# In-Vivo Manganese Enhanced Dynamic Magnetic Resonance Imaging (MEDMRI) to Evaluate Progression of Diabetes in Rodent Pancreas

**M. Haque[1,2], X. Fan[1], E. J. Markiewicz[1], L. Leoni[1], and B. B. Roman[1]**

[1]Radiology, The University of Chicago, Chicago, IL, United States, [2]Radiology, North Shore University Healthcare, Evanston, IL, United States

**Introduction:** Diabetes is a global healthcare issue and the lack of understanding of the pathophysiological process involved in the progression of diabetes is an obstacle to early diagnosis and treatment. Diabetes significantly increases the risk of developing irreversible microvascular or macrovascular disease such as retinopathy, neuropathy, and arteriosclerosis. There have been several applications of MRI techniques towards detection and monitoring the diabetic progress including where T-lymphocyte tracking (1) and beta cell function via manganese (Mn) enhanced MRI (MEMRI) (2,3). Dynamic contrast enhanced MRI (DCEMRI) has proven to be an important tool for early cancer detection due to it's sensitivity to vascular structures by using gadolinium (Gd) as a blood pool agent. Unlike bound Gd, free Mn can enter excitable cells during activation. Here we present a unique combination of MEMRI and DCE MRI called manganese enhanced dynamic magnetic resonance imaging (MEDMRI) to investigate organ perfusion and function.

**Material and Methods:** All surgical procedures were performed in compliance with the University of Chicago animal care guidelines. Pancreata of five healthy male FVB mice (~24 g) were imaged and then treated with a single IP injection of STZ (Sigma Aldrich, St. Louis, MO) 180mg/kg, to induce diabetes. Serum glucose levels were monitored and animals were re-imaged 10 days later. MR Images were obtained on 9.4 T (Bruker-Biospin, Billerica, MA) using 35mm body coil. A bolus injection of $MnCl_2$ (10.0 nmol/g BW) was delivered through a tail vein catheter. A **M**agnetization **P**repared **RA**pid **G**radient **E**cho (MPRAGE) pulse sequence (TR/TE = 8.7/2.4 ms, segment duration = 831 ms, matrix size = 96×96×8, temporal resolution = 50 sec, NEX = 2) was used to acquire 3 pre- and 42 post-contrast dynamic Mn enhanced images. The Mn signal enhancement curves as function of time were calculated as: $\Delta S = (S_n - S_0)/S_0$, where $S_0$ and $S_n$ is the average signal intensity over the region of interesting (ROI) in the pre-contrast and at the $n^{th}$ post contrast time point, respectively. The enhancement curves were then fitted by the following empirical mathematical model (EMM) (4) to quantify the contrast uptake and washout: $\Delta S(t) = A \cdot \left(1 - e^{-\alpha t}\right) \cdot e^{-\beta t}$, where ***A*** is the upper limit of the signal intensity, $\alpha(min^{-1})$ is the rate of signal increase, and $\beta(min^{-1})$ is the rate of the signal decrease during washout. For each mouse, multiple ROIs with pixels size of 5×5 were selected from the splenic region of the pancreas.

**Results and Discussion:** Typical Mn signal enhanced curves for control (circle) and diabetic (triangle) pancreas fitted with the EMM is shown in figure 1. The Mn enhancement was not uniform over the tail region of the pancreas although the EMM model provides a good fit of the Mn enhanced MRI data. It can be seen that the normal pancreas has persistent enhancement while the diabetic pancreas has increased washout. The average results for 48 total ROIs for normal (23 ROIs) and diabetic (25 ROIs) pancreata are given in Table 1. These data support the findings in Fig. 1 that the rate of washout is greater in the diabetic pancreas. There was no significant difference in the maximum signal intensity parameter ***A*** and uptake rate α between normal and diabetic mice which is possibly due to the low temporal resolution. Due to motion and noise, the mathematical model requires refinement to fit the enhancement curves to analyze the data further. The error associated with the goodness of fit parameter ($R^2$) can be contributed to due to the noise and motion of the data. The increased washout rate is likely due to the loss of pancreatic ß-cells and therefore an indication of decreased endocrine function. This technique and the data presented have demonstrated promise in providing unique access to the dynamic functional changes associated with diabetes as it links both organ perfusion and cell function. It is also hoped that this imaging technique will help to develop novel diabetic therapies.

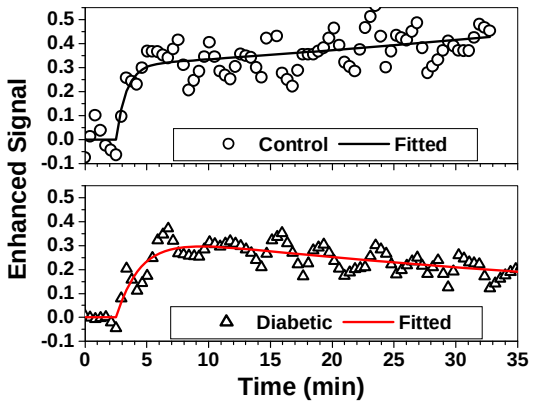


**Figure1.** Kinetic curve of Mn uptake and washout in control (top) and diabetic (bottom) mice. Signal intensity was obtained by selecting multiple slices and ROIs in the tail region of the pancreas

| Table 1 | A | α | β | $R^2$ |
|---|---|---|---|---|
| **Normal** | 0.53±0.31 | 2.11±1.59 | -0.0004±0.011 | 0.60±0.17 |
| **Diabetic** | 0.63±0.32 | 2.14±1.68 | 0.019±0.017 | 0.59±0.14 |
| **p-value** | 0.27 | 0.95 | $10^{-4}$ | 0.73 |

**References:** [1] Medarova et al., MRM 2008. [2] Gimi et al., Cell Transplantation 2006. [3] Haque et al., 6th Molecular Imaging Conference 2007. [4] Fan et al., MRM 2004.