected patients, and to direct development of potential treatments.

II. MRI of Myocardial Infarction, Fibrosis, and Edema

The ability to visualize the presence and extent of MI, evaluate myocardial viability, and quantify myocardial infarct size using CMR with gadolinium-based contrast agents has been a major advance in cardiac imaging [11, 12]. After intravenous injection, gadolinium (which enhances the relaxation rate of neighboring water molecules) quickly washes out of healthy myocardium while remaining trapped within areas of acute MI and scar tissue. Subsequently, T1 weighted MR imaging at an appropriately chosen inversion time (TI) [41] yields images with infarct zone hyperintensity. This technique, which is often referred to as delayed contrast-enhanced (DCE) or late gadolinium enhanced (LGE) CMR, is used regularly in both patients [9, 11] and in animal models of MI [21, 29, 42] to confirm the presence and measure the extent of both acute and chronic MI (Figure 3).

While LGE CMR of dense fibrosis is now well established (Figure 4), identification of diffuse fibrosis with gadolinium-enhanced CMR is an emerging method. Diffuse interstitial fibrosis promotes a progression towards heart failure [43], and increases the likelihood of ventricular arrhythmias [44]. The current gold standard for diagnosis of myocardial fibrosis, measurement of collagen volume fraction (CVF) in heart biopsy samples [45], is invasive and forces clinicians to make assumptions about non-biopsied areas based on a small sample of myocardium. Recently, measurement of gadolinium-enhanced myocardial T1 relaxation times distinguished healthy myocardium from areas of diffuse fibrosis [43]. Gadolinium-enhanced MRI of diffuse fibrosis must be performed carefully, as this method can be effected by choice of pulse sequence, method of gadolinium administration, and glomerular filtration rate [46]. While these methods continue to evolve, quantification of the gadolinium distribution volume (GDV), an *in vivo* surrogate of CVF, appear most promising [45] [47, 48]. In an initial *in vitro* study, the T1 of myocardial samples stored in saline was measured before and 24h after incubation with gadolinium [45]. GDV, which was measured as the change in T1 relaxation of tissue normalized to the change in T1 relaxation of saline, correlated strongly with histological measurements of CVF [45]. In a more recent clinical

study, T1 relaxation of myocardium and blood were measured dynamically before and at several points after injection of gadolinium [47]. The gadolinium partition coefficient was measured using a linear fit of myocardial R1 normalized to R1 of the blood, and from this GDV was calculated by multiplying the gadolinium partition coefficient by (1-hematocrit/100) [47]. The authors demonstrated that in patients with diffuse fibrosis, increased LV dilation and reduced global function correlated better with increased GDV than with enhancement on LGE images [47]. The ability to detect changes in myocardial tissue composition using measurement of GDV may improve early and accurate diagnosis in patients, and may readily be applied to small animal models of diffuse fibrosis, potentially enabling more rapid evaluation of novel anti-fibrotic therapies.

In addition to imaging focal infarction and diffuse fibrosis, T2-weighted CMR of myocardial edema is emerging as a novel method for measurement of area at risk (AAR) in the presence of acute coronary syndrome (ACS) [49], as well as after MI [50–52]. Myocardial edema occurs rapidly after the onset of ischemia, and areas of edema appear hyperintense on T2-weighted images of the heart [49, 51]. Example T2-weighted CMR images which highlight the AAR in a patient and a mouse are illustrated in Figure 5. In the presence of ACS, T2-weighted imaging of edema has recently been used to visualize myocardium at risk of MI and identify patients in need of immediate coronary revascularization [49]. In the presence of MI, AAR represents the combination of infarcted myocardium and salvaged myocardium [50, 51]. In initial studies, determination of AAR by T2-weighted CMR was validated against microspheres in a dog model of MI [53], and later applied in patients after MI [52]. In a recent prospective clinical study by Berry et al., AAR as calculated by T2-weighted CMR correlated strongly with traditional angiographic measures of ischemia [51]. Furthermore, estimation of myocardial salvage, which was estimated as the differences between AAR and infarct size, was possible in all patients regardless of prior medical history [51]. The emergence of CMR methods to measure AAR will likely lead to new clinical applications in patients, as well as use in research of edema and infarct healing.

