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Manganese Enhanced Magnetic Resonance Imaging of Normal and Ischemic Canine Heart

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The ability of $MnCl_2$ to enhance canine myocardium and to delineate ischemic areas is demonstrated. A dose–response curve was measured using T_1 weighted images in 11 dogs. $MnCl_2$ (36, 113, 360, and 3600 μmol) was infused over a period of 3 min. Signal intensity increased linearly with $MnCl_2$ dose. At 113 μmol (~10 μmol/kg) the steady-state increase in intensity averaged 212 ± 34%. No significant physiologic effects due to the infused $MnCl_2$ were detected except at the highest dose where there was a cardiac depressive effect. Ischemia was induced by occluding the left anterior descending coronary artery in 5 dogs. At an infused dose of 113 μmol, $MnCl_2$ clearly demarcated the ischemic zone during coronary occlusion. Contrast enhancement in the ischemic zone was less than 30% compared with normal tissue ($P < 0.03$). In conclusion, the intracellular contrast agent $MnCl_2$ enhances the canine heart and shows promise in detecting ischemia at doses that do not cause adverse cardiac effects. Magn Reson Med 54:196–200, 2005. Published 2005 Wiley-Liss, Inc.†

Key words: manganese; myocardial perfusion; myocardial ischemia; myocardial viability; safety

Intracellular calcium is a central regulator of cardiac contractility but little is known about how calcium dynamics are affected in the various regions surrounding an ischemic zone. Moreover, it is becoming increasingly apparent that alterations in myocyte Ca^{2+} regulation may be critically important for both the mechanical dysfunction and the arrhythmogenesis associated with congestive heart failure (1).

Despite the importance of calcium regulation in the heart, there are currently no established radiologic imaging techniques for visualizing Ca^{2+} channel activity. Recent advances have improved the feasibility of studying ischemic heart disease with MRI (2). Thus, it would be very useful if MRI could be sensitized to calcium dynamics. $MnSO_4$ was the first agent suggested for use as an MRI contrast agent by Lauterbur and colleagues in his seminal paper describing MRI (3). Recently it has been demonstrated in the rodent heart and brain that the influx of manganese ions (Mn^{2+}) can be measured with MRI and that the rate and amount of signal enhancement is related to calcium influx (4,5,6,7). Work in the rodent heart has demonstrated the potential of $MnCl_2$ and MnDPDP for obtaining information with respect to cell viability during ischemia (6,8,9). Therefore, Mn^{2+} has potential both as a monitor calcium influx and as an intracellular viability contrast agent. For example, Mn^{2+} might be suitable for protocols comparable to nuclear medicine studies, where imaging is performed after stress. Indeed, ^{52}Mn has been used as a positron emission tomography (PET) tracer (10,11) to assess myocardial ischemia. Chauncey et al. demonstrated a reduced signal enhancement of infarcted myocardial tissue compared to normal myocardium (10) and Atkins et al. showed a correlation between ^{52}Mn distribution and microsphere determined blood flow (11). Thus, both MRI (6,7,8) and PET (9,10) have demonstrated the potential of Mn^{2+} as both a cell viability agent and a molecular imaging agent for monitoring calcium influx.

A major disadvantage of manganese enhanced cardiac MRI is the toxicity of Mn^{2+} (12). There is also little work applying manganese enhanced MRI to large animal models (9). Therefore, the purpose of this study was to determine whether MRI could detect significant myocardial enhancement at doses that did not cause adverse physiologic consequences in a dog model. A myocardial dose–response curve was generated and the ability to detect a region of myocardial ischemia was demonstrated in vivo.

MATERIALS AND METHODS

Animal Preparation

Manganese enhanced MRI experiments were performed in beagles ($n = 11$; BW 10.8 ± 1.6 kg) as approved by the Animal Care and Use Committee of the National Heart, Lung and Blood Institute at the National Institutes of Health in Bethesda, Maryland. Dosing studies were performed using data from 10 of the 11 animals and ischemia experiments were performed on 5 of the 11 animals. All protocols conducted for this study entailed acute, nonsurvival procedures performed under anesthetized conditions. Initially, the animals were given an intramuscular (i.m.) injection of acepromazine (0.1 mL) for placement of a venous catheter in each of the cephalic veins for drug infusion and maintenance fluids. Initial induction of anesthesia was performed with sodium pentothal (2.5% solution, 1 mL/5 lb) given i.v. Anesthesia was maintained with isoflurane 1–2% throughout the remainder of the experiment. A femoral arterial line was placed percutaneously for blood gas measurements and blood pressure

