

Comparison of rate of islet loss in syngeneic, allogeneic and xenogeneic grafts in rat using quantification of iron oxide labeled islet cells by 3D radial UTE MRI.

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Introduction

An application for serial MR examination of iron labeled islet cells transplanted into the liver is proposed. Rats with varying types of graft and numbers of transplanted cells were imaged using 3D radial ultrashort echo time (UTE) imaging. The images produce quantifiable positive contrast from the iron labeled cells. The reproducibility in stable syngeneic grafts using this method has been reported previously¹. We aim to quantify islet clusters over time by automatic cluster segmentation to observe rates of rejection after transplant.

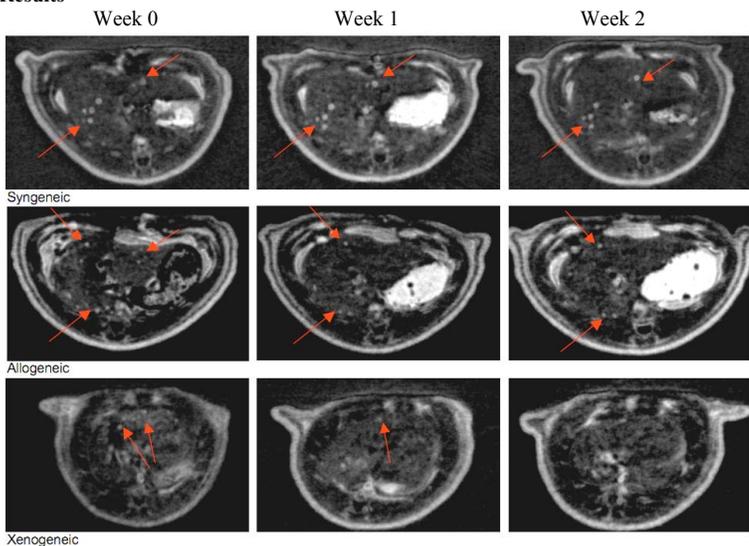
Methods

Rats were transplanted with either syngeneic (Sprague Dawley, n=12), allogeneic (Lewis/Wistar, n=5) or xenogeneic (Lewis/Human, n=7) islet grafts. Number of islet equivalents (IEQ) varied and two methods of labeling – normal incubation with ferucarbotran Resovist® or magnetofection – were included. MR provides an ideal non-invasive method for repeated scans over time. However, as the islets cells do not naturally show contrast from the surrounding liver, a stable, non-toxic label, and appropriate MR methods are needed, however quantification of iron oxide remains challenging. Resovist® (carboxydextran-coated super paramagnetic iron oxide, SPIO) was used in this study². Ultrashort echo time (UTE) imaging^{3,4} has been proposed as a technique for quantifiable enhancement of both localized and diffuse regions of iron⁵. 3D UTE imaging⁶ uses radial sampling with short read-out and echo times⁷. The UTE sequence consists of a 60us non-selective RF pulse and a 100% asymmetric data acquisition starting during ramp-up time of the readout gradient. Radial imaging has a useful diffuse distribution of motion artifact and does not suffer from wraparound making it both robust to flow and motion, and ideal for small FOV imaging of the liver. A UTE image will include all of the species, including the very short T2* islet cells. A second echo image is subtracted from this (when the short T2* species have decayed) resulting in positive contrast from the iron containing cells and nulled background liver signal (d-UTE).

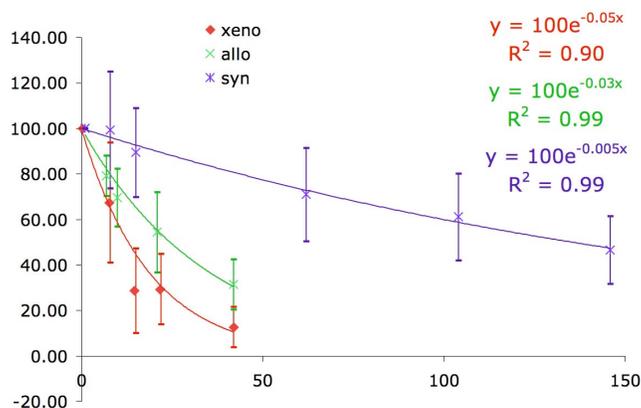
Imaging was carried out on a Siemens MAGNETOM Trio 3T clinical scanner (Siemens AG, Erlangen, Germany) using the system wrist coil. Scanning was from baseline (day 1 after surgery) up to 146 days, depending on conditions. UTE image parameters^{3,4,6} are a 3D isotropic resolution matrix of 320 and a 12cm FOV, with 35000 radial projections. TE(1)/TE(2)/echo spacing/FA = 0.07ms/5.7ms/9.6ms (x 70-110 segments)/10°. A Kaiser-Bessel gridding algorithm (window width = 3 and $\beta = 4.2054$) is integrated into the system online reconstruction along with sampling density precompensation (a modified rho filter with plateau toward the outer part of k-space)⁶. Respiratory triggering, pausing imaging during the short inhale/exhale period, used a pressure pad and external trigger input system (SA Instruments Inc. Stony Brook NY, USA) with a trigger delay of around 150ms to ensure imaging is at a constant respiratory position over the 6 minute scan time.

Quantitative assessment for comparison of the different numbers of cells included automatic segmentation, over all slices, of islet clusters on the background suppressed liver images. Analysis of these data included comparison of different IEQ, graft type and loss of islet cluster hyperintense signal over time. Exponential fit of mean data for each of the three graft types was calculated. To remove the effect of IEQ on the fit of the decay (to isolate time effect) data was normalized to the initial scan.

Results



Example dUTE images, over 2 weeks



Segmentation – number of clusters, normalized to a percentage of the initial scan value, mean over graft type, exponential fit fixed to 100%

Discussion

Both allogeneic and xenogeneic grafts show significant loss of islet cells over 42 days, unlike syngeneic grafts, which stay almost constant.¹ The fastest decay is in the xenogeneic grafts, as is expected from rejection mechanisms. In general, rate of decay with time does not depend on IEQ. The slight decay in the mean syngeneic values comes from significant islet loss in 2 of 12 cases. Statistics show no significant difference over time for all other animals in this group ($p > 0.05$). After normalization, decay rates for each graft are significantly different (allo:xeno $p = 0.03$, allo:syn $p = 0.0006$, syn:xeno $p = 0.0002$).

Conclusions

The success of islet grafts, the effect of labeling techniques and the loss of grafted islets can be quantified and monitored using 3D radial UTE positive contrast images of iron oxide. This shows promise for the monitoring of islet graft survival and the effect of immunosuppressant treatments to delay rejection in both animal models and is directly applicable to clinical patient protocols.

References

- [1] Crowe LA, Ris F, Nielles-Vallespin S, et al. Proc Intl Soc Mag Reson Med 2009:455.
- [2] Toso C, Vallee JP, Morel P, et al. Am J Transplant 2008;8(3):701-706.
- [3] Gatehouse PD, Bydder GM. Clin Radiol 2003;58(1):1-19.
- [4] Robson MD, Gatehouse PD, Bydder M, et al. J Comput Assist Tomogr 2003;27(6):825-846.
- [5] Crowe LA, Wang YX, Gatehouse PD, et al. Proc Intl Soc Mag Reson Med 2005:115.
- [6] Nielles-Vallespin S, Weber MA, Bock M, et al. Magn Reson Med 2007;57(1):74-81.
- [7] Larson PZ, Gurney PT, Nishimura DG. IEEE Trans Med Imaging 2008;27(1):47-57.