

# QUANTITATIVE ISCHEMIA DETECTION DURING CARDIAC MR STRESS TESTING

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**Abstract-** Because ECG alterations due to ischemia cannot be reliably detected in the high-field MRI environment, detection of wall motion abnormalities are often the only method to ensure patient safety. In this study, we investigate the use of real-time Harmonic Phase (HARP) MRI for the quantitative, operator-independent detection of the onset of ischemia during acute coronary occlusion. Six mongrel dogs underwent acute coronary artery ischemia of 2 minutes' duration while continuous HARP MR images were acquired followed by 5 minutes of reperfusion. During a second ischemic episode, conventional cine wall motion images were acquired. The time from occlusion to the detection of ischemia by each MR technique, as well as ECG ischemic alterations, was determined. In 5 of 6 animals, the onset of ischemia was detected significantly earlier by HARP than by cine MRI ( $11 \pm 5$  s HARP vs.  $34 \pm 14.8$  s cine,  $P < 0.03$ ). HARP ischemia detection preceded ECG changes, on average, by 66 seconds. Cine MRI did not detect ischemia significantly earlier than when ECG changes were apparent ( $P = 0.11$ ). The rapid acquisition and detection of ischemia using HARP MRI shows promise as a non-subjective method to diagnose significant coronary lesions in patients while ensuring patient safety during stress testing.

**Keywords** – MRI, MR tagging, cardiovascular function

## I. INTRODUCTION

The safety of cardiac MRI stress testing has been questioned due to the inability to reliably detect ischemic-induced ECG changes in the high-field environment [1]. Often, wall motion changes precede these ischemic ECG changes [2]. However, the detection of these wall motion abnormalities is often subjective and requires an experienced observer for interpretation. A real-time **quantitative** MR imaging technique to detect the onset of ischemia during a stress test would enhance patient safety. In this paper, we describe a method for imaging and detecting the development of ischemia using a novel imaging sequence based on HARP principles [3] that shows promise for replacing subjective real-time techniques such as cine MRI. In order to test the utility of this new real-time HARP MRI acquisition and analysis technique, we determined the time to detection of induced ischemia in a controlled animal model of acute

coronary occlusion relative to time to ischemia detection using conventional cine MRI scan techniques.

## II. METHODOLOGY

### A. Harmonic Phase (HARP) Imaging

Harmonic phase (HARP) imaging was based on the knowledge that SPAMM-tagged MR images [4, 5] have distinct spectral peaks in the Fourier domain. Each spectral peak contains motion information in a certain direction relative to the tags. By taking the inverse Fourier transform of a single spectral peak, a complex image is formed which has a phase that is linearly related to a directional component of the true motion. The material points that share the same harmonic phase in successive cardiac phases can be determined to track small motions [6]. Moreover, the gradient of the phase images from two orthogonal sets of SPAMM tag lines can be calculated to determine the 2D deformation or strain [7].

Real-time HARP imaging exploits the concept that only one of the spectral peaks for each tag direction must be acquired. Thus, a limited portion of the k-space data centered around the spectral peak can be acquired (Fig. 1) thereby reducing image acquisition time without sacrificing information about myocardial motion and strain.

### B. HARP MR Imaging Protocol

The real-time HARP pulse sequence was acquired using an ECG-gated, multiphase, interleaved, fast gradient-echo echoplanar imaging (EPI) pulse sequence. A 1-1 SPAMM tagging pulse (two

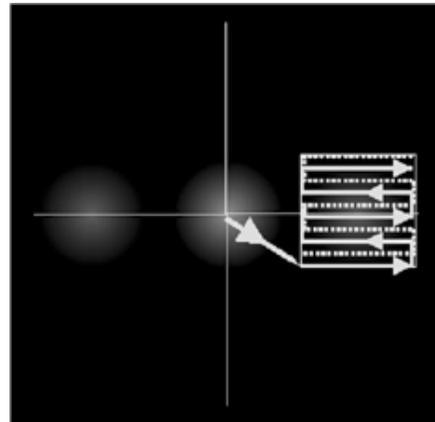


Fig. 1 – In real-time HARP imaging, a limited number of lines of k-space are acquired around a single spectral peak.

