Comparison of low molecular weight and USPIO contrast agents for detection of rejecting transplanted hearts

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Purpose:

The purpose of the study was to investigate three different contrast agents for MR imaging, two different blood pool agents and a low molecular weight gadolinium chelate, and determine which one could discriminate the best between acutely rejecting and non-rejecting transplanted hearts in the rat.

Materials and Methods:

In 36 rats a heterotopic heart transplantation were performed. 20 allogeneic, where operation was performed within different genetic strains (PVG to Wistar/Kyoto) and 16 syngeneic, with operation within the same genetic strain (Wistar/Kyoto to Wistar/Kyoto). They were divided into six groups with 5-7 animals in each group. At the 6th post operative day MR imaging was performed. One allogeneic and one syngeneic group each got three different kinds of contrast agents. Two ultra small superparamagnetic iron oxide particle (USPIO) were used; one with a diameter of 15 nm and coated with modified starch (Amersham Health) and Sinerem (Guerbet) with a diameter of 35 nm and a neutral Dextran coating. Both of these were given at a dose of 2 mg Fe/kg. The remaining two groups were injected with Gd-DTPA-BMA (Omniscan, Amersham Health) 0,2 mmol/kg. The groups that were injected with USPIO the MR imaging was a 3D dynamic scan in 20 phases with the first scan one minute after injection. The scan was a spoiled gradient echo sequence with a TR/TE 20/3.1ms with a flip angel of 35°. FOV was 70 mm with a 256 x 256 matrix yielding an inplane resolution of 0.27 mm. For the groups that were injected with Gd-DTPA-BMA a gradient echo sequence with a TR/TE 14/4,6, flip angel of 10°. FoV was 50 x 34,4 with a matrix of 256 x 256 yielding an in-plane resolution of 0,195 mm was performed. In the USPIO groups, the relative change in signal intensity (SI) was calculated using the first dynamic scan as a reference. For the comparison of the groups we analyzed different parameters from the curve and chose the one that could discriminate the groups the best. For the Gd-DTPA-BMA groups, the signal intensity was measured and the upslope and the slope after the first peak were calculated. Using a bootstrap technique a confidence interval of the difference between each contrast agent was calculated. After scanning the hearts were prepared for histology and the morphology was assessed.

Results:

For both the USPIO's we were able to discriminate 100% between rejecting and non-rejecting hearts. For the 15 nm USPIO we used the slope of the first eight dynamic scans. The mean slope for the allogeneic grafts was 0,87 and for the syngeneic grafts –0,42. For Sinerem we used the mean relative change in SI of the last four dynamic scans. The mean result for the allogeneic group was 8,9 % SI change and for the syngeneic group –4,99 % SI change. With Gd-DTPA-BMA there was no significant difference between rejecting and non-rejecting grafts. In addition, there was no difference between the two USPIOs in their ability to detect acute rejection. In the histological analysis all allogeneic grafts had moderate to severe or severe rejection and all the syngeneic grafts had mild or mild to moderate rejection.

Conclusion:

Acutely rejecting and non-rejecting transplanted hearts can be discriminated from each other using the difference in permeability assessed by blood pool agents and MR imaging. Both blood pool agents could discriminate between syngeneic and allogeneic groups without overlapping. With first pass perfusion of gadolinium chelate no significant difference was found between rejecting and non-rejecting grafts.

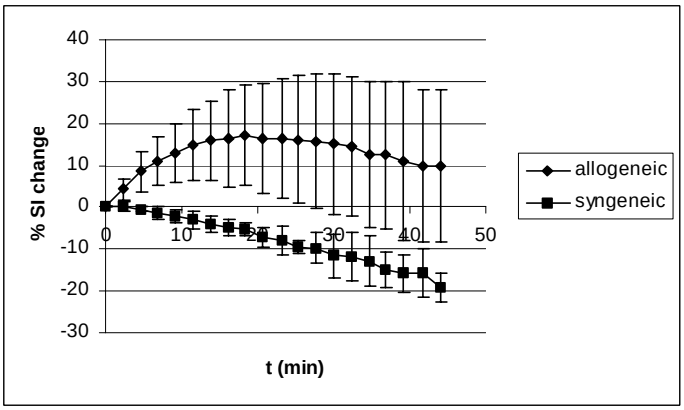

Fig. 1. The relative change in signal intensity over time for the 15 nm USPIO. The curve represent the mean and the error bars the standard deviation.

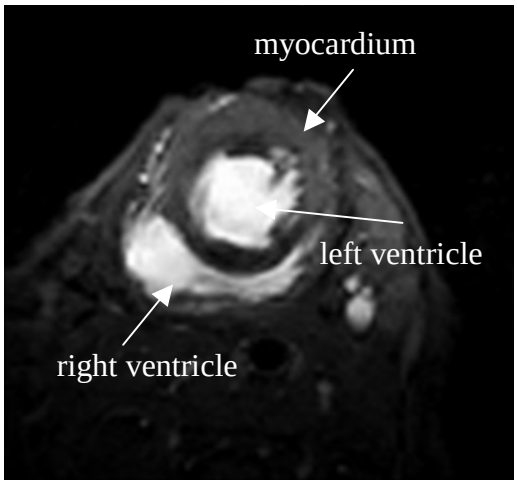

Fig 2 Example of a dynamic scan with 15 nm USPIO