Improved Cardiac Manganese-Enhanced MRI (MEMRI) with T1 Mapping in Rodent

T. C-C. Hu[1,2], K-H. Chuang[2], N. Yanasak[1], and A. P. Koretsky[2]

[1]Department of Radiology, Medical College of Georgia, Augusta, GA, United States, [2]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, United States

Introduction

Manganese ion (Mn^{2+}) is an intracellular contrast agent that enters viable myocardial cells via voltage gated calcium channels (1). Along with its T_1 shortening effect and relatively long half-life in cells, it becomes a very useful molecular contrast agent to study calcium influx. It has been shown that the signal intensity enhancement due to Mn^{2+} can be increased or decreased depending on calcium homeostasis by dobutamine (calcium channel enhancer) or diltiazem (calcium channel blocker), respectively (2). One major concern for using Mn^{2+} is getting quantitative information over a range of concentrations. Therefore, in this study, a T_1 mapping method has been implemented for cardiac manganese-enhanced MRI (MEMRI) to increase the sensitivity and enable the quantitative estimate of a range of concentrations.

Methods

All animal work was performed following the guidelines of the Animal Care and Use Committee and the Animal Health and Care Section of the National Institute of Neurological Disorders and Stroke, National Institutes of Health (Bethesda, MD, USA). Adult male Sprague-Dawley rats (body weights 147-369 g) were used in this study. The animal was initially anesthetized by 5% isoflurane (in a 1:1:1 air:nitrogen:oxygen mixture), positioned prone upon animal cradle, and maintained at 1.5-2.5% isoflurane during the MRI session. During the anesthesia procedure, a tail vein line for manganese infusion was introduced. Manganese concentrations were 0.0-4.0 nmoles/min/g BW with the infusion time of ~20 minutes.

Images were acquired on a horizontal 7.0 T BioSpec MRI spectrometer (Bruker Instruments, Billerica, MA) equipped with a 12.0-cm micro imaging gradient insert (100 gauss/cm). Animal setup procedure followed those previously described (2). A standard volume coil was used for transmit and an active-decoupled surface coil at ^1H frequency for receive (300 MHz; Bruker Instruments, Billerica, MA). ECG and respiratory signals were monitored by a SA Instruments' physiological monitoring system (SA Instruments, Inc., Stony Brook, NY) and the ECG signal was used to gate the MRI Fast Low Angle SHot (FLASH) sequence. Short-axis heart images were acquired. Both pre-Mn^{2+} and post-Mn^{2+} T_1 maps were acquired with an ECG-gated, flow-compensated Lock-Locker MRI pulse sequence as previously described (3).

The T_1 of each pixel was calculated in two steps using a custom-written C^{++} program (3). First, the signal recovery of each pixel was fitted by the Levenburg-Marquardt non-linear three-parameter curve-fitting algorithm. Then, the obtained parameters were substituted to solve for the actual T_1. Region-of-interest (ROI) analysis was performed on 2D Look-Locker data using AMIDE (4) for the average regional T_1 value. The ROI tools were used to select the areas of interest (septum, left ventricular free wall, and chest wall). Absolute manganese content for left-ventricular myocardium (sectioned according to in-vivo MRI location) and blood samples were measured by inductively coupled plasma-mass spectrometry (ICP-MS) analysis (West Coast Analytical Service, Santa Fe Springs, California). These values are then correlated to the in-vivo R_1 values.

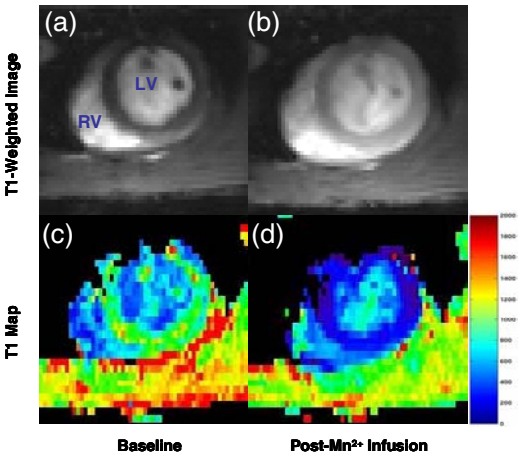

Figure 1. Examples of short-axis rodent heart images. (a) T_1-weighted pre-Mn^{2+} infusion image; (b) T_1-weighted post-Mn^{2+} infusion image; (c) pre-Mn^{2+} T_1 map; (d) post-Mn^{2+} T_1 map.