III. MRI of Myocardial Perfusion

Imaging of myocardial perfusion plays a critical role in the diagnosis and treatment of patients with ischemic heart disease (for a full review see Patel et al.[54]), and is playing an increasing role in pre-clinical cardiac research. While x-ray angiography is the most commonly used method to identify occlusions of coronary arteries, first-pass contrast enhanced CMR has become an established technique for measuring myocardial perfusion and perfusion reserve (PR) in patients [55–58], and is emerging as a technique for use in mice [59–61]. Sample images and data from human and mouse first-pass perfusion imaging studies are shown in Figure 6. Although first-pass perfusion imaging in patients is not new, recent improvements have included the development of dual-bolus [62] and dual-contrast [63] methods for improved quantification of the arterial input function, incorporation of compressed sensing and parallel imaging techniques to improve spatial and temporal resolution and coverage [64], and calculation of pixel-wise values of myocardial blood flow from first-pass images [65]. Implementation of first-pass perfusion imaging in mice has generally been limited by faster heart rates and the subsequent tradeoff between imaging speed and spatial resolution. However, recent studies have implemented spiral imaging (Figure 6B) [59], segmented image acquisition and parallel imaging [61], and accelerated imaging using *k*-space and time domain undersampling with constrained reconstruction [60] to achieve adequate spatial and temporal resolution. In two of these studies, quantitative measurements of regional myocardial perfusion were made before and after MI [59, 60], making this technique appealing for use in pre-clinical studies of myocardial perfusion.

Compared to first-pass perfusion imaging, arterial spin labeling (ASL) is an emerging CMR method in both humans [66–70] and small animals [27, 42, 71–83]. The most common ASL method used in the heart, flow-sensitive alternating inversion recovery (FAIR) - ASL [74], typically uses an ECG-gated Look-Locker [84] acquisition to obtain a series of end-diastolic images at an array of TIs following slice-selective (SS) and non-selective (NS) inversions. Following SS inversion, the inflow and exchange of non-inverted blood spins into the inverted imaging slice imparts an apparent shortening effect on measured T1 ($T1_{SS}$) when compared to that measured after NS inversion ($T1_{NS}$). Based on a T1 difference approach, myocardial perfusion can be measured in units of ml/g/min as $P = (1/T1_{NS} - 1/T1_{SS}) * T1_{NS} / T1_{blood} * \lambda$, where λ is the blood/tissue partition coefficient [72]. While acquisition of ASL images at a rate of 1 image per heart beat in humans results in sparse sampling of T1 relaxation curves, methods to sample T1 relaxation curves at higher densities have been developed [85] [86]. An additional limitation of FAIR-ASL in humans is that normal levels of myocardial perfusion, around 1 ml/g/min [10, 70], correspond to small differences between $T1_{SS}$ and $T1_{NS}$. Thus, ASL is relatively insensitive to changes in resting myocardial perfusion values in humans. However, a recent study using FAIR-ASL at a field strength of 3T demonstrated the ability to measure perfusion in the human heart, and presented analysis of sources of noise and their impact in ASL measurements [70]. In addition, the difference between $T1_{NS}$ and $T1_{SS}$ increases with increasing field strength for a given level of myocardial perfusion, suggesting that ASL measurements in the human heart may improve as higher field strength MRI systems are developed.

While FAIR-ASL has been implemented in small animals to measure myocardial perfusion in healthy tissue [27, 42, 71–73], respiratory motion artifact, variability in heart rate, and problems with ECG triggering have prevented measurement of perfusion during acute MI. Recently, we implemented a FAIR-ASL method in mice which used combined cardiac and respiratory gating during image acquisition (CRG-ASL), and sorted acquired data using a fuzzy C-means clustering algorithm prior to image reconstruction [42]. Using this method, we were able to measure regional myocardial perfusion in healing infarcts in mice. Figure 7 illustrates sample maps of myocardial perfusion acquired in a mouse one day after MI using CRG-ASL, as well as measurements of regional myocardial perfusion during the time-course of infarct healing. While acquisition time in ASL experiments is long compared to first-pass perfusion imaging, ASL enables measurement of perfusion in mice without the need for challenging tail vein injections, and is not limited by the rapid washout of contrast agent, enabling acquisition of high resolution perfusion maps in the mouse heart. A major target in translational cardiac research of infarct healing is restoration of healthy levels of myocardial perfusion to ischemic and remodeling tissue. As novel pro-angiogenic therapies progress from preclinical experiments to clinical application, the ability to serially measure the restoration of myocardial perfusion using either ASL or first-pass perfusion imaging will prove useful.

