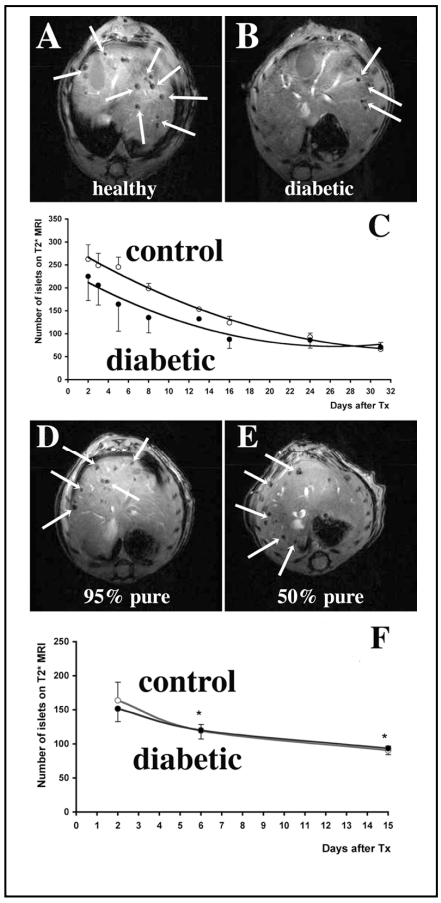
Factors Influencing In Vivo MR Imaging of Transplanted Pancreatic Islets

N. Evgenov[1], J. Pratt[1], P. Pantazopoulos[1], and A. Moore[1]

[1]Molecular Imaging Laboratory, Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts, United States

Background. Pancreatic islet transplantation has recently emerged as a powerful clinical modality to restore normoglycemia in diabetic patients. However, a significant islet loss has been observed immediately after transplantation. Non-invasive MRI allows for longitudinal monitoring of graft loss when islets are labeled with iron oxide nanoparticles. In order to fully interpret the imaging picture, it is critical to investigate factors normally present during clinical transplantation and influencing MR imaging of transplanted islets. Here, we focused on both the effect of hyperglycemia and the effect of contaminating non-endocrine tissue, which is always present in islet preparations, on MRI imaging of islet grafts.

Materials and Methods. To investigate the factor of glucose toxicity on MR imaging of transplanted islets, human pancreatic islets (1000 IEQ) were labeled with Feridex (200 μg/ml) and transplanted into the livers of diabetic and healthy NOD.scid mice. Diabetes was induced by injection of streptozotocin 100 mg/kg. To investigate the factor of islet purity on MR imaging of transplanted pancreatic islets Feridex–labeled human pancreatic islets of 95% and 50% purity were infused into the liver of healthy NOD.scid mice. In vivo MRI in both cases was performed using a 4.7T Bruker Biospec horizontal bore scanner (Billerica, MA) equipped with ParaVision 3.0.1 software. Imaging was performed on days 2, 3, 5, 8, 13, 16, 24, and 31 after transplantation into healthy and diabetic animals. Animals transplanted with 95% and 50% purity islets were scanned on days 2, 6, and 15. The imaging protocol consisted of T2*-weighted gradient echo pulse sequences with the following parameters: TR/TE = 300/7 ms, number of averages = 32, flip angle = 60°, FOV = 2.5 x 2.5 cm^2, matrix size = 200 x 200, resolution = 0.125 x 0.125 mm^2, slice thickness = 0.5 mm, and a total scan time of 32 min. Imaging results were correlated with glucose homeostasis during the study, immunohistochemistry and the level of apoptosis in transplanted islets.



Results. A quantitative analysis of relative islet loss on MR images (Fig. 1A, B, arrows) performed in diabetic and control mice revealed islet loss in both groups. However, the half-life of the islets in the diabetic group was 4.8 ± 1.1 days compared to 12.6 ± 2.9 days for control non-diabetic mice (Fig. 1C). A significant reduction in islet number in diabetic animals was concurrent with persistent hyperglycemia after transplantation and correlated with high apoptotic rate in these animals. Following the reversal of diabetes on day 10, there was no statistically significant difference in the number of apoptotic cells or in blood glucose values between the groups through the end of the study. On MR images the number of islets in diabetic group equalized with the number of islets in healthy group soon after the diabetes was reversed.

The input of non-endocrine elements in islet preparation on interference with MRI data was assessed in animals transplanted with 95% and 50% purity islets (Fig. 1D, E). Our results showed that the two groups of animals did not exhibit any statistically significant difference in islet disappearance rate throughout the study suggesting that non-endocrine tissue does not interfere with MR imaging of islets (Fig. 1F). Consistent with these results there was 4.2 fold higher percentage of TUNEL positive cells in mice transplanted with 50% purity islets than in mice transplanted with 95% purity islets. The amount of acinar and ductal elements decreased more significantly in grafts of 50% purity. This observation is consistent with the higher rate of apoptosis observed for these animals and the fast disappearance rate of non-endocrine tissue from a 50% purity graft.

Conclusion. In the present study we successfully utilized MR imaging modality to monitor the adverse effects of hyperglycemia on transplanted pancreatic islets over time in vivo. MR imaging data revealed significantly shorter half-live of islets transplanted in diabetic mice than in healthy animals, presumably as a result of chronic hyperglycemia. The effect of contaminating non-endocrine tissue was found negligible, and islet disappearance rate on MR images in animals transplanted with 95% and 50% purity islets was similar throughout the study. We believe that this study serves as yet another step on our way to clinical use of *in vivo* imaging of islet transplantation.