A DNA-Targeted Gadolinium Chelate to Selectively Enhance Acutely Injured Myocardium

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Introduction: Delayed enhancement (DE) of gadolinium chelates is frequently used to diagnose myocardial infarction (MI) and other cardiac diseases. However, delayed enhancement (DE) cannot discriminate acute and chronic injury since both produce similar changes in the pharmacokinetics of small gadolinium chelates, such as Gd-DTPA. T2-weighted imaging of myocardial edema is frequently used as an adjunct to DE to differentiate acute vs. chronic injury. However, the addition of T2-weighted imaging adds complexity, may lack sensitivity and still cannot discriminate acute from subacute injury. Here we present a novel approach to selectively produce DE in acute myocardial injury through the use of a DNA targeted small gadolinium chelate, Gadolinium-DTPA Thiazole-Orange (Gd-TO).[1]

Materials and Methods: The selectivity of Gd-TO for exposed DNA in ruptured necrotic cells was demonstrated by flow cytometry and fluorescent microscopy in vitro.[1] In vivo imaging in the current study was performed in infarcted (permanent ligation of the left coronary artery) C57BL6 mice. The infarcted mice were injected with 0.1 mmol/kg of Gd-TO or Gd-DTPA at varying times post-infarction. MRI was performed on a 9.4T scanner (Bruker Biospin) with a gradient strength of 150 Gauss/cm. A cardiac gated Look-Locker FISP sequence (TR: 3000ms, TE 1.3, MTX: 160x160, FOV: 2.5 x 2.5 cm^2) was used to monitor the presence of DE and R1 changes in the infarcted myocardium. The effective longitudinal relaxation rate ($R_{1,eff}$) was calculated by fitting the inversion recovery curve using Equation $S(t) = A - B\exp^{-t/T_{1,eff}}$, and the longitudinal relaxation rate (R_1) was calculated using Equation $R_1 = R_{1,eff} - \ln(\cos(\alpha))/\tau$.[2]

Results: Pronounced and sustained (> 3 hours after injection) DE was seen in the acutely infarcted mice (18 - 48hrs post-infarction) injected with Gd-TO (Figure 1, top panel). In contrast, complete myocardial washout of the non-targeted Gd chelate (Gd-DTPA) was seen within 90 minutes injection. The kinetics of Gd-TO in mice with subacute injury (10 days post-infarction) was similar to that of Gd-DTPA (complete washout from the infarct within 90 minutes, Figure 1, bottom panel).

Conclusion: Gd-TO binds selectively to the exposed DNA in acutely necrotic cells and shows selective retention in acute myocardial injury. The use of Gd-TO involves a single well-validated contrast mechanism, and allows acute myocardial infarction to be distinguished from both subacute and chronic myocardial injury.

References: 1. *Chem Commun (Camb)*. 2009 (29): 4444 - 4446. 2. *Magnetic Resonance in Medicine 46:131-140 (2001)*
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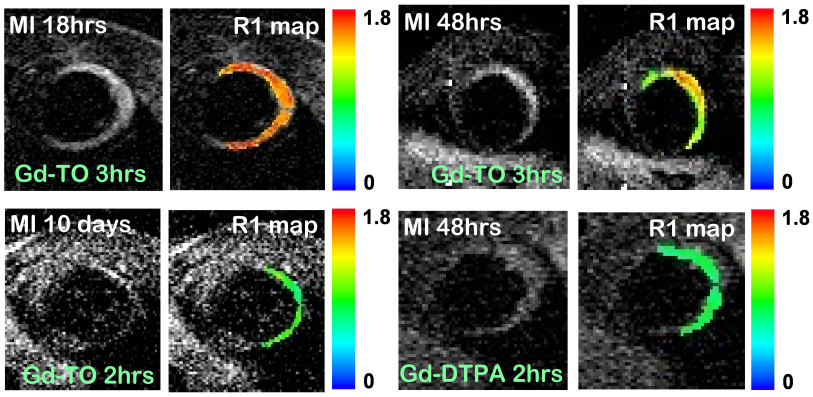

Fig. 1 :Gd-TO shows sustained enhancement in acute myocardial infarcts (18-48 hours post-infarction, top panel). In subacute and chronic infarction (bottom left), however, Gd-TO does not encounter exposed DNA and is washed out much like Gd-DTPA.

R_1 (1/sec)	Infarct	Chest Muscle
Gd-TO		
MI 18 hrs	1.59	1.09
MI 48 hrs	1.25	1.03
MI 10 Days	0.94	1.03
Gd-DTPA		
MI 48 hrs	0.87	1.01

Table 1: The R1 of infarcted myocardium 3 hours after contrast agent injection.