IV. MRI of Cell Tracking and Molecular Imaging

Migration of non-resident cells into remodeling tissue, as well as changes in expression of certain biomarkers, are common to many cardiovascular diseases [87–89]. Traditionally, techniques such as immunohistochemical staining of tissue sections, bioluminescence imaging of labeled cells, and fluorescence microscopy with targeted ligands have been used to examine such changes in cardiovascular diseases. MRI tracking of labeled cells and targeted molecular MRI are emerging techniques for the heart and vasculature [90]. Although these techniques are mainly investigated in small animals, they have significant translational potential.

Amongst MRI cell tracking studies, cell labeling typically involves the use of either gadolinium based agents or a variety of super-paramagnetic iron oxide (SPIO) particles. While clusters of cells labeled with gadolinium agents appear hyperintense in T1 weighted images [91], cells labeled with SPIO particles typically appear as hypointense regions on T2* weighted images [92]. In a recent study in mice, stem cells labeled with a gadolinium based agent were injected into infarct zone myocardium and visually tracked using T1 weighted imaging for up to 14 days [93]. In a similar study, the migration of macrophages (labeled after phagocytosis of gadolinium labeled liposomes) into the mouse heart after MI was quantitatively assessed using T1 mapping (Figure 8) [94]. Limitations of gadolinium agents include lower sensitivity and the potential for alterations in proliferation and gene expression amongst certain cell types [95]. For these reasons, cell labeling with iron oxide particles has been more common amongst MRI cell tracking studies [92, 96] [97, 98]. Recent studies have used MRI cell tracking with iron oxide particles and T2* weighted imaging to track both embryonic stem cells [99] (Figure 9) and bone marrow stromal cells [100] after implantation into the infarcted rat heart, to label and track macrophages in a mouse model of MI [101], and to track cells involved in heart transplant rejection in a rat model [102]. While uncertainty remains as to whether signal loss originates from labeled cells or from other sources of signal loss [91], a number of techniques have recently emerged to produce positive contrast from cells labeled with iron oxide particles in order to improve visualization and eliminate some uncertainty [103] [104] [105]. A significant limitation to the use of iron oxide particles for cell tracking, particularly in studies of cell transplantation therapy, is the ability to distinguish between living and dead labeled cells. In a recent study, SPIO-labeled adult epicardium derived cells, one group living and the other dead, were injected directly into the hearts of mice following MI [106]. Serial CMR imaging demonstrated similar signal voids in the vicinity of both dead and living cells over the time course of imaging, while histological examination demonstrated that iron oxide particles from dead cells were slowly absorbed by macrophages [106]. In an attempt to overcome this limitation, conditional over-expression of ferritin heavy chain (h-ferritin) to obtain T2* contrast in living cells has been explored [107, 108]. In one such study, mouse skeletal myoblasts were engineered to over express h-ferritin and were successfully tracked using T2* weighted CMR for a period of 3 weeks after implantation in the hearts of mice with experimental MI [107]. As cell based therapies for cardiac repair progress from pre-clinical to clinical application, CMR techniques which enable tracking of labeled cells will likely be more widely used.