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90° radiofrequency pulses separated by a gradient pulse) was played out immediately after detection of the R wave so that the tags were laid down at end-diastole. A single short-axis imaging slice was repetitively acquired to monitor for the presence of ischemia.

Pulse sequence parameters were optimized to achieve maximum SNR without extending acquisition time. A single spectral peak in k-space was selected using the read dephaser and phase encoding gradients. The vertical and horizontal tag lines were played out on successive heart beats to acquire a complete tagging grid every other heartbeat. On each heartbeat, a 32x32 matrix was acquired, centered on the spectral peak (see Fig. 1). Multiple cardiac phases were acquired each heartbeat for 60% of the cardiac cycle. Temporal resolution of each HARP image was ~ 46 msec.

In addition, a train of increasing imaging flip angle was used to provide more constant image intensity throughout the cardiac cycle and minimize fading due to T1 decay. Other imaging parameters were: 62.5 KHz BW; 28 cm FOV; TR=11.2 ms; ETL= 8; 32 views per segment (vps); 0.875 mm tag spacing; 10 mm slice thickness; and 15° flip angle.

MR k-space data was synchronously transferred to an external Sun Ultra II workstation (Sunnyvale, CA) The 4-coil, 32x32 data sets were interpolated to a 128x128 image matrix for real-time reconstruction and display of synthetic tagged images.

Synthetic tagged images were created by running an isocontour algorithm at an arbitrary angle on the HARP phase images [7]. The synthetic tagged images from the vertical and horizontal HARP phase images were combined using the data from the 2 preceding heartbeats to create a multiphase, grid tagged movie that was displayed on the workstation. The real-time HARP cine movie loop was updated with new data from the succeeding R-R interval, such that the movie loop was refreshed every other heartbeat. Images were played out in real-time at the patient's heart rate. Circumferential strain was calculated from the HARP images and overlaid as a pseudocolor map on the synthetic tag images for determination of strain alterations.

### C. Cine MR Imaging

Cine MR images were acquired using the standard cine monitoring mode for stress testing on our 1.5 T cardiovascular MR scanner (CV/i, General Electric, Milwaukee, WI). The cine monitoring mode is a non-ECG-gated, fast gradient echo EPI sequence. The imaging parameters were: 125 KHz BW; ETL=8; TR=11.2; TE=1.2; 128x128 matrix; and 64 vps. Due to image buffer limitations, only approximately 30 seconds of images could be acquired at a shot. Thus, small pauses to restart the scan occurred during the 2-minute cine acquisition.

After two studies, an improved cine monitoring mode was developed using a Fast Imaging Employing STeady-state Acquisition (FIESTA) pulse sequence [8]. Because of the improved image quality, 2D FIESTA cines were acquired during the second occlusion for the remaining studies. The imaging parameters were: 125 KHz BW; 128x256 image

matrix interpolated to 256x256; 28cm FOV; 0.5 NEX; 0.7 phase FOV; TR=3.9 ms; TE=1.9 ms; 45° flip angle; and 12 vps.

### D. Animal Protocol

All animal studies were approved by our Institutional Animal Care and Use Committee and comply with the "Guide for the Care and Use of Laboratory Animals" (NIH Publication no. 80-23, revised 1985). Six mongrel dogs (20-25 kgs) were preanesthetized with 10 mg/kg ketamine, 2.4 mg/kg xylazine, and 0.02 mg/kg atropine intramuscularly. The dogs were induced with 25 mg/kg intravenous thiopental, intubated, and mechanically ventilated with 1-2 % isoflurane and 100% oxygen.

