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Feasibility of complementary spatial modulation of magnetization tagging in the rat heart after manganese injection

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ABSTRACT: It has been shown that manganese-enhanced MRI (MEMRI) can safely depict the myocardial area at risk in models of coronary occlusion–reperfusion for at least 2 h after reperfusion. To achieve this, a solution of $MnCl_2$ is injected during coronary occlusion. In this model, the regional function quantification deficit of the stunning phase cannot be assessed before contrast injection using MR tagging. The relaxation effects of manganese (which remains in normal cardiac myocytes for several hours) may alter the tags by increasing tag fading and hence the quality of strain measurement. Therefore, we evaluated the feasibility of cardiac MR tagging after manganese injection in normal rats. Six normal Sprague–Dawley rats were imaged *in vivo* using complementary spatial modulation of magnetization (C-SPAMM) at 1.5 T, before and 15 min after intraperitoneal injection of $MnCl_2$ solution ($\sim$17.5 μmol kg^{-1}). The contrast-to-noise ratio of the tag pattern increased significantly ($P < 0.001$) after injection and remained comparable to the control scan in spite of the higher myocardial relaxation rate caused by the presence of manganese. The measurements of circumferential strain obtained from harmonic phase imaging analysis of the tagged images after $MnCl_2$ injection did not differ significantly from the measurements before injection in the endocardial, mid-wall, and epicardial regions. In particular, the transmural strain gradient was preserved. Thus, our study suggests that MR tagging could be used in combination with MEMRI to study the acute phase of coronary artery disease. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: myocardial tagging; complementary spatial modulation of magnetization (C-SPAMM); cardiac MRI; harmonic phase imaging (HARP); manganese; area at risk; contrast media; myocardial function

INTRODUCTION

Experimental studies of myocardial viability and assessment of therapies after infarct define the infarct size as a percentage of the area at risk (the myocardial area that experiences a perfusion deficit after the coronary occlusion). For instance, in experimental models of coronary artery disease (CAD), the area at risk is an internal reference to assess the efficiency of a treatment in the final infarcted zone, as the area at risk corrects the effect of the variability in the coronary occlusion in the infarcted zone. In clinical routine, the area at risk is also an important parameter that is often difficult to assess. Comparing area at risk with infarcted area allows quantification of the amount of salvaged myocardium and treatment benefit in patients (1,2), and therefore intensive research is being performed to improve non-invasive measurement of the area at risk.

As manganese cations enter normal cardiac myocytes through calcium channels and remain there for hours, the use of MRI in the presence of $MnCl_2$ has recently been proposed for the non-invasive assessment of the myocardial area at risk (3). $MnCl_2$ is infused during coronary occlusion so that the manganese cations enter only the perfused myocytes and not the area at risk. Thus, MR images after $MnCl_2$ injection reveal the area at risk as a dark zone for at least 2 h after reperfusion. Therefore, manganese-enhanced MRI (MEMRI) appears to be a powerful tool for measuring the area at risk.

For coronary occlusion–reperfusion studies, evaluation of global and regional function is needed. Myocardial contraction defects are early indicators of ischemic disease and can be used to evaluate treatment response. MRI has been widely used to measure myocardial mass, end-systolic and end-diastolic volumes, and ejection fraction and has gained clinical acceptance in these applications (4). In addition to measurement of global function by cine MRI, cardiac tagging allows accurate

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Abbreviations used: CAD, coronary artery disease; CNR, contrast-to-noise ratio; CS, circumferential shortening; C-SPAMM, complementary spatial modulation of magnetization; ECG, electrocardiogram; FA, flip angle; HARP, harmonic phase imaging; MEMRI, manganese-enhanced magnetic resonance imaging; RF, radio frequency; ROI, region of interest; SNR, signal-to-noise ratio.

quantification of regional myocardial strain with transmural resolution (5). MR tagging uses spatial modulation of magnetization (SPAMM) (6) or complementary SPAMM (C-SPAMM) (7), to impose stripes or grids (''tags'') of saturated spins in tissue. Modulation of magnetization is obtained by application of binomial radio frequency (RF) pulses interspersed by dephasing gradients, before the cine imaging sequence. The taglines follow the cardiac deformation during the cardiac cycle, and thus allow accurate quantification of cardiac motion. Cardiac contraction can be examined qualitatively or quantitatively from MR tagging series. There is an increasing need to quantify myocardial contraction in small rodents at the subendocardial scale (8,9). This drives the development of tag MRI despite the significant challenges because of the high cardiac frequency (about 400 bpm) and the small field of view required (about five times smaller than for a human heart). Moreover, when the area at risk is studied using manganese in an experimental model of CAD, manganese is injected during occlusion of the coronary (10). Thus the entire MRI examination is performed in the presence of manganese, especially in tagged MRI. However, the T_1 relaxing effect of manganese may affect tag fading and hence the accuracy of the strain measurements.