In addition to cellular imaging, molecular MRI is emerging to evaluate changes in expression of cell surface receptors, ligands, and other biomarkers common to cardiovascular disease. Recently, an increasing number of molecular MR imaging probes have been developed using principles similar to other molecular imaging modalities, namely the conjugation of an MR contrast agent to a targeted molecular probe or peptide (for full reviews see [109–112]). In a recent study by Helm et al., a gadolinium based collagen targeted MRI contrast agent (EP-3533, Epix Pharmaceutical) was used to study myocardial fibrosis in chronic MI in mice [113]. Areas of fibrotic scar tissue, which appeared bright on T1 weighted CMR images, demonstrated strong correlation with regions of fibrosis as identified using picrosirius red histological staining (Figure 10) [113]. In a separate study, a magnetofluorescent nanoparticle (AnxCLIO-Cy5.5) targeting apoptotic cardiomyocytes was used in the hearts of transgenic mice [110]. Using T2* weighted imaging, the authors demonstrated discrete regions of hypointensity in areas identified as containing apoptotic cardiomyocytes [110]. The persistent and low levels (1–2%) of apoptosis in this mouse model are similar in heart failure patients [110], suggesting a novel mechanism by which to evaluate the presence of apoptosis in heart failure patients. While the use of targeted molecular MRI has demonstrated significant promise in preclinical studies, translation to clinical imaging has progressed more slowly. In a recent clinical study, a gadolinium based

fibrin targeted contrast agent (EP-2104R) was used to visualize thrombi formation in the heart and vasculature in patients (Figure 11) [114].

V. Manganese Enhanced MRI of Calcium Channel Function

Calcium (Ca^{2+}) cycling plays a critical role in maintaining homeostatic function of the heart [115], with changes in Ca^{2+} cycling often causing or accompanying various forms of cardiomyopathy [116]. As a result, research into the roles of individual genes involved in maintaining calcium homeostasis, as well as potential therapies to restore normal calcium cycling to the failing heart have garnered significant attention. Manganese (Mn^{2+}), which is fairly similar in size and identical in charge to Ca^{2+} , enters cardiomyocytes through the trans-membrane L-type Ca^{2+} channel (LTCC) in proportion (~8%) to Ca^{2+} flux [117], and shortens T1 relaxation in relation to concentration [118]. Based on this, Mn-enhanced CMR has been used to assess LTCC function both outside [119] and inside the heart [120]. Prior studies have used Mn-enhanced CMR in the canine heart in conjunction with surgically induced MI to assess myocardial viability (Figure 12)[121], and area at risk [122]. In the mouse heart, dynamic Mn-enhanced CMR has been used to observe changes in LTCC function during increased cardiac inotropy [123], as well as following MI [124] using a timed infusion of MnCl_2 and T1 weighted imaging. Recently, Mn-enhanced CMR has been used to probe changes in Ca^{2+} uptake and extrusion in the mouse heart with T1 mapping [125, 126]. We recently used dynamic Mn-enhanced CMR and a timed infusion of MnCl_2 (Figure 13) to measure a quantitative index of LTCC function (LTCCI) [127], which is analogous to the traditional *in vitro* measurement of LTCC current density [116], in order to elucidate the roles of different isoforms of NOS in Ca^{2+} cycling [116]. Although Mn-enhanced CMR has emerged as a powerful preclinical research tool, the potential toxicity of free Mn^{2+} remains an obstacle to clinical translation. Interestingly, a recent study in healthy human volunteers demonstrated significant myocardial T1 shortening with minimal side effects in response to a short low level infusion of MnCl_2 [128]. While such results are encouraging, more safety studies will be required to investigate the potential for clinical use of MnCl_2 .

VI. MRI of Blood Flow in Large Vessels

While this review has focused on the heart, emerging CMR methods also play a significant role in translational research in vascular diseases such as atherosclerosis. Clinically, Doppler ultrasound has been used extensively to measure blood flow velocity (BFV) in order to examine atherosclerotic progression in major blood vessels [129]. However, such BFV measurements are restricted in dimension depending upon transducer orientation [129]. Alternatively, computational fluid dynamics has been implemented to model wall shear stress (WSS) [129], which is reduced in atheroprone arteries [130]. Similarly, phase contrast (PC) MRI is an established technique that has been used to measure blood flow velocity (BFV) and volume flow in two and three dimensions [129, 131], however measurement of WSS from such experiments has been limited to regional measurement in 2D slices [132]. Recently, improvements to flow-sensitive 3D cine (or 4D) PC-CMR have led to better measurements of the 3D time-varying BFV, WSS, and oscillatory shear index (OSI) in humans [132–135] and mice [136]. In a recent pre-clinical study performed in mice, 4D PC-CMR was used to generate maps of WSS along the aortic arch (Figure 14), which demonstrated decreased WSS along the inner radius of the aortic arch [136]. In a recent clinical study in humans, 4D PC-CMR was used to measure BFV, WSS, and OSI at 8 points along the aorta in healthy volunteers and patients with atherosclerosis (Figure 14) [134]. Compared to healthy volunteers, measurements of lower WSS magnitude along the aorta in patients correlated with the presence and size of plaque in the aortic wall (Figure 14). Continuing improvements to these methods will enable increased use of 4D PC-CMR for

assessment of atherosclerotic progression in patients, as well as for investigation of the roles of individual genes in disease development, and assessment of novel anti-atherosclerotic therapies.

