Magnetic Resonance Imaging of the Pancreatic Vasculature in Type 1 Diabetes

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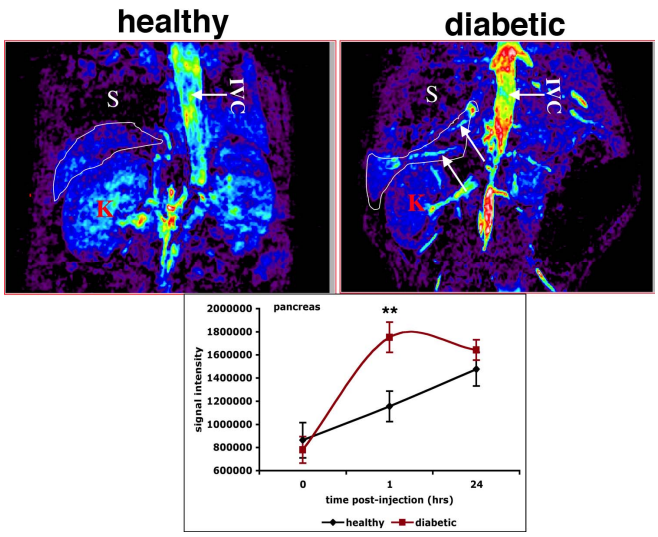
Background.

Vascular changes are commonly associated with many pathologies, including, cancer, arthritis, and diabetes. In type 1 diabetes, autoimmune lymphocytic infiltration, termed insulitis, progresses over many years, culminating in the destruction of a critical mass of insulin-producing beta-cells, and ultimately, in hyperglycemia and metabolic dysregulation. In type 2 diabetes, the presence of systemic inflammatory markers (including complement activation) suggests chronic inflammation. Vascular parameters, such as vascular volume, flow, and permeability are an important disease biomarker. Therefore it is important to be able to monitor the dynamics of pancreatic microvasculature noninvasively. Here, we describe the application of the long-circulating, paramagnetic T1 contrast agent, PGC-GdDTPA-F (Protected graft copolymer bearing covalently linked gadolinium diethylenetriaminepentaacetic acid residues and labeled with fluorescein) for the noninvasive semi-quantitative evaluation of vascular changes in RT6-depleted BB-DR rats as a model of type 1 diabetes.

Methods and Materials.

MRI. Diabetic animals and non-diabetic controls were monitored by magnetic resonance imaging (MRI) following injection of PGC-GdDTPA-F. MR imaging was performed on a 9.4T Bruker horizontal bore scanner (Billerica, MA) equipped with an RF transmit and receive volume coil. 3D-angiograms were obtained using a gradient echo imaging sequence comprising first-order flow compensation (GEFC). The following imaging parameters were utilized: TE = 2.43ms, TR = 40ms, FOV = 38.4 x 50.0 x 38.4mm^3, Spatial resolution = 0.3 x 0.312 x 0.3mm.pixel^{-1}, matrix size = 128 x 160 x 128, and a total imaging time of 13min 32sec. The pancreas was manually segmented and subjected to region-of-interest (ROI) analysis for the determination of pancreas-associated T1 relaxation times. Fluorescence microscopy on frozen pancreatic tissue sections was performed to assess contrast agent tissue distribution in relationship to the vasculature.



MR images at 1hr post PGC-Gd injection. Pancreas is outlined. S, stomach; IVC, inferior vena cava, K, kidney. Arrows point to blood vessels.

Results.

We observed a significantly higher accumulation of PGC-GdDTPA-F in the pancreata of diabetic animals, as compared to non-diabetic controls at 1 hr post-injection (Figure). No differences were seen in the blood pool, kidney, or muscle, indicating that the effect is specific to the diabetic pancreas. Fluorescence microscopy revealed a marked increase in contrast agent availability in tissue with the development of the pathology. This effect appeared to extend both from an increase of vascular volume and permeability (not shown).

Summary.

High-molecular weight paramagnetic blood volume contrast agents are valuable for the in vivo definition of pancreatic microvasculature dynamics in type 1 diabetes by MRI. The increase in vascular volume and permeability, associated with diabetic inflammation, can be monitored noninvasively and semi-quantitatively by magnetic resonance imaging in RT6.1 depleted DR-BB rats. This imaging strategy represents a valuable research tool for the better understanding of the insulitic process.