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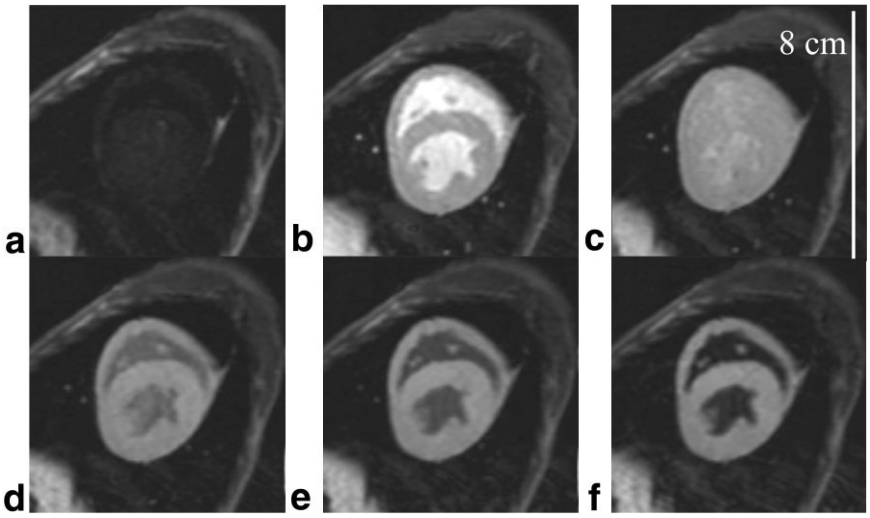

FIG. 1. Examples of short-axis inversion recovery images from the heart during the Mn^{2+} infusion time course. (**a**) Pre-Mn^{2+} infusion. (**b**) During Mn^{2+} infusion where the blood pool shows the maximum signal intensity enhancement. (**c**), (**d**) Post-Mn^{2+} infusion where the blood pool Mn^{2+} is washing out. (**e**), (**f**) Post-Mn^{2+} infusion (blood pool washed out) with residual myocardial enhancement.

monitoring. Blood gases were monitored periodically throughout the experiment to adjust the ventilator. Intravenous fluids, primarily normal saline, were used to maintain vascular volume and blood pressure.

A midline thoracotomy and placement of a hydraulic occluder around the left anterior descending coronary artery was performed in five animals. For ischemia experiments, the occluder was inflated after obtaining baseline images. The $MnCl_2$ infusion was started 1 min later and continued for a total of 3 min. The coronary artery was reperfused after a total occlusion time of 15 min. $MnCl_2$ was infused at a rate of 9.0 mL/min for 3 min using 4.0 mM $MnCl_2$ (a total amount of 113 μmol).

Cardiac MRI

Cardiac imaging was performed on a 1.5-T CV/i magnet (General Electric, Milwaukee, WI, USA) using a four-element phased array knee coil. During the imaging experiment, the respirator was suspended for 20–30 s to allow imaging during a breath-hold. In some animals high frequency ventilation was used when available to avoid the need for breath holds. This was done for optimizing Mn^{2+} infusion protocols. An inversion recovery pulse sequence with a GRE readout was used for measuring T_1 with inversion times (TI) of 66, 200, 500, 750, 1000, 1250, 1500, 1750, 2000, 2250, and 2500 ms. The TI to null the myocardium (TI_{null}) was estimated by fitting the data. For serial imaging, a TI longer than TI_{null} was selected in order to simplify data acquisition from magnitude images and to preserve measurement dynamic range.

The typical gradient echo imaging parameters were: matrix dimensions 256 × 64; inversion time 650–750 ms; inversion pulse every 10 cardiac cycles; 16 lines of *k*-space per inversion pulse acquired with a repetition time of 8.5 ms and an echo time of 3.8 ms; readout flip angle of 20°; slice thickness, 8.0 mm; field of view 24 × 12 cm; bandwidth 31.25 kHz. Images collected were analyzed with custom software using IDL (Research Systems, Inc., Boulder, CO, USA). Regions of interest (ROI) were selected in normal myocardium (typically the inferior septum) and ischemic myocardium (typically the anterior wall). The ischemic region was visually determined based on anatomic location distal to the occluder.

