Novel Manganese Porphyrins as Potential MR Contrast Agents for Diagnostic Evaluation of Myocardial Perfusion and Viability

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Introduction: SPECT imaging using the lipophilic radiotracer Technetium (^{99m}Tc) sestimibi remains the most common method for assessing myocardial perfusion and cellular viability. ^{99m}Tc sestimibi distributes in myocardium proportionally to blood flow, and accumulates transiently within myocytes based on its avidity for mitochondria. Recurrent problems involving radiotracer manufacture and supply, as well as inherent limitations of the SPECT method itself, however, result in the need for new approaches to evaluating cardiac integrity. MRI techniques such as contrast-enhanced inversion recovery GRE are useful for identifying regions of myocardial infarction, but do not provide reliable detail on at-risk myocardium. Stress CMR perfusion methods hold promise for tissue viability assessment, but depend on pharmacological rather than exercise-dependent myocardial stress. In this study, we present initial results investigating the use of two novel, water-soluble, lipophilic manganese-based porphyrins with remarkably high T1 relaxation properties and strong avidity for cardiac mitochondria [1].

Methods: *In vitro* and *in vivo* experiments were performed on a horizontal bore Bruker Biospec 7T MR scanner (Bruker, Billerica, USA) using a quadrature volume coil for RF input and receive. 3D volume acquisitions covered the mouse hearts from base to apex. Variable flip angles (α = 2, 8 and 14 degrees) were incorporated using Bruker's intraGATE FLASH sequence at a TE/TR =1.8/10 ms [2]. The 3D intraGATE reconstruction was performed on Paravision 5.1 software. For subsequent T1 determination using DESPOT1 analysis, Osirix software on the Mac OS X platform was utilized. *In vitro* T1 relaxivity of MnTMOHex-PyP and MnTButOE-PyP porphyrins (MnPs)was measured in phantoms using conventional saturation recovery RARE T1. Different concentrations of porphyrin phantoms were prepared with 1x PBS at physiological pH. *In vivo* experiments were performed in 6-8 weeks old C57/black mice (n=6). MnPs were administered through femoral *i.v.*

Results and Discussion: Figures 1A and B demonstrate T1 relaxation properties *in vitro* of MnTMOHex-PyP and MnTButOE-PyP porphyrins, revealing relaxavities that are nearly twice those of the commercial lanthanide Magnevist. Figure 2A and 2B show cardiac

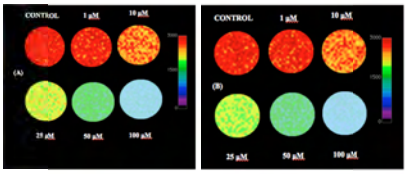

Fig. 1 A) MnTMOHex **B)** MnTBuE2-PyP

Table1:

Compound	Relaxivity
MnTMOHex-PyP	5.57
MnTBuOE2-PyP	5.35
Magnevist	2.85

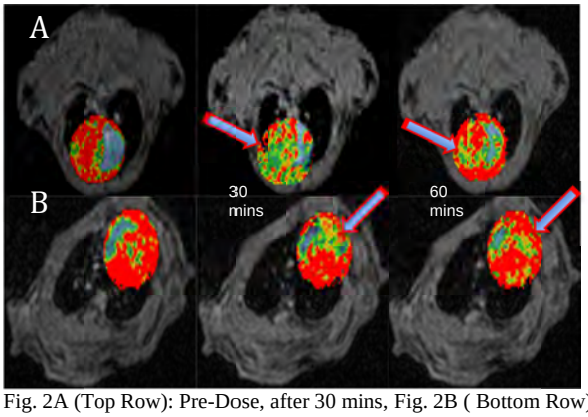

Fig. 2A (Top Row): Pre-Dose, after 30 mins, Fig. 2B (Bottom Row): Pre-Dose, after 30 mins, after 60 mins

T1 maps pre and post i.v. administration of MnTMOHex-PyP (4mg/kg) and MnTBuOE2-PyP (1 mg/kG) at 30 and 60 mins. For MnTMOHex-PyP, T1 relaxation in left ventricular myocardium decreased from 3392 ± 130 ms to 3082 ± 80 ms at 30 minutes and returned to predose relaxation at 60 minutes. For MnTBOE2, T1 relaxation decreased from 3590±180 ms to 2967 ± 100 ms at 30 minutes and returned nearly to pre-dose levels at 60 minutes. Relaxivity decreases averaged 12-15% for both compounds after 30 minutes, although the relaxation change was significantly greater for MnTBuOE2-PyP despite a 4-fold decrease in administered dose.

Conclusions: *In vitro* and *in vivo* quantitative MR imaging experiments demonstrate the potential of a novel class of manganese-based porphyrins for diagnostic characterization of myocardial perfusion and viability. Initial pharmacokinetic and pharmacodynamic behavior as revealed by quantitative MR imaging and prior biochemical and histological characterization suggest the potential diagnostic use of these compounds in a manner analogous to Tc sestamibi. The time course of myocardial enhancement and washout, as determined both qualitatively and quantitatively using a novel 3D variable flip angle steady state acquisition technique, would allow for the use of physiological rather than pharmaceutical stress, and also offer the possibility of quantitation at high isotropic resolution.

References:

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