Results

ECG gated cardiac MRI provided high quality images for left-ventricular function determination as shown in Figure 1 (a) and (b). The infusion of Mn^{2+} in rodent hearts clearly showed a large change in T_1 values even with the relatively low amounts of Mn^{2+} infused (Figure 1 (c), (d)). The effect of altering the amount of infused Mn^{2+} on left ventricular wall relaxivity change, ΔR_1, is shown in Figure 2. Mn^{2+} infusion leads to a biphasic relaxivity changes with a smaller rate of change from 0-165 nmoles/gm BW and a larger rate of change in the range 165-250 nmoles/gm BW. For this data the T_1 maps were taken approximately 10 minutes post-Mn^{2+} infusion. Interestingly the myocardial tissue R_1 was linear with respect to the total Mn content in heart tissue as determined by ICP-MS (Figure 3). These results indicate that the biphasic relation found between cardiac R_1 and infused Mn^{2+} is due to a non-linear relation between infused Mn^{2+} and blood concentrations of Mn^{2+}. It was confirmed by direct measurement of the blood-pool Mn content that the blood level of Mn^{2+} was non-linear with respect to the total Mn^{2+} infused (data not shown). These results indicate that T_1 mapping of the myocardium gives a good measure of Mn^{2+} uptake into heart and should enable quantification in a number of patho-physiological states.

Conclusions

This study demonstrates that T_1 mapping of cardiac Manganese-Enhanced MRI can derive quantitative information over a range of Mn concentrations. One interesting observation is the non-linear relationship between the total Mn^{2+} infused and LV wall ΔR_1. Myocardium and blood-pool R_1 was linear with Mn concentration. However blood level of Mn^{2+} was not linear with the total Mn^{2+} infused, most likely due to liver or kidney clearance.

References

1. Narita K, Kawasaki F, Kita H. Brain Res 1990;510:289-295.
2. Hu TC-C, Pautler RG, MacGowan GA, Koretsky AP. Magn. Reson. Med. 2001;46(5):884-890.
3. Chuang KH, Koretsky A. Magn. Reson. Med. 2006; 55(3):604-11.
4. Loening A, Gambhir S. Mol. Imaging 2003; 2:131-137.

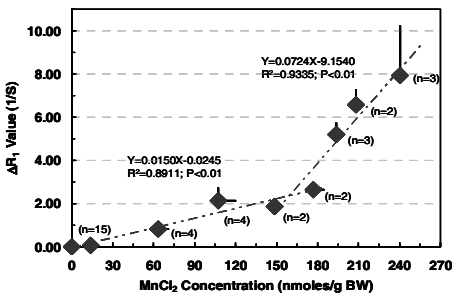

Figure 2. Effect of altering the concentration of infused Mn^{2+} on relaxivity of left ventricular wall. The x-axis shows the total concentration of onset infused Mn^{2+} normalized to rat BW. The y-axis shows the difference of relaxivity pre- and post-infusion (error bars = 1 SD)

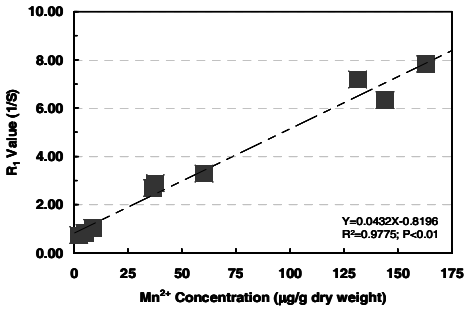

Figure 3. Effect of total manganese concentration determined by ICP-MS on relaxivity of LV wall. The x-axis shows the total concentration of Mn^{2+} normalized to gram of myocardium dry weight. The y-axis shows the relaxivity post-infusion.