The purpose of our study was to evaluate the effect of $MnCl_2$ injection on strain measurement in the rat heart, using C-SPAMM tagging (7) and peak-combination harmonic phase imaging (HARP) analysis (11,12) on a clinical 1.5 T scanner.

METHODS

Animal preparation

The study was performed on six normal male Sprague–Dawley rats weighing 457 ± 27 g (mean $\pm$ SD). They were anesthetized by intraperitoneal bolus injection of $50\,mg\,kg^{-1}$ sodium pentobarbital (Nembutal Sodium Solution; Abbott Laboratories, North Chicago, IL, USA) producing a deep anesthesia of at least 2 hours. All animal procedures were approved by the ethics committee of the institution's review board.

Image acquisition

Imaging was carried out about 15 min after the injection of the anesthetic. The rats were placed in a cradle in the prone position. A rectal thermal probe was used to check their temperature (37–37.5°C). A respiratory pillow was placed on the abdomen to control the breathing rate for monitoring of the anesthesia. The respiratory rate was 60–80 breaths per minute. Subdermal electrodes were placed to record an electrocardiogram (ECG), which was used as a cardiac trigger signal (approximate heart rate 400 bpm). The rats and probes were placed in a heated box to maintain physiological temperature (37.5°C) during the experiment. ECG, respiratory, and temperature probes were connected to the monitoring and gating system [SA Instrument, Inc (SAII), Stony Brook, NY, USA; MR-compatible model 1025]. These physiological variables were continuously monitored. MR images were acquired on an Intera 1.5 T MR system (R9; Philips Medical Systems, Best, The Netherlands) with C-SPAMM tag preparation (two line directions and 1 mm tag distance), segmented cine FFE sequence, 47 mm Philips surface micro-coil, prospective ECG trigger, free breathing, and $TR/TE = 12/6$ ms. A flip angle (FA) ramp (7,13,14) with a final FA of 10° was used. The objective of this FA ramp was to correct for the effect of varying signal intensity (tag fading):

$$\alpha_{k-1} = \arctan\lfloor \sin(\alpha_k) \cdot \exp(-\Delta t/T_1) \rfloor \quad for\ 1 < k \leq n$$

α_k stands for the successive RF excitation FA ($\alpha_n = 10°$), Δt is the time between two successive RF excitations, and T_1 is a reference T_1. This FA ramp was optimized in our study for the normal rat myocardium.

We acquired a 128×256 matrix sampled on a Cartesian grid, no partial Fourier, field of view = 80 mm and 2 mm slice thickness. For technical reasons and to cover the whole cardiac cycle, images were acquired over two heart beats, resulting in 12–15 phases per heart beat (depending on heart rate), for a temporal resolution of 12 ms. The first frame was acquired 29 ms after the R-wave has been detected. Total acquisition time per slice was about 1 min 40 sec. The tagging prepulse consisted of a 1–1 binomial RF pulse with interspersed tagging gradients. Two images with opposite modulations were subtracted yielding the final C-SPAMM image. Slice following was not used. Volume shimming was performed before each scan. After three-plane scout images and two long-axis cine images (two cavities and four cavities), short-axis C-SPAMM images were acquired. Images were acquired before and 15 min after injection of manganese.

Manganese injection

An intraperitoneal bolus injection of 8 mL of $MnCl_2$ solution (corresponding to a total amount of 8 μmol or about $17.5\,\mu mol\,kg^{-1}$) was performed. This dose was determined in the context of our area at risk protocol (10). The injection was performed without moving the rat.

The duration of the whole study was about 50 min for each rat.