$MnCl_2$ Administration

The first dose tested for $MnCl_2$ administration (3600 μmol) was estimated using previous data from mice (4). At this $MnCl_2$ dose, which caused no adverse physiologic effects in mice, the blood pressure of the dog dropped and a large cardiac depressive effect was observed ($n = 1$, data not shown). Subsequently, all doses in the dogs were at-least 10-fold lower than the murine dose. In order to vary the $MnCl_2$ dose, both the amount infused and the concentration of $MnCl_2$ were altered. The total amounts infused were: 3.0 mL/min for 3 min of 4.0 mM $MnCl_2$ (36 μmol; $n = 1$); 9.0 mL/min for 3 min of 4.0 mM $MnCl_2$ (113 μmol; $n = 5$); 9.0 mL/min for 3 min of 8.0 mM $MnCl_2$ (216 μmol; $n = 3$); and 3 mL/min for 3 min of 40 mM Mn^{2+} solution (360 μmol, $n = 1$).

Statistics

Unless otherwise stated, the differences between different groups were assessed using ANOVA with the Scheffé test. A paired *t* test was used to compare signal intensity before and after $MnCl_2$ infusion. Values reported are means ± SD. Contrast enhancement was defined as signal intensity minus baseline signal intensity.

RESULTS

Figure 1 shows images depicting myocardial enhancement at a dose of 113 μmol of $MnCl_2$. At a TI_{null} of 650 ms, the myocardium appears uniformly dark prior to $MnCl_2$ infusion (Fig. 1a). Normal myocardium enhances uniformly both during and after $MnCl_2$ infusion (Fig. 1b–f). Figure 2 shows that the myocardial signal-dose response was linear over the range studied (36–360 μmol $MnCl_2$). Measurements were made after myocardial enhancement reached steady-state. There were no effects on blood pressure or heart rate at any of these doses of Mn^{2+}.

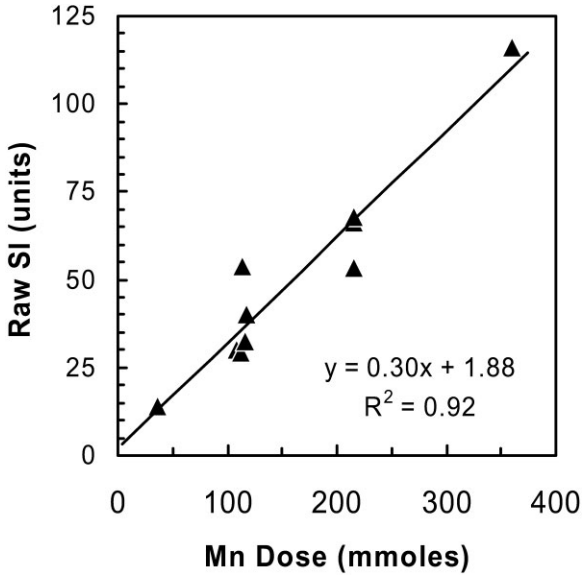

FIG. 2. Relationship between manganese dose and myocardial enhancement. The *X*-axis shows the total dose of Mn^{2+}. The *Y*-axis shows the steady-state T_1-weighted myocardial signal intensity.

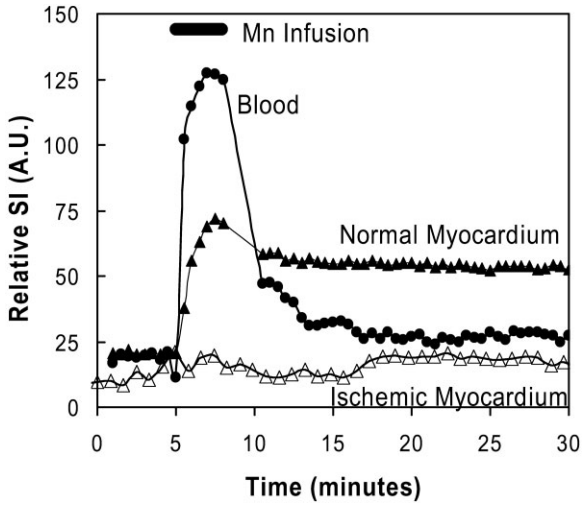

FIG. 4. The time course of enhancement with manganese for ischemic and normal myocardium. The horizontal bar at the top of the diagram indicates the timing of manganese infusion. The blood in the left ventricular cavity enhances rapidly but also clears rapidly after the infusion (circles). Normal myocardium enhances to a lesser degree but shows significant retention of manganese 30 min later (dark triangles). Ischemic myocardium shows relatively little enhancement throughout the experiment (open triangles). A.U. = arbitrary units.