A right carotid artery cutdown was performed to place a 10 F introducer sheath (Meditech, Boston Scientific, Natick, MA). A 6 Fr pigtail catheter (Cordis, Diamond Bar, CA) was advanced via the carotid artery into the left ventricle (LV) for injection of radiolabeled microspheres to measure baseline regional myocardial blood flow. The pigtail catheter was then removed.

Prior to coronary catheterization, the dog was placed on a continuous infusion of intravenous lidocaine (2 mg/kg/min). The electrocardiogram and arterial blood pressure were monitored throughout the remainder of the study. From the carotid introducer, the left main coronary artery was engaged under x-ray fluoroscopy with an 8 F right Judkins guiding catheter (Cordis, Diamond Bar, CA). A 0.014-inch coronary guidewire was advanced into either the left anterior descending (LAD) or left circumflex (LCX) coronary artery. A deflated coronary angioplasty balloon (Cordis, Diamond Bar, CA) was advanced over the guidewire into the proximal LAD or LCX. The guiding catheter was then removed from the left main coronary artery without disturbing the angioplasty balloon.

After balloon placement, the animal was transported to the adjacent MRI suite. Once at the MR scanner, the guidewire was removed from the coronary artery without disturbing the coronary balloon. All animals were imaged using a 4-channel phased array, transmit-receive coil. The animal was placed in right decubitus and axial scout images were acquired to locate the left ventricle. Five to six short axis scouts were acquired to span the left ventricle.

Acute ischemia without infarction was induced by a 2-minute inflation of the angioplasty balloon while continuous HARP MR images were acquired for 15-30 seconds prior to balloon inflation and 1-2 minutes after balloon inflation to monitor the onset of ischemia. The balloon was then deflated for at least 5 minutes to allow for reperfusion. The balloon was then reinflated for another 2 minutes to induce acute ischemia, during which a cine MR images acquisition were acquired. Intermittent breath-holds were performed by pausing the ventilator at end-expiration during both HARP and cine MRI scans to minimize the effect of respiration.

After imaging, the animal was returned to the x-ray fluoroscopy suite and the pigtail catheter was placed in the left ventricle via a femoral artery approach. The balloon angioplasty catheter was reinflated and injection of radioactive microspheres were injected in the LV to determine the ischemic bed. After humane euthanasia, the chest was opened, balloon placement was confirmed, and the heart was excised and sliced along the short axis planes for 2,3,5-triphenyl tetrazolium chloride (TTC) staining to assess myocardial viability and microsphere analysis to assess regional myocardial blood flow.

### E. Data Analysis

Synthetic grid tagged images were automatically generated from the HARP k-space data using techniques previously described [7]. The apparent 2D circumferential strain was then calculated from the HARP images and overlaid as a pseudo-color display on the synthetic grid tagged images using a MATLAB tool kit. The cine MRIs were displayed as continuously looping movies. The MRI data were interpreted by two investigators without knowledge of the coronary occlusion bed. Myocardial regions of abnormal contraction were identified in the HARP movies as regions with reductions in end-systolic circumferential strain relative to the pre-occlusion state. A consensus of the two observers determined the time after occlusion when the reduction in end-systolic circumferential strain, relative to the pre-occlusion state on the HARP image, could be identified.

The cine MRI movie loops were assessed for hypokinesis and akinesis as evidence of wall motion abnormalities induced by coronary occlusion. The first cardiac phase during which wall motion abnormalities were present was determined by a consensus of the two investigators. Comparison of the time to ischemia detection between HARP MRI, cine MRI, and ECG alterations was determined using a paired Student's t test.

After formalin fixation, the excised heart rings were divided into transmural wedges (approximately 500-900 mg), which were subdivided into 3 transmural layers (i.e., endocardial, midwall, and epicardial). These myocardial samples were weighed and counted in a gamma emission well spectrometer (Model 5986, Hewlett Packard, CA) along with the reference blood samples. Regional myocardial blood flow in the samples was calculated using standard techniques.