Tag analysis

Image domain or k-space domain approaches can be used for quantitative measurement of myocardial tissue motion. We chose the harmonic phase imaging (HARP)

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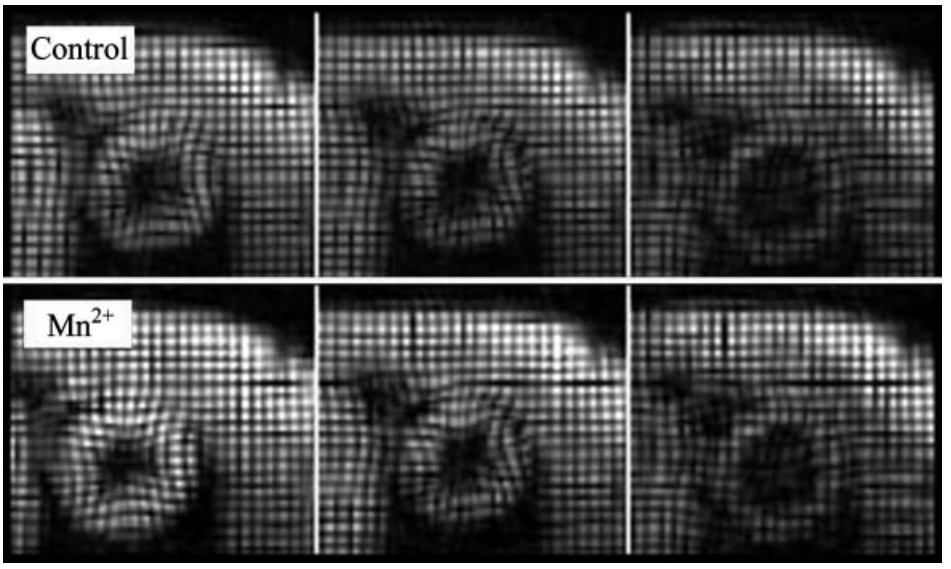

Figure 1. C-SPAMM image evolution through heart phases (left to right) before (top row) and after (bottom row) intraperitoneal injection of $MnCl_2$ in rat 2.

(11) method, which is based on filtering data surrounding a harmonic peak in k-space. Osman & Prince (15) showed that the phase of these filtered images could be used to track material points through time. We used the HARP method on the PRIDE research platform (Philips Medical Systems). Complex-valued images served as data input, thereby avoiding the additional signal peaks obtained with absolute-valued data. In addition, tagline distortions due to field inhomogeneities were compensated for by using peak-combination HARP (12).

Endocardial, epicardial, and mid-wall contours were defined in a semi-automated manner on one cardiac phase image. Contours were then automatically tracked throughout the entire cardiac cycle. Tracking errors were manually corrected when necessary. Circumferential shortening (CS) was calculated from the tracked contours in four cardiac sectors (septal, anterior, lateral, and inferior) according to the following formula:

$$CS(hp) = \frac{SL(hp)}{SL(hp = 0)} - 1$$

where *hp* indicates the heart phase, and *SL* the sector length. Myocardial circumferential strain was expressed as the maximum–minimum difference of the CS curve over the whole cardiac cycle. Myocardial circumferential strains were then averaged over the four cardiac sectors. Owing to the very high heart rate of the rat, the CS curved measurement started in early systole rather than end-diastole. The use of measurements over two heart beats verified that this results in a time shift of the CS curve, and that myocardial strain can be expressed as the maximum–minimum difference of the measured curve.

Contrast measurements

Averaged tag signal (TAG) was measured in a manually drawn region of interest (ROI) of 10 pixels on a tagged line (dark) in the myocardium on the magnitude images. Similarly, the average untagged signal (UNTAG) was

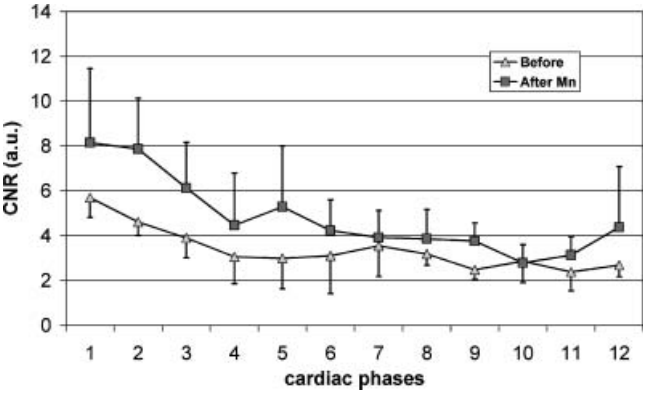

Figure 2. Evolution of the CNR in C-SPAMM images before and after intraperitoneal injection of 17.5 μmol kg^{-1} $MnCl_2$.

