

Analysis of MR Myocardial Perfusion Imaging Using a "Radial" Algorithm

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Abstract

Purpose: The goal of this study was to evaluate a radial analysis of dynamically enhanced turbo-fast low-angle shot (Turbo-FLASH) MR imaging during Gd-DTPA bolus intravenous administration in detecting myocardial ischemia with and without Dipyridamole (DP) stress.

Methods: 10 subjects presenting with symptoms suggestive of myocardial ischemia were examined at rest and under DP stress. Rest images were acquired using electrocardiogram (ECG) gated MR (Turbo-FLASH :TE=6,TR=12,Flip=12°,TI=100) 10 to 45 and up to 90 seconds after bolus injection of Gd-DTPA (0.04 mmol/kg) using a Siemens 1.0T Magnetom SP. Stress was induced within the MRI scanner (0.56 mg/Kg DP over 4 minutes) followed by stress MRI after a second bolus of Gd-DTPA in the same position and identical time intervals. Comparison was made with simultaneously obtained rest and stress SPECT imaging after administration of 7-10mCi (259-370 MBq) and an additional 10-30 mCi (370-1110 MBq) of Tc99m-sestamibi respectively.

Results: Analysis of the subtraction images and the integrated stress and rest images combined yielded sensitivity and specificity of 90% (95%CI:80-99%) and 91% (95%CI:82-99%) respectively in detecting myocardial ischemic zones compared to SPECT. McNemar analysis determined that subtraction MRI is comparable to SPECT analysis.

Conclusion: Turbo-FLASH can provide adequate time and spatial resolution in cardiac perfusion MRI with detectable changes during DP stress. These changes in perfusion are comparable to SPECT when time-signal curves are analyzed using an objective radial technique.

INTRODUCTION

Intravenous administration of Gd-DTPA improves in vivo imaging of myocardial infarction as Rehr [1] found that infusion of Gd-DTPA after 1 to 2 days of coronary artery occlusion in dogs moderately improved the conspicuity of the infarcts on in vivo MR images, whereas infusion of the contrast agent after 4 to 5 days of coronary artery occlusion markedly improved infarct conspicuity. McNamara [2] showed alterations in myocardial relaxation times that occurred after 2 minutes of coronary artery occlusion in a canine model when Gd-DTPA was injected after the first minute of occlusion. In another canine study, Gd-DTPA [3] was infused 2 minutes after coronary artery occlusion, followed by heart excision 1 minute later. These studies have implied that, in an experimental setting, early myocardial ischemia can be detected with Gd-DTPA before the onset of myocardial edema formation or irreversible ischemic

damage.

These findings suggest that MR contrast enhancement of normal and infarcted myocardium depends on the duration and timing of image acquisition relative to contrast material administration. Because of the rapid extravascular redistribution of Gd-DTPA, rapid MR imaging techniques are required for Gd-DTPA to be useful in evaluating perfusion or blood-volume abnormalities such as early myocardial ischemia. The ongoing development of such techniques by Wilke and others [4] has shown the increased utility of Gd-DTPA in the study of ischemia. Following the work of Klein [5] using Dipyridamole to enhance regional blood flow differences with turboFLASH MR imaging during dynamic enhancement with Gd-DTPA complex quantitative analysis techniques have followed to evaluate MR and Scintigraphy [6]. This was followed by modeling the wash-in of Gd-DTPA in the heart by Matheijssen et, al. [7]

which also required sophisticated curve generation and analysis. Thus an objective visually based comparison technique to evaluate stress and rest MR time-signal curves has been developed for single slice acquisition with a "radial" presentation. This paper describes a new analysis technique and it is compared to (Tc99m hexakis-2-methoxyisobutylisonitrile) Tc99m-Sestamibi SPECT which is the current standard for clinical evaluation of myocardial perfusion [8]. Though parametric maps have been investigated by others [9] we present here the results of radial MR zonal categorization of myocardium as normal, ischemia, or infarction based on evaluation of radial images determined by myocardial Gd-DTPA kinetics as compared to Tc99m-Sestamibi SPECT.