Conclusions

CMR has become a powerful tool for use in translational cardiovascular research. Both emerging CMR methods and knowledge gained from preclinical experiments using CMR can be translated to clinical use. Emerging CMR techniques now enable multi-scale *in vivo* characterization of the heart, from changes in global LV structure and function, to changes in tissue composition, mechanics, and perfusion, and to changes in calcium channel function and gene expression. In addition, novel techniques for cell tracking and molecular imaging can be used in both clinical and preclinical research. Many of the techniques described in this review can be combined in a single imaging study, providing a comprehensive assessment of the heart as a function of disease progression or treatment. A major challenge for the future will involve translation of molecular and cellular imaging to clinical practice.

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Fig. 1. Cine CMR of LV structure and function in a human patient and a mouse. Post-infarct cine images acquired at end diastole (ED) (A) and end systole (ES) (B) in a human, and at ED (C) and ES (D) in a mouse. Blood appears dark in (C) and (D) due to the use of a dark-blood magnetization preparation [137]. Thinning of the anterior wall of the LV can be seen (white arrows) in both the patient and the mouse at ED and ES. At ES, the thinned infarct zone demonstrates akinesis compared to noninfarcted myocardium in both the patient and the mouse. Human images were reprinted with permission from [9] Salerno et al. *Expert Opinions Medical Diagnostics*. 2009 November 1; 3(6): 673–687

Fig. 2. Cine DENSE MRI of human and mouse hearts after myocardial infarction (MI). (A) End diastolic, mid-ventricular short axis image of the human heart. (B) Late gadolinium enhanced (LGE) CMR image, in which infarcted myocardium appears hyperintense (white arrows) as compared to dark non-infarcted myocardium, indicating the location and extent of MI. (C) The corresponding end-systolic displacement map demonstrates regionally reduced displacement in close spatial-agreement to the region of infarction as defined in (B). (D) Similarly, the map of end-systolic circumferential shortening (E_{cc}) demonstrates regionally reduced E_{cc} in the infarcted zone. Similar results are seen in the mouse heart (E–H) following surgically induced reperfused MI

Fig. 3. LGE CMR images of MI in a human (A) and a mouse (B). Images were acquired using inversion recovery pulse sequences. Regions which appear hyperintense (white arrows) represent areas of infarcted myocardium. In (A), a dark area is seen at the core of the infarct, representing a region of microvascular obstruction. In (B), enhancement of the infarcted anterior wall is transmural. Figure components reprinted with permission from [9] Salerno et al. *Expert Opinions Medical Diagnostics*. 2009; 3(6): 673–687

Fig. 4. LGE CMR of myocardial fibrosis. Accumulation of gadolinium in areas of fibrosis can be visualized using LGE-CMR as foci of hyperintensity (white arrows) in inversion recovery images. (A) Images acquired from a patient displaying predominantly mid-wall enhancement at the mid-ventricle. (B) Images from a patient displaying enhancement of the intra-ventricular septum towards the base of the heart. Patterns of focal enhancement represent regions of dense fibrosis. Images reprinted with permission from [15] Wu et al. *Journal of the American College of Cardiology*. 2008;51:2414–21

Fig. 5. T2-weighted CMR of myocardial edema and area at risk (AAR). (A) Bright-blood T2-weighted long-axis image from a patient presenting with chest pain demonstrates significant myocardial edema along the anterior wall without accompanying MI (black arrow) [50]. (B) LGE CMR illustrates no MI along the anterior wall, although an unrelated subendocardial posterior MI was present. (C, D) Black-blood T2-weighted CMR images of a mouse heart acquired using a T2-prepared sequence [138] demonstrate myocardial edema 2 days after experimental reperfusion MI (arrows). The AAR is larger than the corresponding region of MI (E), and includes salvaged myocardium. Figure components reprinted with permission from [50] West et al. *Current Problems in Cardiology*. 2010;35:176–220, and [138] Beyers et al. *Magnetic Resonance in Medicine*. 2011; In Press

Fig. 6.