To determine whether Mn^{2+} enhanced MRI can detect the likely ischemic regions in the dog heart, $MnCl_2$ infusion was performed during a coronary artery occlusion to create an ischemic zone. Figure 3 shows images 6 min after the onset of occlusion and 5 min after beginning the $MnCl_2$ infusion. Blood enhancement was maximal at that time. The occluded zone can be clearly observed as an area of lower myocardial enhancement compared with normal myocardium.

Figure 4 shows the time course of signal change from a normal region (filled triangle) and a likely ischemic region of the heart (open triangle) during $MnCl_2$ infusion. The steady-state signal enhancement in the likely ischemic zone was markedly lower than for normal myocardium. For five animals studied during ischemia, myocardial signal intensity from an unaffected region of the heart increased from 16.5 ± 14.6 to 54.9 ± 20.5 at 40–43 min after beginning $MnCl_2$ infusion. Average values are summarized in Table 1. The likely ischemic area had a significantly lower signal intensity compared with the normal myocardium ($P = 0.016$). Contrast enhancement in the ischemic zone was 26% of normal myocardium during the occlusion while the $MnCl_2$ was being infused and 28% after reperfusion (Fig. 5).

DISCUSSION

The majority of MRI studies using Mn^{2+} have been performed in rodents (8,13,14) with one report on dogs over 20 years ago (9) and one recent report using a new manganese formulation in pigs (15). There is renewed interest in Mn^{2+} as an MRI contrast agent due to its unique potential to monitor a range of biologic processes (4–6,8). The present work extends the use of manganese enhanced MRI to a canine model to determine the myocardial signal-dose response curve and the ability to visualize ischemia. The results indicate that $MnCl_2$ can be used safely in the dog to enhance myocardium. There was a linear response of myocardial signal enhancement versus the total dose of Mn^{2+} infused. The preferred protocol was to infuse at 9 mL/min for 3 min for a total infusion concentration of 113 μmol (10 μmol/kg) because it yielded significant myocardial enhancement (275% above pre-Mn^{2+} infusion) and was 30 times lower than the dose that showed acute cardiac depressive effects. At this dose, ischemic myocardium was readily visualized.

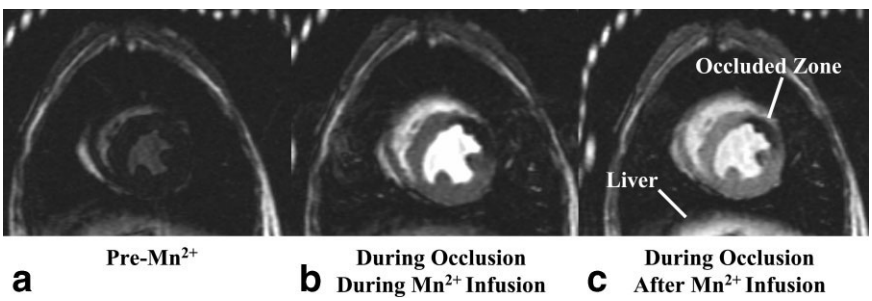

FIG. 3. Sample short-axis inversion recovery images from the heart during ischemia. (**a**) Pre-$MnCl_2$ infusion. (**b**) During both $MnCl_2$ infusion and coronary artery occlusion. (**c**) After $MnCl_2$ infusion but still during coronary artery occlusion. The ischemic zone was clearly observed as a region with lower intensity compared with unaffected myocardium. A.U. = arbitrary units.