METHODS

SUBJECTS

Ten patients (8 males, 2 females) who were referred for scintigraphic stress scintigraphy due to symptoms indicative of myocardial ischemia (unstable angina with ECG abnormalities) and who were expected to be evaluated with coronary angiography within 24-48 hours were recruited. The mean age of these patients was 57 years (range: 49-77) with a mean weight of 77 Kg (range 60-114 Kg). The described protocol was submitted and approved by the institutional review board committee at our institution. Criteria for inclusion in the study were: 1) the ability to safely undergo pharmacologic stress, 2) no unstable angina, 3) no contra-indication to MR imaging, 4) the ability to give informed consent, and 5) no cardiac event or significant change in clinical status between all imaging studies. Informed consent was obtained after the procedure was fully discussed with each subject. Each subject abstained from any substances containing xanthines for 48 hr and fasted for 8 hr, all other medical therapy was continued as prescribed. Vital signs and ECG were obtained prior to the examination and ECG leads were placed on the back. All subjects were imaged on a Siemens Magnetom 1.0T unit (Siemens Medical Systems, Iselin, NJ) in a supine position using the vendor supplied torso coil. Preliminary resting MR images were obtained during the administration of 0.04 mmol/kg gadopentate dimeglumine (Magnevist, Berlex, Montvale, NJ.).

IMAGING PROTOCOLS

Preliminary rest scintigraphic images were performed in the nuclear medicine area under physician supervision and the patient was administered 7-10mCi (259-370 MBq) of

Tc99m-sestamibi (Dupont, Billrica MA) at rest and SPECT images were obtained on a planar camera (Siemens Orbiter, Hoffman Estates Ill) with a Strichman medical equipment 600 system (Strichman, Medfield MA) and a Macintosh IIVX (Apple, Cupertino, CA). The patient was then escorted to the MR unit a short distance away. ECG leads were placed on the patients back and the patient was placed into the MR unit, and preliminary MR images were obtained during the administration of 0.04 mmol/Kg gadopentate dimeglumine (Magnevist, Berlex, Wayne NJ).