All data were expressed as mean  $\pm$  SD with a P value of  $<0.05$  considered statistically significant.

## III. RESULTS

In one animal, no region of ischemia was present with coronary artery occlusion as assessed by radioactive microspheres. No area of wall motion abnormalities was detected on cine MRI or HARP imaging.

### A. Real-time HARP images

Images from representative end-systolic time frames of the real-time HARP acquisition are shown in Fig. 2. In all studies, the pseudocolor map of circumferential strain was a fairly uniform green overlay on the synthetic tag images prior to coronary artery occlusion. A decrease in circumferential shortening or circumferential stretching was seen as a red color in the region of coronary artery occlusion. In some animals, there was an increase in circumferential shortening (seen as a blue area) in the opposite non-ischemic myocardial wall. A graphic portrayal of the alterations in circumferential strain with ischemia for the same animal as in Fig. 2 is shown in Fig. 3.

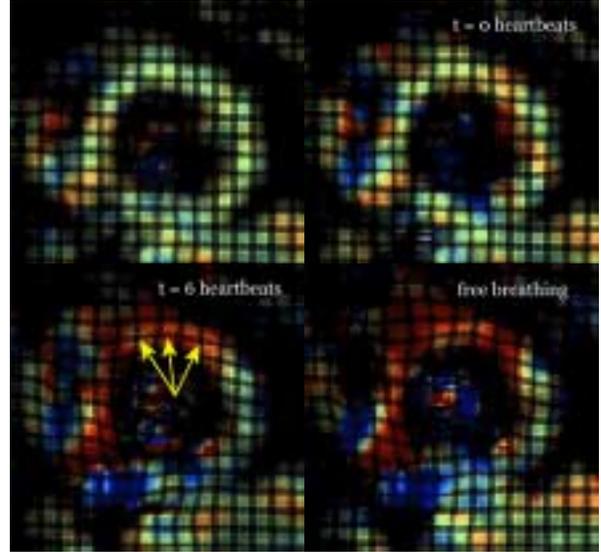


Fig. 2 – Pseudocolor end-systolic circumferential strain map from HARP MRI overlaid on end-diastolic synthetic tag image prior to LAD coronary artery occlusion (top left), at start of occlusion (top right), 6 heartbeats after occlusion (bottom left), and during free breathing (bottom right). The color scale ranges from increased shortening (blue) to no change in shortening (green) to decreased shortening (red). The induced ischemia was detected as a red area at 10 seconds after coronary artery occlusion. The septal wall is from 9 o'clock to 12 o'clock

### B. Ischemia Detection

The onset of ischemia was detected significantly earlier by RT-HARP than by cine MRI ( $11 \pm 5$  s HARP vs.  $34 \pm 14.8$  s cine,  $P < 0.03$ ). HARP ischemia detection preceded ECG changes, on average, by 66 seconds. Cine MRI did not detect ischemia significantly earlier than when ECG changes were apparent ( $P = 0.11$ ). The timing of ischemia detection by animal is given in Table 1.

An LCX coronary occlusion was confirmed post-mortem in two animals; the remaining animals had LAD coronary artery occlusion. Based on TTC staining, all animals had 100% viable myocardium

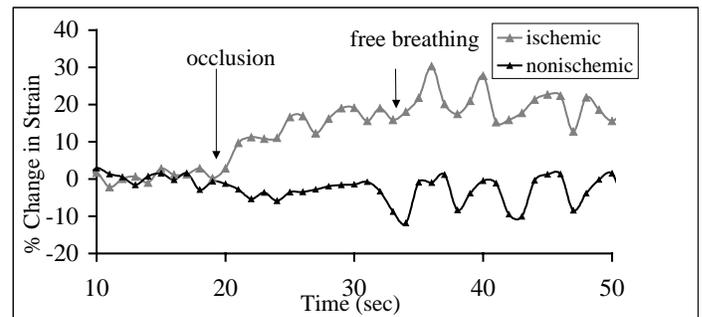


Fig. 3 – Graph of percentage change in end-systolic circumferential strain after coronary artery occlusion in same animal as in Fig.2. Note large decrease in strain in ischemic bed and increase in strain in nonischemic bed after coronary artery occlusion.

