Steady-State Detection of Ischemia with AngioMARK

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Introduction

Most MR based perfusion methods to date have relied on evaluation of the first pass dynamics of contrast agent passage through the myocardium and the resulting signal intensity changes. However, this method relies on fast imaging with whole heart coverage, with accompanying sacrifices in spatial resolution and image quality. An agent that allows late imaging of perfusion defects with higher resolution sequences, after the initial distribution of the agent, would potentially allow for easier implementation of perfusion based stress tests and thus clinical acceptance. Therefore, the purpose of this work was to evaluate AngioMARK (EPIX Medical/Mallinckrodt Inc) for potential use for steady-state perfusion imaging.

Methods

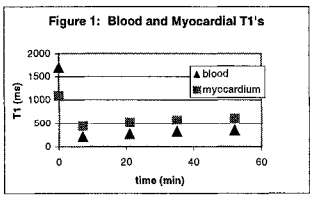
AngioMARK is a gadolinium-based agent that binds to albumin in the body during circulation [1]. Up to 95% of the agent is bound to albumin in the blood at equilibrium with the free fraction able to move into the interstitial space. We hypothesized that if AngioMARK were injected during ischemia due to acute occlusion of a coronary artery, the normal myocardium would be exposed to intravascular drug bound to albumin and the accumulation of the free drug in the interstitium during first pass which subsequently can bind to albumin there. In contrast, the ischemic myocardium would only be exposed to AngioMARK after blood flow is restored [2] at which time the equilibrium concentration of free drug is much lower than the first pass concentration. Thus we would predict that signal intensity differences due to differences in the amount of Gd in the interstitial space would persist for some period of time after the initial injection, enabling delayed imaging.

A balloon occluder was surgically placed around the left circumflex coronary artery (LCX) in 8 pigs (30-40 kg). Immediately following placement of the occluder, MR imaging was performed on a 1.5T clinical scanner (Gyroscan ACS-NT, Philips Medical Systems, NL). First, a T1-weighted SE-EPI sequence (TE 21 ms, TR=RR interval, EPI factor 3) was used to obtain short axis images in 6 mm slices from apex to base. Following this, short axis cine imaging was performed at baseline and during a 1 minute occlusion to confirm the location of the ischemic area (lateral to inferior segments) by wall motion. First pass perfusion imaging was then performed in a single short axis slice using a saturation recovery T1-weighted turbo gradient echo sequence (TE/TR/α 4.8/2.8/15°), with a manual bolus injection of 0.05 mmol/kg AngioMARK in an ear vein. Images were obtained every heartbeat for approximately 2-3 minutes. The LCX was occluded for the first minute of the first pass perfusion study and then released. Following the initial perfusion study, the SE-EPI sequence was repeated at time points 7 ± 3, 21 ± 4, 35 ± 10, and 52 ±11 minutes post injection. In four animals, an additional occlusion was performed at the 52 minute timepoint during acquisition of the SE-EPI images to test sensitivity to reduction in blood flow late after injection. Fluorescent microspheres were used to estimate regional myocardial blood flow at baseline, during occlusion and following occlusion.

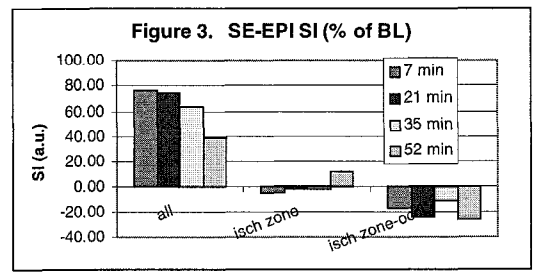
Delineation of the endocardial and epicardial borders was performed using the MASS software (Medis, NL) to calculate wall thickening (%) and myocardial signal intensity (SE-EPI scans). The short axis slice was divided into eight circumferential regions for comparison between imaging sessions and between animals.

Results

Wall thickening (% ED thickness) at baseline and during occlusion showed normal wall motion at rest and akinesis during occlusion. A decrease in wall thickening of approximately 40% in the lateral and lateral-inferior segments was observed, as expected for the location of the occluder. Microsphere measurements showed a corresponding decrease in these same segments to approximately 20% normal flow during occlusion, with restoration of flow after release of the balloon.



The mean myocardial and blood T1's across all animals for the timepoints studied are shown in Figure 1. The SE-EPI images showed uniform signal intensity at baseline, and regions of dark signal intensity on images obtained 7 ± 3 minutes after the occlusion and injection of AngioMARK. These dark regions persisted on the SE-EPI images throughout the imaging experiments (Figure 2- left:baseline and right: nine minutes post occlusion) and were still visible at the late timepoints. Occlusion of the LCX at 52 minutes resulted in further decrease in signal intensity in these areas. In all cases, the area of dark signal intensity on the SE-EPI images corresponded to the region of initial hypoperfusion as seen on the 1st pass perfusion images. Figure 3 shows the SI (expressed as percent of baseline SI) averaged over all eight circumferential segments (left) and also in an irregular ROI placed surrounding the area of dark signal intensity. The middle set of bars represents the 4 animals that did not undergo occlusion during imaging at the 52 minute timepoint, while the rightmost set of bars represents the 4 animals that did undergo occlusion during imaging. The decrease in SI over time in the normal myocardial segments was linearly related to the measured R1 (r=0.85). In the animals without occlusion at the late timepoint, the signal in the ischemic zone increased over time, as contrast presumably washed into the area, but the signal intensity remained well below the normal segments for our observation period of 52 ± 11 minutes. In the animals with an occlusion at the late timepoint, a further decrease in signal intensity was observed, consistent with the loss of perfusion and blood volume.



Conclusions

Steady state imaging of perfusion defects appears feasible using AngioMARK and thus may be valuable for development of a stress test analogous to thallium SPECT. The initial results here indicate that it may be feasible to use the agent for injection during peak stress with subsequent delayed high resolution imaging. Further work will involve pharmacokinetic modeling to validate the expected relative distribution and kinetics of agent in the normal and ischemic myocardium, and sequence optimization for T1-weighted anatomic imaging.

References

1. Lauffer RB, Parmelee D, Ouellet H, et al., Acad Radiol, 3:356-358, 1996.
2. Marcus ML. Coronary Circulation in Health and Disease, 1983.