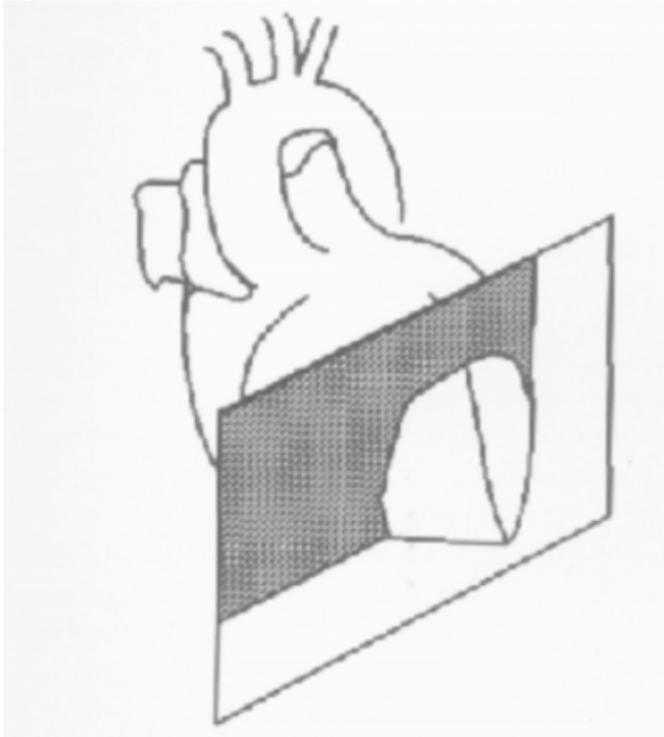
MRI PROTOCOL

The fast imaging method used in this study relies on a gradient echo sequence with a very fast repetition time (TR) and a reduced number of phase encoding steps. A very short echo time (TE) minimizes signal loss due to local magnetic field inhomogeneities (T2* effects) and flow-related dephasing. To emphasize T1 contrast, the data acquisition interval is prefaced with a 180° inversion pulse. Because the total time for data acquisition is short relative to the T1 of the myocardium, tissue contrast is similar to a standard inversion-recovery sequence with an infinite TR. The inversion time (TI) is selected to null the signal from the unenhanced myocardium. During contrast administration myocardium perfused by Gd-DTPA will produce nonzero signal. Low flip angle ECG gated MR imaging with predominantly T1-weighted imaging parameters performed 10 to 45 and up to 90 seconds after rapid bolus injection of Gd-DTPA with images every 3-4 seconds, each within a breathhold (at end inspiration), similar to the technique reported by van Ruggie [10] with the Turbo-FLASH technique (as a single shot) was the basic acquisition technique [11] using a short axis double oblique angulation (as demonstrated in figure 1) at a level mid way between the cardiac apex and base. The number of R-R intervals between each acquisition was chosen to be as close to 3 sec as possible (for example if heart rate is 75 then R-R interval is 800 ms and 4 R-R intervals is 3.2 sec) to allow full T1 relaxation between each image [18]. Twenty minutes later (to allow dominant clearance of most of the Gd-DTPA) the subject was administered 0.56 mg/Kg of Dipyridamole over a 4 min period under constant physician supervision with ECG , blood pressure, and pulse monitoring using a Marshal TM94 digital BP monitor (Omron Health, Vermont Hills, Il) and oxygen saturation measurements with a 4500 MRI Pulse oximeter (In-vivo medical instruments Winter Park, Fl). Two minutes later an additional 0.04mmol/Kg gadopentate dimeglumine was given by bolus technique as was an additional 10-30 mCi (370-1110 MBq) of Tc99m-sestamibi.

Stress MRI images were therein obtained with the same technique and angulation. Sixty minutes after stress the SPECT images of the heart were obtained back in the nuclear medicine area.

Figure 1

Figure 1: Short axis slice at mid heart level half way between apex and base is where MRI studies were performed and compared to comparable level scintigram data.

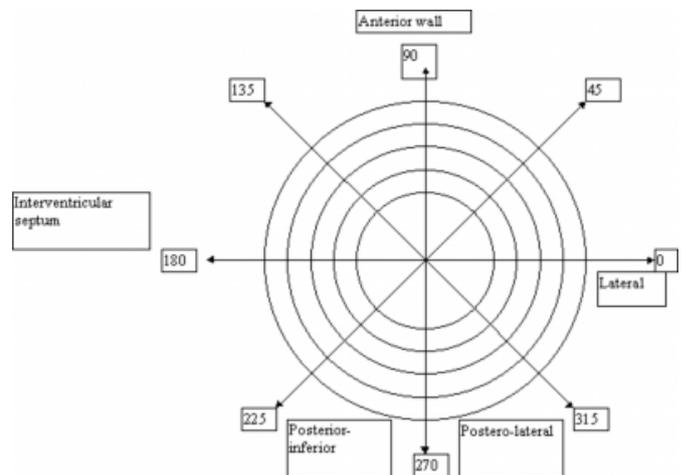


All patients were imaged on a Siemens Magnetom 1.0T unit (Siemens medical systems, Islin NJ). Short axis turboFLASH images of the heart were obtained with the double oblique method described by others [5]. Imaging parameters included a bandwidth of 350 HZ/pixel, a repetition time (TR) of 12msec, and an echo time (TE) of 6 msec. The flip angle was 12°. Representative image is demonstrated in figure 3. An inversion time of 400 msec was selected. Since the myocardial T1 relaxation time at 1.0T of approximately 750 msec the null point for the tissue calculates to 500 msec. Because the net imaging time was 380 msec, the central views in k space, would be acquired at 590 msec (400+380/2), within the theoretical null point for myocardium. The images obtained were 10m thick and 64 X 128 interpolated to 256 x 256 with a 35-cm field of view (FOV). After the intravenous (via antecubital vein) bolus of 0.04mmol/Kg of gadopentate dimeglumine was administered, imaging was begun immediately so that 20-30 short axis images were obtained at the same level every 3-4

heart beats with interpolated voxel size of 1.37 x 1.37 x 10mm. All images were prospectively triggered from the R wave of the cardiac cycle and all were obtained within 380 msec during the RR interval. The patients were instructed to breathe quietly and to stop breathing during each brief acquisition which provided reproducible slice positioning. The relationship between signal intensity and contrast concentration [12] and thus perfusion has been shown by others using similar MR techniques [13].