First-pass CMR of myocardial perfusion in humans and mice after MI. (A) Images acquired in a patient before injection of a bolus of gadolinium, as the bolus arrives in the LV blood pool, as it transits the myocardium, and during washout (left to right). As the bolus of gadolinium transits the myocardium normally perfused myocardium becomes hyperintense, while diminished myocardial perfusion causes the infarct zone to remain hypointense (white arrow). (B) First-pass CMR images acquired in a mouse heart demonstrate similar gadolinium kinetics to humans in infarct (white arrow) and remote zones of myocardium. Higher heart rates in mice necessitate faster image acquisition, resulting in relatively low resolution images. (C) Graphs of myocardial signal intensity from (A) demonstrate significant differences in the rate of signal enhancement and maximal signal enhancement between remote and infarct zones (left). In the mouse experiment (right), signal intensity is converted to gadolinium concentration as detailed by Cernicanu et al. [139]. Using such a technique, perfusion in units of $\text{ml}_{\text{blood}}/\text{g}_{\text{tissue}}/\text{min}$ can be estimated. Figure components reprinted with permission from [59] Antkowiak et al. *Journal of Cardiovascular Magnetic Resonance*. 2010; 12(S1):M10

Fig. 7.

Changes in myocardial perfusion during the process of infarct healing in the mouse heart as measured using FAIR-ASL. (A) LGE CMR image of a mouse heart acquired one day after experimental MI demonstrates hyperenhancement of the infarcted region (red arrow). (B) Map of myocardial perfusion generated using cardiac and respiratory gated ASL (CRG-ASL [42]) demonstrates a significant perfusion defect in close spatial agreement with the region of infarction as defined in (A). (C) Time course of perfusion in infarct and remote myocardium as measured using CRG-ASL. One day after MI, perfusion was very low in the infarct zone and normal in remote myocardium. Between days one and fourteen, perfusion increases in infarct zone myocardium, while remaining unchanged in remote zone myocardium (* $P < 0.05$ vs. remote, § $P < 0.05$ vs. day1 remote, # $P < 0.05$ vs. day1 infarct). The time-course of recovery of perfusion in infarct zone myocardium reflects changes in perfusion secondary to growth of new blood vessels (E, black bars). (D) Neovascularization of medium sized blood vessels in infarct zone myocardium was demonstrated to occur primarily between two and fourteen days after MI in a study using a similar model of reperfused MI in mice (* $P < 0.05$, ** $P < 0.01$, ligation vs. reperfusion). Images AD were reprinted with permission from [42] Vandsburger et al. *Magnetic Resonance in Medicine*. 2010; 63(3):648–57. Figure E was reprinted with permission from [140] Vandervelde et al. *Cardiovascular Pathology*. 2006; 15(2): 83–90

Fig. 8.

CMR of gadolinium-labeled macrophages in the mouse heart after MI. (A) A relaxivity (R1) map calculated from a Look-Locker image series demonstrates enhanced R1 in the infarct zone (white arrows), indicating the presence of labeled macrophages. (B) A map of end-systolic E_{cc} acquired using cine DENSE in the same location delineates the infarcted region as a region of diminished contractile function. Together, these images demonstrate that macrophage infiltration is confined to the infarcted region, with greatest intensity in the core of the infarct. Figure components reprinted with permission from [94] Naresh et al. *Circulation*. 2010; 122: A17344

Fig. 9. CMR tracking of SPIO labeled embryonic stem cells (ESC) for cardiac repair after MI. (A) The region of injection of SPIO labeled ESC appears as a large hypointensity (white arrow) compared to surrounding myocardium at 1 day after MI. (B) At 4 weeks after MI signal loss is still observed in the same region, however, histological analysis demonstrated significant uptake of SPIO by macrophages. Figure reprinted with permission from [99] Qiao et al. *Radiology*. 2009; 250(3): 821–829

Fig. 10.