Table 1. Circumferential strain measurements before and after manganese injection

	Control	After Mn
Endocardium	0.33 ± 0.06	0.33 ± 0.06
Mid-wall	0.23 ± 0.06	0.24 ± 0.03
Epicardium	0.15 ± 0.05	0.15 ± 0.01

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measured in a ROI (same area) in an adjacent untagged line (bright). Contrast-to-noise ratio (CNR) was defined as follows:

$$\mathrm{CNR} = \frac{\mathrm{UNTAG} - \mathrm{TAG}}{\sigma}$$

where σ is the background noise standard deviation measured in a ROI of 50 pixels. Note that measuring the signal in the magnitude image, rather than the real one, leads to a reduction factor of 2 in contrast.

Signal-to-noise ratio (SNR) was also measured in an untagged region in the liver, on C-SPAMM images:

$$\mathrm{SNR} = \frac{\mathrm{UNTAG\_L}}{\sigma}$$

where σ is the background noise standard deviation measured in a ROI of 50 pixels, and UNTAG_L, the average signal in an untagged ROI of 20 pixels in the liver.

Statistical analysis

All data are expressed as mean $\pm$ SD. The statistical significance between regions in the same group was assessed by a paired *t* test with a Bonferroni correction for multiple measurements. The threshold of significance was set at $p = 0.01$. To assess the hypothesis that manganese injection does not affect the strain measurements, Bland–Altman plots of the circumferential strain values in endocardial, epicardial, and mid-wall regions were produced comparing measurements before and after injection.

RESULTS

Animal physiology

For all animals, the physiological variables monitored (especially heart rate and ECG) did not change after manganese injection.

Contrast measurements

An increase in SNR (mean 62.5%, $p < 0.001$) was observed between the initial liver signal before and after injection, as expected in MEMRI. A minimal qualitative increase in signal intensity and contrast was seen after manganese injection (as shown for rat 2 in Fig. 1). CNR measurements were performed and averaged over all animals. The resulting curves are shown in Fig. 2. Manganese injection induced a significant increase in CNR in the first image of the time series ($p < 0.001$). It then decreased faster through the heart phases than the control acquisitions. Finally, in the last phases, it remained comparable in the post-injection images to the pre-injection images.

Strain measurements

Good image quality for analysis was obtained in all animals. CS curves for endocardial, mid-wall, and epicardial regions for rat number 2 before and after manganese injection are shown in Fig. 3. Circumferential strain results are summarized in Table 1 and Figs 4 and 5. The circumferential strain values before and after manganese injection are shown to be equivalent by Bland–Altman plots in the endocardial, epicardial, and mid-wall regions (Fig. 5). Significant differences were found between these three regions in both post-manganese and control analysis (Fig. 4).

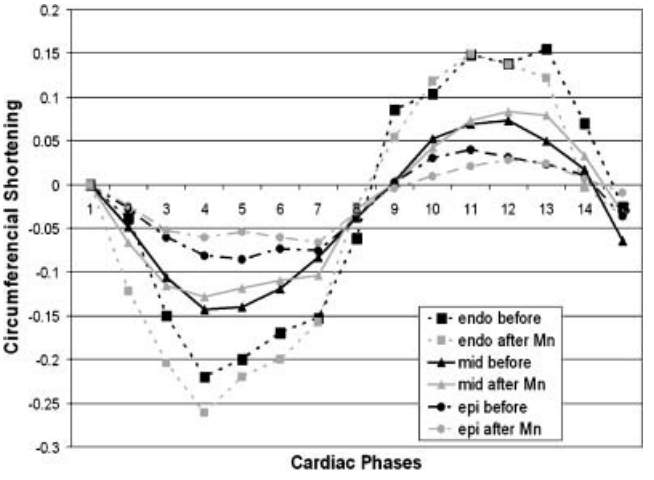

Figure 3. CS curves over the whole myocardium in rat 2 before and after intraperitoneal injection of 17.5 μmol kg^{-1} $MnCl_2$. Temporal resolution is 12 ms. endo, Endocardial; epi, epicardial; mid, mid-wall.