Figure 2

Figure 2: Radial sectors are measured in 45 degree increments and the time signal curves are collected for each sector. This data is normalized and interpolated to create the radial analysis presentation. Each concentric shell represents a time point, hence the signal intensity at radial position 0 corresponds with the signal intensity as a function of time at the lateral wall. In this example 4 shells correspond to 4 sequential time measurements.



SPECT PROTOCOL

Tc99m-sestamibi images using technique similar to that of Taillefer [14] were obtained with a wide FOV rotating gamma camera (Siemens Orbiter, Hoffman Estates, IL) equipped with a low-energy, high-resolution parallel-hole collimator. Thirty-two images over 180° arc (45 sec per view for all images) were acquired from the right anterior oblique position to the left posterior oblique position. Both stress and rest imaging data were reconstructed in short-axis, vertical long-axis, and horizontal long-axis tomograms using a 64x64 matrix.

ANALYSIS OF MR IMAGES

The MR images were analyzed in a prospective manner both quantitatively and qualitatively by 2 reviewers who were blinded to each others results and to other imaging data. The immediate post contrast images were qualitatively evaluated

for perfusion defects. Images were transferred onto a Macintosh Quadra 950 (Apple, Cupertino CA) with analysis performed using the NIH Image V.1.49 (NIH, Bethesda MD) program. Signal intensity was measured with an operator-adjustable circular region of interest, which was set at 30 pixels. Signal intensity measurements were obtained circumferentially along the myocardium with the anterior wall defined between 45-135°, the interventricular septum (135-225°), the posterior-inferior wall (225-270°), the postero-lateral wall (270-315°), and the lateral wall (315-45°) as delineated in figure 2. Similar measurements of the pectoral muscle, right and left ventricles, and epicardial fat were performed. Once the region of interest was placed for a particular measurement on the baseline image, it was kept constant in position and size with respect to the myocardium with adjustments made to compensate for respiratory induced motion within the field of view for subsequent images. All signal-intensity measurements on MR images were standardized to (divided by) the signal intensity of the epicardial fat and logarithmic scaling was calculated by $-\text{Log}(SI(t)/SI(0))$ (where $SI(t)$ is signal at time t , representative curves are shown in figure 4). Note that $SI(0)$ is the standardized (relative to epicardial fat) value of myocardial signal intensity before gadolinium administration (at time zero). The linearity of this transformation for the dose and imaging protocol used has been established in other studies [13,15]. Note that the prior demonstration of lack of change in cardiac output during the early washin phase allows for processing of washin kinetics data at stress and rest without having to correct for potential effects due to change in cardiac output [13,17].

Figure 3

Figure 3: Representative short axis MR image showing contrast in both ventricles.



Figure 4

Figure 4a: Representative signal-time curves for 2 representative myocardial sectors (at 0 and 45 degrees) in a 50 year old male subject during rest state. Note that the y axis has been normalized as described in methods.

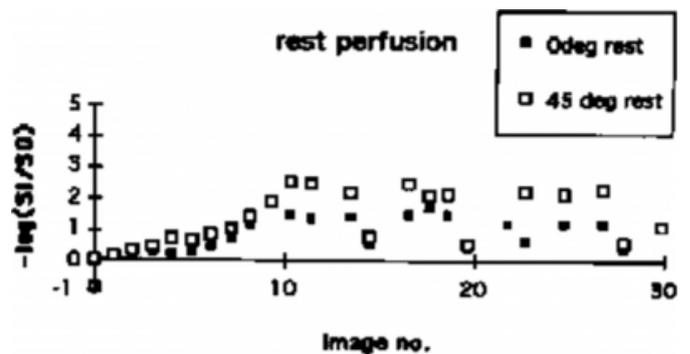
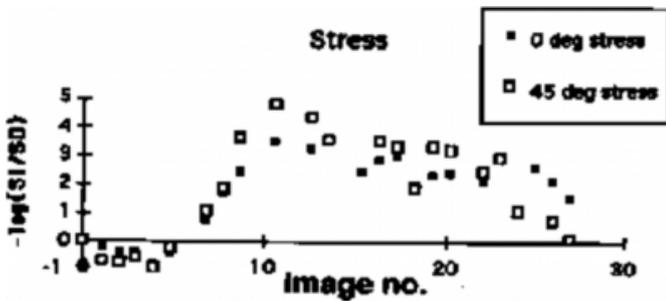


Figure 5

Figure 4b: Representative signal-time curves for 2 representative myocardial sectors (at 0 and 45 degrees) in a 50 year old male subject during stress state. Note that the y axis has been normalized as described in methods.