Table 1
Manganese Enhancement of Normal and Ischemic Myocardium (n = 5, 113 μmol Infusion Dose)

Experimental period	Ischemic region signal intensity	Normal region signal intensity	Ischemic/normal signal intensity ratio
Preocclusion	13.8 ± 8.9	16.5 ± 14.6	0.98 ± 0.29
During occlusion, During Mn^{2+} infusion	29.5 ± 8.9	77.5 ± 31.6	0.44 ± 0.28*
During occlusion, After Mn2 + infusion	24.7 ± 9.5	54.9 ± 20.5	0.50 ± 0.27*

Note. Values are expressed in means ± SD. *$P<0.05$, the signal enhancement of ischemic myocardium was lower than normal myocardium (two-tailed paired t test).

Myocardial enhancement in the dog was similar to that shown in mice (4) but at a much lower dose. A dominant mechanism for Mn^{2+} accumulation in the heart is flux through voltage gated calcium channels (16). In vivo evidence for this comes from the fact that calcium channel blockers inhibit Mn^{2+} induced MRI contrast enhancement and positive inotropes, which increase calcium influx, increase Mn^{2+} induced MRI contrast (4). Therefore, the similar enhancements at lower Mn^{2+} doses observed in the dog may be due to the fact that larger hearts rely on a larger influx of extracellular Ca^{2+} to trigger myocardial contraction (17). This may also explain why the mouse heart was not physiologically affected by higher doses of $MnCl_2$ that caused cardiovascular depressive effects in the dog.

It is generally accepted that the enhancement in both the heart and the brain by Mn^{2+} is due to uptake into the intracellular space (6,8). Evidence for this comes from the fact that calcium channel blockers inhibit uptake (4,16) and that the volume of distribution for Mn^{2+} is larger than for extracellular agents (8). In addition, tissue enhancement lasts long after Mn^{2+} has cleared from the blood. This is clearly shown for the canine model in Figs. 1 and 4 where tissue enhancement remains in steady state long after blood enhancement returns to pre-Mn^{2+} levels. In the rodent heart and brain, Mn^{2+} enhancement can last for many days. Indeed, due to the long lasting enhancement after Mn^{2+} accumulation, it has been suggested that Mn^{2+} can be given outside of a MRI system and the subject imaged later (7,15). This opens the possibility of delivering Mn^{2+} during a stress test using standard equipment and imaging the extent and area of accumulation at a later time.

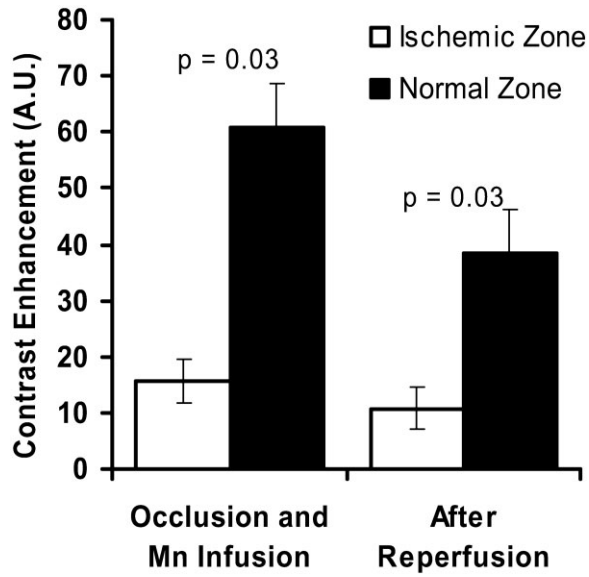

FIG. 5. Contrast enhancement was significantly lower in the ischemic zone compared with normal myocardium both during the infusion and after reperfusion. A.U. = arbitrary units.

An important issue for interpreting the enhancement detected during infusion of $MnCl_2$ is defining what limits uptake of Mn^{2+} under different conditions. In the heart, either delivery or uptake can dominate the observed amount of enhancement. Previous work in the rodent heart indicates that the rate of myocardial uptake limits accumulation in the normally perfused heart (4,18). This conclusion is based on the fact that calcium channel blockers inhibit uptake and that the dose response saturates at high levels of Mn^{2+}. In the dog heart, the dose-dependent experiments shown in Fig. 2 reveal a linear response of signal enhancement versus the total Mn^{2+} infused. This makes it difficult to determine whether delivery or uptake limits the observed enhancement from the current experiments. The fact that enhancement is proportional to dose indicates that delivery may be limiting; however, it is possible that the concentrations of Mn^{2+} used are below the K_m for the uptake process, which would also lead to a linear rate of enhancement with concentration. The fact that the uptake is slow compared to the rate of recirculation argues that uptake may be limiting. It will be interesting in the future to see whether pharmacological manipulation of calcium influx and perfusion in independent manners alters uptake in the dog heart.