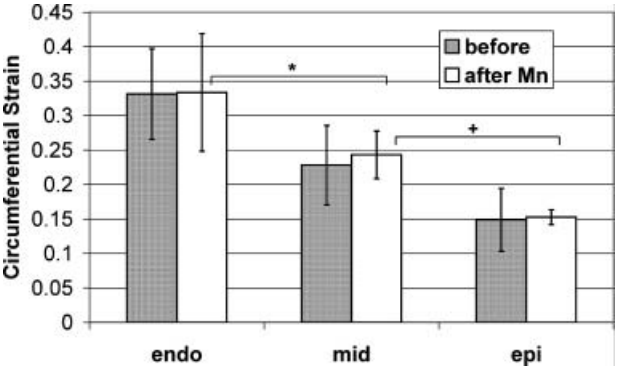

Figure 4. Myocardial circumferential strain in endocardial (endo), mid-wall (mid) and epicardial (epi) regions before and after intraperitoneal injection of 17.5 μmol kg^{-1} $MnCl_2$. $^{+}p < 0.001$; $^{*}p < 0.01$.

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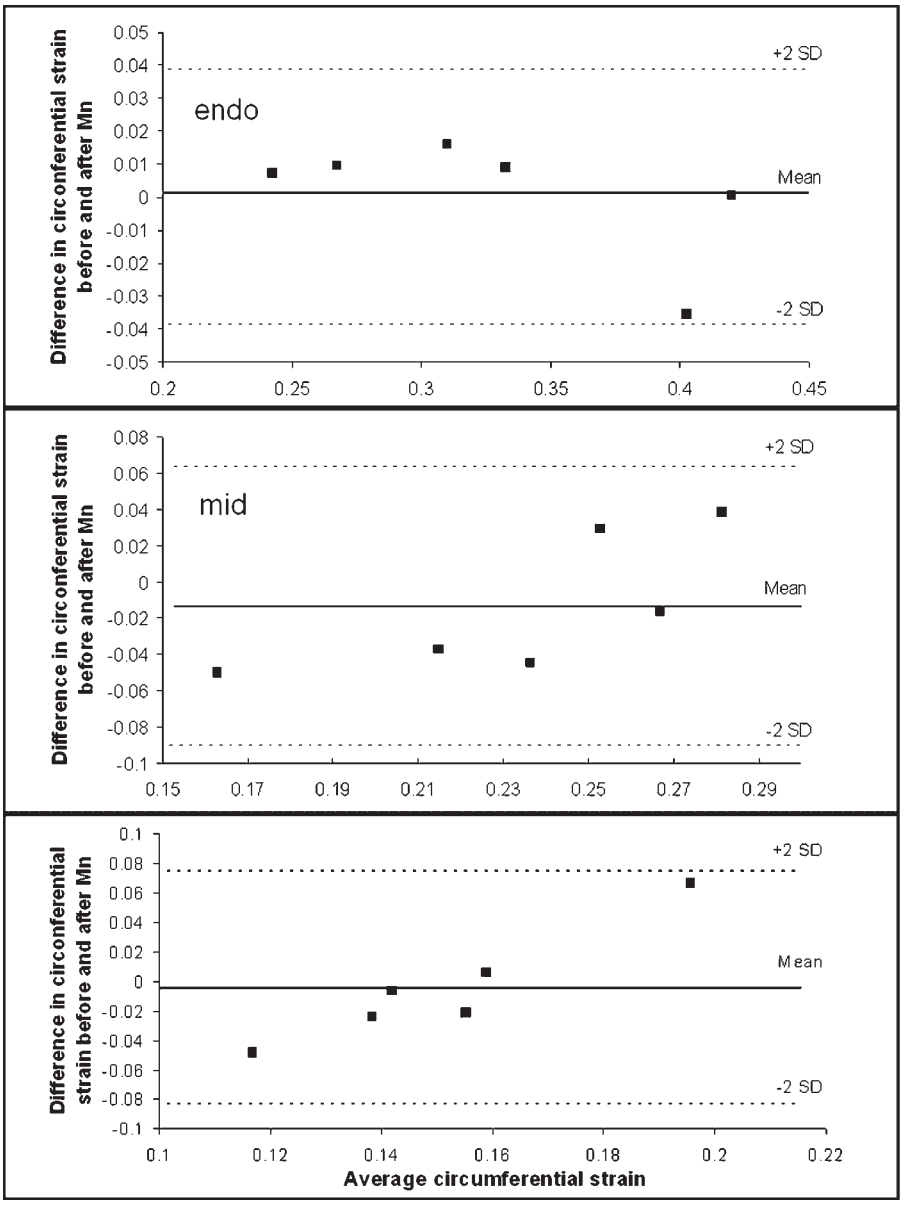

Figure 5. Bland–Altman plot of strain measurements before and after intraperitoneal injection of 17.5 μmol kg^{-1} $MnCl_2$ in endocardial (top), epicardial (bottom) and mid-wall (middle) regions.