ANALYSIS OF SPECT IMAGES

The SPECT data were evaluated prospectively by two other reviewers who did not know any of the other imaging results. The anterior wall, antero-lateral wall, postero-lateral wall, posterior/inferior wall, and interventricular septum were each evaluated at a level midway between apex and base. Myocardial segments that demonstrated decreased activity in the stress SPECT study were labeled as perfusion defects. Abnormal walls were then further characterized as either reversible or fixed defects on the basis of the rest SPECT study. The kappa statistic was applied to test the observer agreement for the SPECT technique [16].

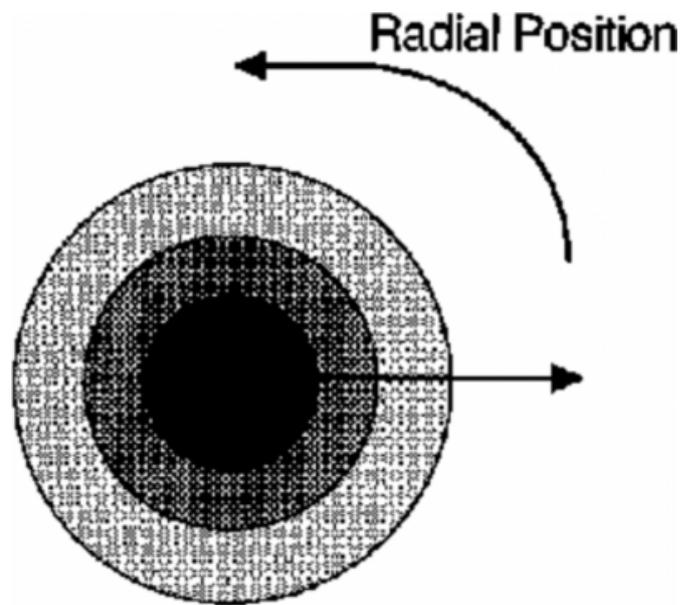
QUANTITATIVE ANALYSIS

The MR time signal analysis curves were then reprocessed using Mathematica 2.0 (Wolfram Research, Urbana, IL) on a Macintosh Quadra 950 (Apple, Cupertino, CA) and a "radial" time signal analysis display. This methodology maps the individual myocardial time-signal curve into concentric shells which represent increasing time along a given radial position of the myocardium, a conceptual diagram is presented in figure 5. The white areas represent high signal intensity, the dark areas represent the low signal intensity. Thus in the "radial" approach the signal in each myocardial segment is mapped as concentric circles where time increases as one travels out in a radial direction. Stress, rest, and subtraction (stress-rest) images were generated and all were evaluated compared to the SPECT interpretations at a slice midway between base and apex based on segmental analysis (anterior, antero-septal, septal, infero-septal, inferior, infero-lateral, lateral, and antero-lateral) using McNemar analysis with 95% confidence intervals calculated for the population. Note that this methodology only presents perfusion at a given short axis slice of myocardium over time over the complete thickness of the myocardium at that

point in time since the data is arrived at from the ROI placed on the myocardium. In particular dynamics relating Gd-DTPA signal enhancement in ischemic myocardium will demonstrate delayed wash in during stress. Infarcted myocardium will demonstrate slow and steady wash in due to leakage into the extravascular space that is more rapid than in normal myocardium. It is also to be expected that hibernating myocardium should demonstrate normal washin and washout though perhaps with delayed peak due to diminished blood perfusion [2,3,7]. As such on the subtraction images normal perfusion is uniformly gray (i.e. neutral shade), a fixed defect is "bright" early on due to the greater amount of water in the infarct available to interact with Gd-DTPA during stress and a reversible defect is "dark" due to filling in of defect at rest with delayed or uniform washing of contrast.

