Determining Tissue Kinetics of Gd(ABE-DTTA), an Infarct-Avid, Persistent Contrast-Agent in Canine Myocardial Infarction

P. Surányi[1,2], P. Kiss[1], B. C. Brott[3], T. Simor[1,2], A. Elgavish[2,4], G. A. Elgavish[1,2], ,., [3]

[1]Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Birmingham, AL, United States, [2]Elgavish Paramagnetics Inc., Birmingham, AL, United States, [3]Department of Medicine, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, United States, [4]Department of Genetics, University of Alabama at Birmingham, Birmingham, AL, United States

INTRODUCTION

Detection of viability is crucial in the monitoring of myocardial infarction (MI). Contrast-enhanced MRI offers a high spatial resolution method that can distinguish irreversible cellular injury from myocardial hibernation or stunning[1,2]. Contrary to signal intensity (SI), the contrast agent (CA) induced longitudinal relaxation rate enhancement ($\Delta R1$) is an intrinsic parameter which is linearly proportional to the concentration of CA in any given voxel[3]. Accurate determination of $\Delta R1$ is possible only with an inversion-recovery approach, using multiple inversion times (TI)[4]. Covering the entire left ventricle (LV), using this method, takes at least 30-45 minutes. Thus, $\Delta R1$ mapping can be achieved only with a CA sufficiently long-lived in the myocardium not to change its concentration within 30-45 minutes to an extent that would cause a change in T1 larger than the experimental error of T1 measurements. We call such a CA a Persistent Contrast Agent (PCA). In this work the tissue kinetics and the infarct-specificity of Gd(ABE-DTTA)[5] were studied in-vivo in a closed-chest canine model, using an inversion-recovery sequence with six TIs. Pixel-by-pixel T1-maps were converted to R1-maps to follow PCA kinetics in blood and in viable and non-viable myocardium.

METHODS

Following the administration of 0.05mmol/kg Gd(ABE-DTTA) to LAD-occluded (180 min) and reperfused dogs (n=6), high spatial resolution inversion-recovery images were generated with six inversion times (TI) in one equatorial short axis slice daily during the first week following PCA administration. Infarcted area was selected by assessing regional wall motion with the FIESTA cine sequence. In one dog, PCA kinetics was followed during the first four hours after administration with repeated T1-mapping, and in two dogs the measurement was repeated at two and three weeks following administration. T1 was calculated from the TI dependence of the signal intensity (SI), using di-exponential, three parameter, least squares curve-fitting. R1 values were calculated in a pixel-by-pixel manner, and the hourly change in R1 throughout the first week was calculated for both viable and non-viable tissue. Location of PCA accumulation in irreversibly injured myocardium was validated by postmortem TTC-staining, and determination of gadolinium content in infarcted vs. viable tissue, using plasma emission spectroscopy (PES) (Galbraith Laboratories Inc.). An Accumulation Factor (AF) was defined as the PES-determined regional Gd content divided by the originally administered dose. Samples were taken from the confluent infarct core, the marginal infarct zone (infarcted islets mixed with viable tissue) and remote areas, as delineated by TTC-staining within the first week following the initial administration of the agent.