DISCUSSION AND CONCLUSION

We successfully performed circumferential strain measurements using C-SPAMM and HARP analysis in normal rats on a 1.5 T clinical scanner before and after injection of manganese. Improvements in image quality could be achieved by using respiratory gating. However, the images in this study were acquired during free breathing for faster acquisition. Despite the difficulties inherent in imaging the heart of small animals, the accuracy of the technique allows subendocardial, mid-wall and subepicardial circumferential strain measurements over the complete cardiac cycle. A gradient in strain (16) from epicardium to endocardium was observed.

The intraperitoneal injection of $MnCl_2$ resulted in no changes in the physiological variables monitored. Even though manganese cardiotoxicity is still a major problem in cardiac MEMRI research (17), our result is in good agreement with other studies (3, 18–20) that used a limited amount of manganese and infusion over a long period. Here, the slow injection rate is achieved by using the intraperitoneal route (21), manganese ions being released slowly from the peritoneum into the vascular system and hence to the heart. Wolf & Baum (22) showed that intravenous administration of manganese promotes

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acute changes in cardiac variables. However, it appears that these findings may be linked to the fast injection rate (10–100 μmol kg^{-1} intravenously over 30 s in dogs and rabbits) (3). Manganese cardiotoxicity appears to be associated with an acute increase in the extracellular rather than the intracellular concentration of the free ion, which inhibits calcium channels (23). As in the use of a chelate complex, slow infusion of $MnCl_2$ may be the answer, as it allows slow release of ions, keeping the extracellular concentration of manganese very low.

The study was kept much shorter than the anaesthesia duration to avoid potential changes in cardiac function due to a progressive wake up.

A significant effect of the manganese injection was observed in all images. CNR in the tagged myocardium clearly increases, as manganese shortens the T_1 of the myocardium. Another repercussion of the relaxing effects of manganese is the faster tag fading. Indeed, even with the C-SPAMM technique, CNR evolution in magnitude tagged images is directly linked to the T_1 value, as extensively described by NessAiver & Prince (24). Indeed, in magnitude C-SPAMM images, image intensity becomes a Rician distribution. Thus the noise distribution is more complicated than in real images, especially in regions with low SNR (background image or tagged areas) where the Rician distribution becomes a Rayleigh distribution. However, NessAiver & Prince show that, in the high- and low-SNR part of a magnitude C-SPAMM image, CNR evolution is still linked to T_1. The FA ramp is designed to compensate for this so-called tag fading.

The final goal of this study was to validate the use of MRI tagging in combination with manganese in our experimental model of CAD. Then, ultimately, in contrast with this feasibility study, we will have heterogeneous repartition of manganese in the myocardium (3,10), and different T_1 values in the myocardium. Adjusting the FA ramp in the present study with the actual shortened T_1 would have given less fading effect and a better quality of post-manganese images. However, as this will not be possible in our future CAD studies, in the present study, we decided to use a fixed T_1 reference value for FA ramp calculation, for acquisitions both before and after manganese injection. Thus, in the post-manganese acquisition, the FA ramp inaccurately compensates for this shortened T_1, leading to a faster decrease in CNR. However, the high heart rate (about 400 bpm) of the rat leads to a very short acquisition time. Thus despite the greater tag fading after manganese injection, CNR remains comparable to that in control images.

Any improvement in tagged image contrast might lead to a reduction in artifacts in circumferential strain maps (25). This gain in CNR leads, here at least, to a qualitative amelioration of the tag analysis in easier contour detection and tracking. We were then able to perform circumferential strain measurements in the three myocardial regions. Analyses were performed on the same slices during the same acquisition, so identical contraction values can be assumed. Measurements were then pooled within a group (control and post-manganese) from several rats. The difficulty of obtaining exactly the same midventricular slice from one rat to another may explain the variability within a group (expressed as the standard deviation). The results of these analyses indicate that manganese injection, in our experimental conditions, does not have any effect on the quality of circumferential strain measurements nor on the myocardial contraction. Future work will need to include a more systematic study with various doses and injection rates to be able to generalize the latter conclusion.

Thus, MR tagging can be used for regional function quantification in combination with quantification of the myocardial area at risk in rat using $MnCl_2$ injection. Our study supports the use of MR tagging as a powerful tool for studying injury after coronary occlusion and follow up of recovery after pharmacological, cellular, or genetic treatment in a small animal research model.

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