Figure 6

Figure 5: Concept behind radial analysis relies on concentric shells where intensity level at a given position is a function of time (shell, or distance from center), and position in the myocardium (radial).



RESULTS PATIENTS

Though all had a measurable response to DP with depression of blood pressure, none had a depression of blood pressure requiring clinical intervention. There was compensatory elevation of heart rate during stress with the heart rate (HR) - mean arterial pressure (MAP) product stable over the imaging period. Though the product of HR*MAP is a measure of cardiac work and not function, the HR*MAP product was normalized by dividing by the baseline

HR*MAP product before initiation of stress over the first 10 minutes remained at 0.95 ± 0.08 , indicating essentially no change in cardiac function or net output, corroborating previous measures of cardiac output during Dipyridamole stress [13,17]. No subject suffered complications from the examination, and none required premature aminophylline reversal (criteria for this were; angina of greater than 4/10, shortness of breath, or dysrhythmias), but 100 mg aminophylline IV was administered routinely after all studies were completed. Of the ten subjects examined 3 were diabetic (2 males, 1 female). Since the goal was to compare the radial analysis of Gd-DTPA kinetics in myocardium with SPECT evaluation of perfusion, coronary angiography results were not included in this analysis and thus are not presented.

DATA ANALYSIS

All SPECT studies were classified as diagnostic quality without motion or other artifacts. Kappa statistic demonstrated excellent interobserver agreement ($K:0.80$) in SPECT interpretation. Comparison of only the radial stress images to mid heart SPECT as gold standard after classifying each segment as normal, ischemic or infarcted on SPECT and on the Radial images demonstrated sensitivity and specificity of 75% (95%CI:55-95) and 75% (95%CI:55-95). Analysis of the subtraction images improved sensitivity to 90% (95%CI:80-99%) and specificity 91% (95%CI:82-99%). McNemar analysis established that subtraction MRI (images generated after subtracting the rest image from the stress image) is identical to SPECT analysis at the $P < 0.05$ level within 95% confidence intervals. Representative normal, ischemic and infarcted segments are presented in figure 6.

Figure 6: A representative mid level SPECT image in a 66 year old male that underwent stress perfusion MRI and scintigraphy demonstrated a fixed inferoapical defect and reversible posterolateral defect on scintigraphy (6a). This is identified on the radial image by a stress defect (white arrow on 6b) that persists at rest (6c). The area of ischemia is identified by the area of delayed contrast uptake (black arrow 6b) that has greater contrast uptake at rest (white arrow 6c). Subtraction image denotes a fixed (infarcted) defect as having white in the center and progressing radially out white a reversible defect has a delayed outer ring of white areas. Note gray denotes no defect or change in perfusion.

Figure 7

Figure 6a: A representative mid level SPECT image in a 66 year old male that underwent stress perfusion MRI and scintigraphy demonstrated a fixed inferoapical defect and reversible posterolateral defect on scintigraphy



Figure 8

Figure 6b: These defects are identified on the radial analysis by a stress defect (white arrow on 7b) that persists at rest as seen in figure 6c. The area of ischemia is identified by the area of delayed contrast uptake (black arrow 6b)