Among current cardiac techniques, cine MRI, T_2-weighted MRI, first-pass perfusion, and delayed contrast-enhanced T_1 weighted MRI are most commonly used to assess myocardial ischemia and viability. It is known that the size of the abnormal signal area on Gd-enhanced T_1-weighted MRI correlates well with infarct area (19). However, the size of the nonperfused area on first-pass perfusion images is often smaller than the final infarct area. Therefore, there is a need to obtain other measures of cell viability.

Ca^{2+} homeostasis changes due to ischemia and reperfusion. Since Mn^{2+} influx can be related to calcium influx, Mn^{2+} enhanced MRI may detect physiologic differences among normal, stunned, and infarcted myocardium. As a first step in this direction, we show that a likely ischemic zone can be detected during $MnCl_2$ infusion in the dog heart (Fig. 4). Here we demonstrate enhancement in the ischemic zone that was only 26–28% of enhancement measured in the normally perfused myocardium. Detailed

comparison to pathologic specimens was not performed; therefore, it is not clear whether the regions of hypoenhancement post-Mn^{2+} were from ischemic, infarcted, or noncontractile but viable myocardium. Previous work in rodent heart indicates that Mn^{2+} based contrast agents can delineate ischemic regions of myocardium (8). In the case of low perfusion, it is expected that delivery of Mn^{2+} limits enhancement. However, alterations in the rate of Mn^{2+} uptake in the ischemic region may also contribute to the hypoenhancement detected. It will be important to quantify the relative limitations of uptake under varying conditions of ischemia in the future.

A limitation of manganese enhanced MRI is the potential toxicity. In this study, the doses we used did not cause acute effects with respect to heart rate and blood pressure. The dose used in the current study was approximately 10 μmol/kg, which is within a factor of 2 of the FDA approved dose (5 μmol/kg) for MnDPDP (Teslascan) The U.S. Phase III clinical trial on MnDPDP has recently been published as a hepatic MRI agent without many adverse effects (20). Encouragingly, MnDPDP has also been used for imaging of human myocardium (21). At 5, 10, and 15 μmol/kg of MnDPDP by 30 min infusion, close to a 45% rise in R_1 with an imaging window of 2–4 h was observed. The fact that Mn^{2+} enhances excitable cells within MR images and that MnDPDP releases Mn^{2+} has caused a re-evaluation of MnDPDP's mechanisms of cardiac enhancement (6,14,18,22). Therefore, MnDPDP enhances the heart and this agent might be promising in MRI assessments of myocardial function and viability (6). The dose of $MnCl_2$ used is much larger than the parenteral nutrition guideline (0.5 mg/day for 70 kg adult; 0.137 μmol/kg); however, the large enhancements obtained in the present study indicate that it should be possible to significantly decrease the dose used. In conclusion, these studies indicate that there is potential for useful and safe ways of delivering Mn^{2+} for enhancing MRI of the heart during a variety of pathophysiological conditions, certainly in animal models and possibly in humans