RESULTS

Representative pixel-by-pixel R1 maps from four different dogs and different time points are shown in Figure 1. Control R1 values for myocardium and blood were 0.95 and 0.7 s^{-1}, respectively. One hour following its administration, PCA was evenly distributed throughout the myocardium, with average myocardial and blood R1 values of $1.7s^{-1}$, and $6.15s^{-1}$, respectively. Accumulation of PCA in the infarct became detectable at two hours ($R1=1.88s^{-1}$).Average infarct R1 was $2.1s^{-1}$ at 24 hours, peaked at $R1=2.5s^{-1}$ at 72 hours, and was still $1.9s^{-1}$ 144 hours after PCA administration. Clearance from normal myocardium and blood started practically at the time of administration. PCA was cleared from the blood stream 96 hours, and from the normal myocardium 144 hours, after administration. Peak myocardial R1 contrast was observed at 72 hours, with R1 values of $2.5s^{-1}$ and $1.18s^{-1}$, in infracted and normal myocardium, respectively (Figure 2). At this time point, blood R1 was $0.87s^{-1}$, which provided excellent blood-myocardium contrast, and a good delineation of endocardial contours. The hourly change in myocardial R1 in all areas was less than 1% throughout the first week. The areas highlighted with PCA were matched by the results of postmortem TTC staining. In the infarct core we found 0.285 mmol/kg Gd six days (AF=5.7), and 0.183 mmol/kg Gd (AF=3.65) nine days after reperfusion. In the spotted infarct regions (mixed infarcted and non-infarcted areas surrounding the core of the infarct) we found 0.12 mmol/kg Gd (AF=2.4) and 0.045 mmol/kg Gd (AF=0.9) on the same days, respectively. Nine days after administration the Gd content in remote areas was 0.01mmol/kg (AF=0.195).

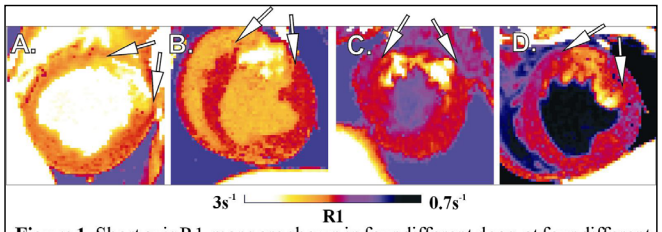

Figure 1. Short axis R1-maps are shown in four different dogs, at four different time points. Figures A. through D. were generated 24, 48, 72 and 96 hours following PCA administration, respectively. R1 is shown on a heat-color map. Higher R1 values in the myocardium reflect PCA-accumulation in infarcted tissue (bracketed by arrows). Note that PCA clearance is fastest from the blood.

DISCUSSION

We have shown that Gd(ABE-DTTA) meets the requirements for a PCA, and its infarct specificity suggests its potential use as a myocardial viability agent. Following a single administration of this PCA, good visualization of infarcted tissue was demonstrated from 24 hours to 144 hours after administration. Multiple-TI T1-mapping offers accurate analysis of myocardial infarction, superior to single-TI inversion-recovery images[6]. T1-mapping also eliminates confounders such as T2-effects, field-inhomogeneity, or differences in equipment and pulse sequence used. PCA could be administered one day ahead of the planned MRI examination, possibly at the time of presentation of the patient with infarction. Infarct expansion and salvage could be monitored at any point throughout the first week thereafter and further clinical interventions could be adjusted accordingly.

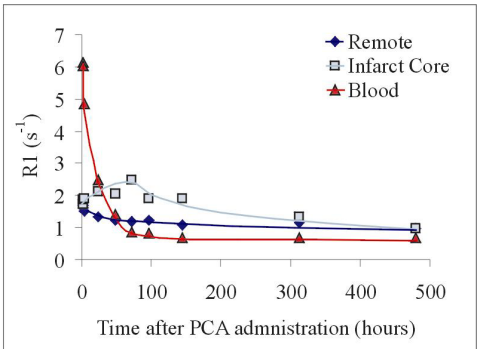

Figure 2.

REFERENCES

1. Kim RJ, Hillenbrand HB, Judd RM. *Herz*. 2000;25:417-30.
2. Kim RJ, Wu E, Rafael A, et al. *N. Engl. J. Med.* 2000;343:1445-53.
3. Fritz-Hansen T, Rostrup E, Ring PB, et al. *Magn Reson Imaging*. 1998;16:893-9.
4. Kaldoudi E, Williams SCR. *Concepts in Magnetic Resonance*. 1993;5:217-242.
5. Saab-Ismail NH, Simor T, Gaszner B, et al. *J Med Chem*. 1999;42:2852-2861.
6. Messroghli DR, Niendorf T, Schulz-Menger J, et al. *J Cardiovasc Magn Reson*. 2003;5:353-9.