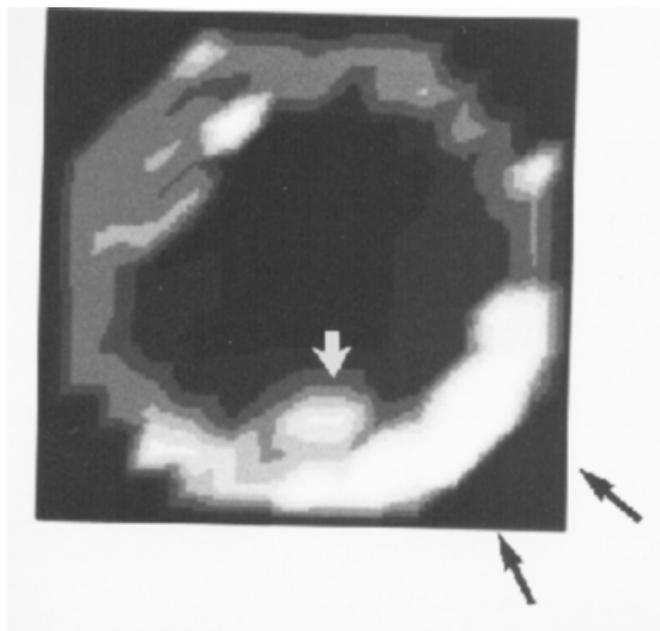


Figure 9

Figure 6c: The area of ischemia identified by the area of delayed contrast uptake by the black arrow in 6b has greater contrast uptake at rest (white arrow 6c)

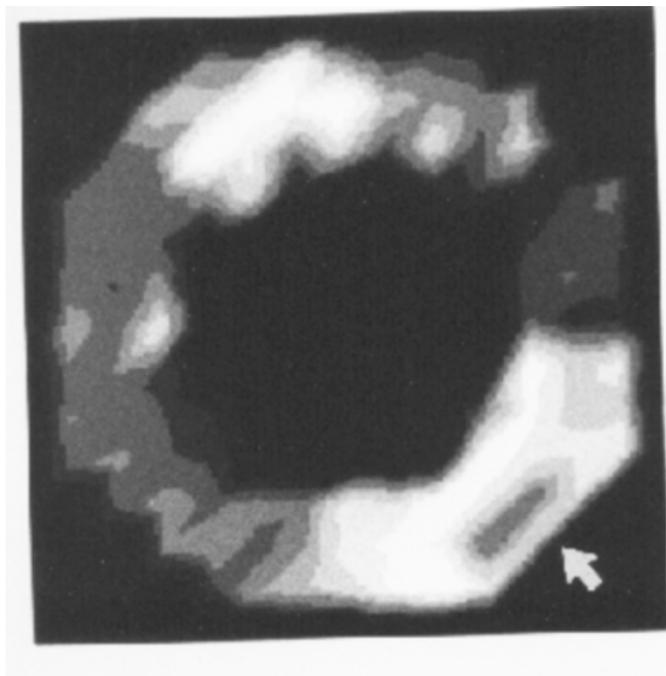
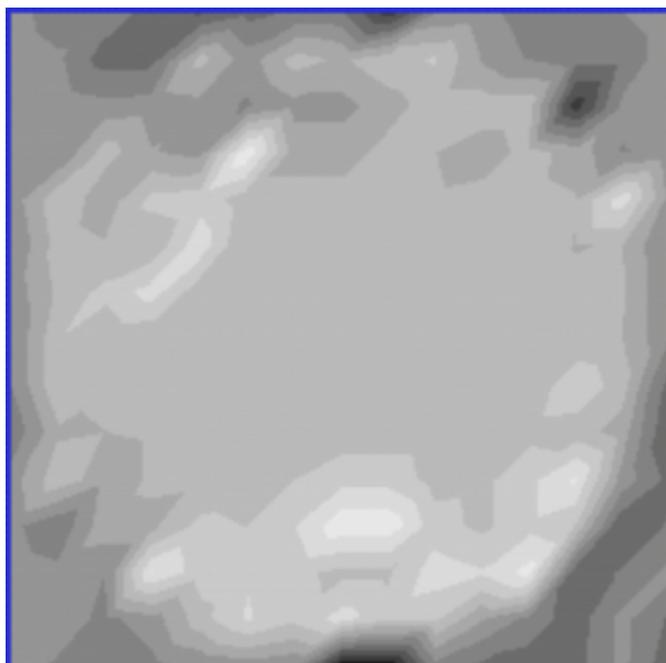


Figure 10

Figure 6d: The subtraction image denotes a fixed (infarcted) defect as having white in the center and progressing radially out white, a reversible defect has a delayed outer ring of white areas. Note gray denotes no defect or change in perfusion.



