Model for manganese dynamic contrast-enhanced MRI of passive and glucose-stimulated active pancreatic β-cell function

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Introduction: Alteration of the pancreatic microvasculature may be a biomarker predictive of type I diabetes development [1]. These alterations are induced by an autoimmune ablation of β-cells. β-cells maintain glucose homeostasis through insulin release, triggered by a calcium influx through the voltage-gated calcium channel. Manganese (Mn) is a T_1-weighted MRI contrast agent analogous to calcium, and can enter these channels [2]. Unlike gadolinium, Mn can provide a link between cell functionality and perfusion. The purpose of this study was to develop a model of dynamic contrast-enhanced MRI to monitor pancreatic β-cell function and vasculature modifications as indicated by passive and glucose-stimulated kinetics in the pancreata of normal and diabetic mice.

Material and Methods: 11 normal and 9 diabetic 8-10 week old FVB/N mice were used in this study (procedures approved by IACUC). Diabetes was induced by streptozotocin treatment (188 mg/kg body wt), with serum glucose levels > than 300 mg/dL considered as diabetic. Imaging was performed on a 9.4T Bruker BioSpec Scanner within a 35 mm quad volume coil. After acquiring high-resolution anatomic images for pancreas localization, dynamic Mn enhanced coronal imaging was performed on eight slices through the pancreas using a Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence (TR/TE = 2000/2.9 ms, flip angle = 10°, FOV = 40×20 mm, matrix size = 128×64, slice thickness = 0.5 mm, inversion time = 700 ms, NEX = 1) with a temporal resolution of ~24 s. At least one slice of the left and/or right kidney was also obtained. Dynamic images were acquired pre-contrast, and during an IV Mn bolus (10 mg/kg body wt) and an IP glucose bolus (1.5 g/kg body wt) at ~2 and ~30 min, respectively. The average signal enhancement, ΔS(t), of the dynamic MRI series over a region of interest (ROI) in the pancreas was calculated as $\Delta S(t) = (S(t) - S_0) / S_{kidney}$, where S(t) is the signal intensity as a function of time, and S_0 and S_{kidney} are the averaged signal enhancement in pre-contrast ROIs and at 30 min in the kidney, respectively. A novel empirical mathematical model (EMM) was developed based on Jansen et al. to fit the passive Mn uptake over the pancreatic ROIs:

$$\Delta S(t) = A \cdot (1 - e^{-\alpha t}) \cdot e^{-\beta t} \cdot (1 + \varepsilon e^{-\gamma t}),$$

where A(1+ε) is the upper limit of the signal intensity, α(min^{-1}) is the rate of contrast uptake, β(min^{-1}) is the rate of contrast washout, γ(min^{-1}) is the earlier rate of contrast washout, and ε accounts for contrast kinetics due to blood vessels (e.g., pancreas head). Additionally, the initial area under the curve (iAUC$_\tau$) at τ=2 min and the initial slope (iSlope) were calculated directly from the EMM parameters. Finally, glucose-induced activation of the normal and diabetic mouse pancreatic β-cells were evaluated by calculating the angle between the linear slope pre/post glucose injection.

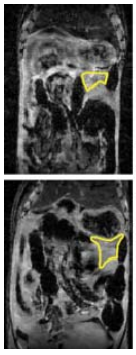

Figure 1. Pancreatic tail MR images and kinetic curves.

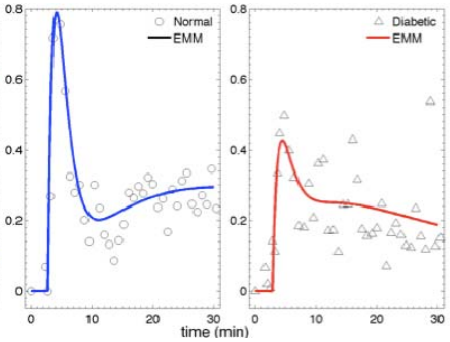

Figure 2. Pancreatic head kinetics.

Results: Fig. 1 shows normal (top)/diabetic (bottom) mouse coronal MR images of the pancreatic tail and associated plots of ΔS(t). The EMM (blue&red lines) and linear function (green line) accurately fitted the passive/active regions, respectively. The passive Mn uptake rate in the normal pancreatic tail was significantly faster than in the diabetic (P<0.05). The angle between the tendency of the Mn curve pre/post β-cell activation showed significant difference between normal/diabetic pancreatic tails (P<0.05). Fig. 2 shows example plots of ΔS(t) for the pancreatic head with blood vessels and fitted by the EMM. Overall averaged EMM parameters for normal/diabetic mice pancreata are given in Table 1. Pancreatic tails of normal mice had a steeper iSlope and a larger iAUC$_\tau$ compared to diabetic (P<0.03). No statistical differences were found between normal/diabetic pancreatic head/body for EMM or linear parameters.

Discussion: β-cell loss and alteration in supportive vasculature in the tail of the diabetic pancreas was indicated by a decreased rate of uptake and iSlope and smaller iAUC compared to normal. This indication of beta cell loss was further supported by a smaller angular change following glucose activation compared to the normal pancreas. This imaging technique has potential for developing into a non-invasive methodology for monitoring diabetes progression and/or therapy.

Region	A	α(min^{-1})	β(min^{-1})	ε	γ(min^{-1})	iSlope	iAUC$_\tau$	θ(°)
Tail (n=11)	0.46±0.15	**1.4±0.5**	-0.008±0.007	-	-	**0.66±0.30**	**0.56±0.20**	**0.50±0.20**
Head (n=5)	0.57±0.09	0.2±0.2	0.011±0.010	19.8±16.7	0.64±0.17	1.30±0.68	19.79±6.21	0.33±0.31
Tail (n=9)	0.35±0.13	**1.0±0.4**	-0.001±0.010	-	-	**0.34±0.20**	**0.35±0.17**	**0.28±0.12**
Head (n=5)	0.55±0.15	0.1±0.1	0.022±0.009	21.0±14.8	0.49±0.12	1.55±0.21	12.01±3.58	0.38±0.36

Table 1. EMM parameters/angle for normal (blue) and diabetic (red) mouse pancreatic regions.

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References:

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[2] Gimi et al., Cell Transplant, 2006
[3] Jansen et al., Magn Reson Med, 2008