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REFERENCES

1. Pogwizd SM, Schlotthauer K, Li L, Yuan W, Bers DM. Arrhythmogenesis and contractile dysfunction in heart failure: Roles of sodium-calcium exchange, inward rectifier potassium current, and residual beta-adrenergic responsiveness. Circ Res 2001;88:1159–1167.
2. Saeed M. New concepts in characterization of ischemically injured myocardium by MRI. Exp Biol Med (Maywood) 2001;226:367–376.
3. Mendonca-Dias MH, Gaggelli E, Lauterbur PC. Paramagnetic contrast agents in nuclear magnetic resonance medical imaging. Seminin Nucl Med 1983;13:364–376.
4. Hu TC, Pautler RG, MacGowan GA, Koretsky AP. Manganese-enhanced MRI of mouse heart during changes in inotropy. Magn Reson Med 2001;46:884–890.
5. Pautler RG, Silva AC, Koretsky AP. In vivo neuronal tract tracing using manganese-enhanced magnetic resonance imaging. Magn Reson Med 1998;40:740–748.
6. Brurok H, Skoglund T, Berg K, Skarra S, Karlsson JO, Jynge P. Myocardial manganese elevation and proton relaxivity enhancement with manganese dipyridoxyl diphosphate. Ex vivo assessments in normally perfused and ischemic guinea pig hearts. NMR Biomed 1999;12:364–372.
7. Lin YJ, Koretsky AP. Manganese ion enhances T1-weighted MRI during brain activation: an approach to direct imaging of brain function. Magn Reson Med 1997;38:378–388.
8. Saeed M, Higgins CB, Geschwind JF, Wendland MF. T1-relaxation kinetics of extracellular, intracellular and intravascular MR contrast agents in normal and acutely reperfused infarcted myocardium using echo-planar MR imaging. Eur Radiol 2000;10:310–318.
9. Brady TJ, Goldman MR, Pykett IL, Buonanno FS, Kistler JP, Newhouse JH, Burt CT, Hinshaw WS, Pohost GM. Proton nuclear magnetic resonance imaging of regionally ischemic canine hearts: effect of paramagnetic proton signal enhancement. Radiology 1982;144:343–347.
10. Chauncey DM, Jr., Schelbert HR, Halpern SE, Delano F, McKegney ML, Ashburn WL, Hagan PL. Tissue distribution studies with radioactive manganese: a potential agent for myocardial imaging. J Nucl Med 1977;18:933–936.
11. Atkins HL, Som P, Fairchild RG, Hui J, Schachner E, Goldman A, Ku T. Myocardial positron tomography with manganese-52m. Radiology 1979;133:769–774.
12. Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. Neurotoxicology 1999;20:227–238.
13. Ni Y, Petre C, Bosmans H, Miao Y, Grant D, Baert AL, Marchal G. Comparison of manganese biodistribution and MR contrast enhancement in rats after intravenous injection of MnDPDP and MnCl2. Acta Radiol 1997;38:700–707.
14. Brurok H, Schjott J, Berg K, Karlsson JO, Jynge P. Effects of MnDPDP, DPDP–, and MnCl2 on cardiac energy metabolism and manganese accumulation. An experimental study in the isolated perfused rat heart Invest Radiol 1997;32:205–211.
15. Storey P, Danias PG, Post M, Li W, Seoane PR, Harnish PP, Edelman RR, Prasad PV. Preliminary evaluation of EVP 1001–1: a new cardiac-specific magnetic resonance contrast agent with kinetics suitable for steady-state imaging of the ischemic heart. Invest Radiol 2003;38:642–652.
16. Narita K, Kawasaki F, Kita H. Mn and Mg influxes through Ca channels of motor nerve terminals are prevented by verapamil in frogs. Brain Res 1990;510:289–295.
17. Langer GA. Calcium and the heart. New York: Raven Press; 1990. p199–268.
18. Brurok H, Schjott J, Berg K, Karlsson JO, Jynge P, Schojtt J. Effects of manganese dipyridoxyl diphosphate, dipyridoxyl diphosphate–, and manganese chloride on cardiac function. An experimental study in the Langendorff perfused rat heart. Invest Radiol 1995;30:159–167.
19. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.
20. Federle MP, Chezmar JL, Rubin DL, Weinreb JC, Freeny PC, Seminelka RC, Brown JJ, Borello JA, Lee JK, Mattrey R, Dachman AH, Saini S, Harmon B, Fenstermacher M, Pelsang RE, Harms SE, Mitchell DG, Halford HH, Anderson MW, Johnson CD, Francis IR, Bova JG, Kenney PJ, Klippenstein DL, Foster GS, Turner DA. Safety and efficacy of mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: results of the U.S. multicenter phase III clinical trials (safety). J Magn Reson Imaging 2000;12:186–197.
21. Skjold A, Vangberg T, Kristoffersen A, Haraldseth O, Larsson HW, Jynge P. Preliminary experience with intracellular manganese ions as contrast agents in the human myocardium. In: Proceedings of the 12th Annual Meeting of ISMRM, Kyoto, Japan, 2004. Vol 11, p 1722.
22. Jynge P, Brurok H, Asplund A, Towart R, Refsum H, Karlsson JO. Cardiovascular safety of MnDPDP and MnCl2. Acta Radiol 1997;38:740–749.