Molecular MRI in mice using a collagen targeted contrast agent: EP-3533. (A,D) Black-blood gradient echo images of the mouse heart at 2 locations, acquired 6 weeks after surgically induced MI, demonstrate a thinned LV wall in the area of the healed infarct (white arrows). (B,E) Inversion recovery images of the heart acquired 40 minutes after injection of EP-3533 demonstrate hyperintensity (white arrows) within areas of collagen-rich scar tissue. The patterns of hyperintensity (B,E) correlate closely with photomicrographs of picrosirius red-stained tissue sections (9x magnification), in which areas of high collagen content appear red compared to surrounding myocardium (white arrows). Figure reprinted with permission from [113] Helm et al. *Radiology*. 2007; 247(3): 788–96

Fig. 11. Molecular imaging of the fibrin targeted contrast agent EP-2104R in the descending thoracic aorta of a human patient. (a) Inversion recovery, black-blood gradient echo image demonstrates clear hyperintensity of the forming clot (white arrow) within the patient's blood vessel. (b) Contrast enhanced computed tomography image confirms the location of plaque within the aortic wall (gray area), as well as the presence of calcification (white arrowhead). Figure reprinted with permission from [114] Spuentrup et al. *European Radiology*. 2008;18:1995–2005

Fig. 12.

Assessment of myocardial viability using Mn-enhanced CMR in the ischemic dog heart. Mid-ventricular short axis images were acquired using an inversion recovery pulse sequence. (A) Prior to infusion of Mn²⁺, signal intensity appears uniform throughout the myocardium. (B) During Mn²⁺ infusion in the presence of induced ischemia, viable myocardium appears hyperintense compared to ischemic and necrotic myocardium. (C) While uptake of Mn²⁺ in viable myocardium is immediate, washout time is on the order of hours. Subsequently, even after the end of Mn²⁺ infusion, viable and ischemic myocardium can be clearly delineated. Figure reprinted with permission from [121] Hu et al. *Magnetic Resonance in Medicine*. 2005; 54:196–200

Fig. 13.

Mn-enhanced CMR of the mouse heart. (A–D) Mid-ventricular short-axis T₁ weighted images from a mouse demonstrate increasing SNR over time during IP infusion of MnCl₂. Images were acquired over 90 minutes, while MnCl₂ was infused from 20min until 50min. The specific times corresponding to each image are 15min, 30min, 50min, and 80min for A–D, respectively. (E) When acquiring images using the technique outlined in [127], accumulation of Mn²⁺ within cardiomyocytes results in a linear increase in SNR during infusion. The rate of increase in SNR (solid black line) over the points corresponding to MnCl₂ infusion (filled gray symbols between the start and end of infusion), provides an index of integrated Mn²⁺ flux through the L-type calcium channel (LTCC) (LTCCI, bold numbers). Sample data from one WT mouse demonstrate an increase in LTCCI over baseline in response to β-adrenergic stimulation with dobutamine, and a decrease from baseline in response to partial LTCC inhibition with nifedipine. Figure reprinted with permission from [127] Vandsburger et al. *Circulation*. 2010; 122:A12386

Fig. 14.

Time-resolved 4D phase contrast (PC) MRI of blood flow velocity (BFV) and wall shear stress (WSS) in the human and mouse aorta. (A) Visualization of systolic 3D blood flow in the human aorta demonstrates heterogeneity in BFV. Assessment of WSS was performed along 8 analysis planes (white lines) normal to the direction of blood flow in the ascending aorta (AAo), the aortic arch (arch), and the descending aorta (DAo). (B) Average measurements of the magnitude of WSS in healthy volunteers and patients with acute retinal or cerebral ischemia demonstrate a correlation between decreased WSS beginning at the aortic arch and plaque size. (C) 3D map of peak-systolic WSS measurements along the aortic arch in a mouse demonstrate higher WSS values near the outer radius and lower WSS values near the inner radius. Figure A,B reprinted with permission from [134] Harloff et al. *Magnetic Resonance in Medicine*. 2010; 63:1529–1536. Figure C reprinted with permission from [136] Janiczek et al. *Proceedings of the ISMRM*. 2009; 17:3857