DISCUSSION

More recent investigation of Gd-DTPA as a myocardial perfusion agent has involved rapid imaging techniques to define time-dependent accumulation of the agent in normal and ischemic myocardium during the first pass after intravenous injection [10,18]. Differential enhancement of myocardium is proposed to be due to greater blood flow to and greater blood volume in viable myocardium, whereas differential enhancement in ischemic and infarcted tissue may be due to increased extracellular space and resulting increased permeability of the damaged cell membrane in the infarcted tissue. Though Klein et. al.[5] have represented discrepancy in MR and SPECT which they attribute to small perfusion abnormalities which yielded a sensitivity of 77% and specificity of 75% which are comparable to our stress only analysis, they were limited to 5 patients, and did not perform Gd-DTPA enhanced images at rest to compare to. In addition in Klein's work there was normalization to an arbitrarily chosen normal wall, thus creating a difficult scenario should a patient with no normal myocardium be analyzed with their technique. Additionally no compensation for magnetic susceptibility effects when the contrast bolus is in the right ventricle and not in the left ventricle causes suppression of septal signal intensity was accounted for [5].

In other studies, the work of Pennel established the utility of MR imaging but perfusion imaging was not performed [19]. In the work of Schaefer [20] similar radial analysis of stress only images were performed, however patients with infarcts were excluded, thus this population data set was not available for potential normalization. In particular the ability to generate a quantitative difference image enhances the ability to identify fixed and reversible defects. These results demonstrate that Turbo-FLASH can provide adequate time and spatial resolution in cardiac MR perfusion imaging and may be a promising tool for non-invasive assessment of myocardial perfusion. Advantages of MR imaging over SPECT include improved spatial resolution, lack of ionizing radiation, no time delay incurred between stress and perfusion imaging, and the potential ability to obtain ventriculometric parameters at the same study.

The biggest limitations in this study stems from the single level imaged and from the assumption of the ability to linearly correct Gd_DTPA signal enhancement to a measure proportional to actual concentration. The ability to image early on with a low concentration of Gd-DTPA does attempt to minimize these undesired effects. It is anticipated that multilevel imaging would also increase the sensitivity of this

technique. Because images were obtained over multiple heartbeats images did suffer from motion blurring with resulting poor differentiation of subendocardial and transmural abnormalities with imaging limited to a single slice of myocardium representing 10% of all myocardial tissue. In addition inter- and intra observer evaluation of this means of presenting data will need to be quantified with larger numbers to validate the accuracy of a subjective visual analysis of myocardial perfusion. Though theoretically deconvolution might be necessary to quantify myocardial perfusion MR prior work demonstrates that the input functions at rest and stress are comparable, thereby simplifying analysis [13]. Lastly the use of a baseline study with subtraction analysis allows a potential standardization of measurement in each individual patient, however further work will be necessary to validate this technique in a larger population of patients.

In conclusion, at the dosage used, the signal enhancement using this MR protocol is proportional to perfusion with Gd-DTPA and shows reasonable correlation with the results of nuclear myocardium perfusion imaging, particularly when coupled to objective subtraction analysis as is possible with the "radial" methodology presented herein.

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APPENDIX

A sample analysis for generating the Radial plot of single slice perfusion during first pass perfusion MR is presented herein. Resting is an array of sequential vectors of 8 values. In each vector the values consist of the normalized signal intensity at positions 0, 45, 90, 135, 180, 225, 270, and 315

degrees as shown in figure 2. Each sequential vector represents a new point in time. Stress is a similar array for the stress images. The command
ContourPlot[GetIt[Resting,(Abs[(x+I*y))-
.5),Arg[x+I*y]],{x,-1.5,1.5},{y,-1.5,1.5}] generates the radial plot for the resting state. The command
ContourPlot[GetIt[Stress,(Abs[(x+I*y))-
.5),Arg[x+I*y]],{x,-1.5,1.5},{y,-1.5,1.5}] generates the radial plot for the stress state and the command
ContourPlot[GetIt[Stress,(Abs[(x+I*y))-
GetIt[Stress,(Abs[(x+I*y))-
.5),Arg[x+I*y]],{x,-1.5,1.5},{y,-1.5,1.5}] generates the radial plot for the difference or subtracted situation.

In this example There is uniform perfusion at stress and rest with assumption of a residual baseline Gd-DTPA concentration, thus the subtracted image being a solid grey indicates no ischemia or infarcted areas.

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