Table 1 – Time of Ischemia Detection in Seconds by Study

Study	HARP MRI	Cine MRI	ECG
1	6	25	90
2	6	30	90
3	10	60	38
4	17	24	75
5	15	31	45

post-mortem. In addition, microsphere analysis demonstrated severely reduced flow in the occluded coronary bed in 5 of 6 animals.

#### IV. DISCUSSION

Dobutamine stress cardiovascular MRI has been shown to compare favorably with other noninvasive stress imaging modalities, such as stress echocardiography, to identify patients with ischemic heart disease [9-11]. Dobutamine stress MRI may be particularly useful in patients who are unable to undergo stress echocardiograms due to limited acoustic windows. However, the long scan times and the inability to reliably detect ischemic ECG changes in the high field MRI environment have limited the widespread acceptance of dobutamine stress MRI.

Presently, the accepted method for monitoring patients during MRI stress testing is the subjective assessment of wall motion abnormalities. Thus, a team of highly trained individuals, including an observer experienced in interpreting wall motion abnormalities, is required to safely examine patients. While quantitative assessment of wall motion abnormalities using tagging techniques is possible, the analysis of these data sets is typically very time consuming and thus not suited for rapid assessment of ischemic-induced changes.

In this study, we have proposed a rapid image acquisition, which can be performed without breathholding, and a quantitative analysis technique using HARP MRI to detect ischemia. The quantitative results can be obtained with minimal delay after image acquisition. Because the changes in strain are displayed as a pseudocolor map, the observer training that is required is minimal. Thus, we have presented a technique that circumvents many of the problems of conventional cine wall motion studies. Moreover, in this pilot study of an animal model of induced ischemia, the wall motion abnormalities were detected significantly earlier than with conventional cine wall motion assessment or ECG alterations. The additional time afforded by HARP MRI would allow more rapid intervention to circumvent an adverse event in the MR scanner.

The animal model of complete coronary artery occlusion, which we used, represents the most severe ischemic event that we would anticipate in the clinical situation. While there was some concern that the two ischemic episodes would be equivalent, in all studies the pressures and heart rate rapidly returned to values prior to coronary artery occlusion with restoration of normal wall function.

#### V. CONCLUSION

We have demonstrated the potential for rapid acquisition and detection of induced ischemia using HARP MRI, as would be required for safe stress-testing protocols. This technique was able to consistently demonstrate ischemic changes earlier than either ECG alterations or conventional cine MRI. Thus, this method shows promise as a non-subjective method to diagnose significant coronary lesions in patients while ensuring patient safety during stress testing.

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#### REFERENCES

- [1] E. Nagel, H. Lehmkuhl, W. Bocksch, C. Klein, U. Vogel, E. Frantz, et al., "Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography," *Circulation*, vol. 99, pp. 763-770, 1999.
- [2] M. Grover-McKay, M. Matsuzaki, and J. J. Ross, "Dissociation between regional myocardial dysfunction and subendocardial ST segment elevation during and after exercise-induced ischemia in dogs," *J Am Coll Cardiol*, vol. 10, pp. 1105-1112, 1987.
- [3] N. F. Osman and J. L. Prince, "Visualizing myocardial function using HARP MRI," *Phys Med Biol*, vol. 45, pp. 1665-1682, 2000.
- [4] L. Axel and L. Dougherty, "MR imaging of motion with spatial modulation of magnetization," *Radiology*, vol. 171, pp. 841-845, 1989.
- [5] L. Axel and L. Dougherty, "Heart wall motion: improved method of spatial modulation of magnetization for MR imaging," *Radiology*, vol. 172, pp. 349-350, 1989.
- [6] N. F. Osman, W. S. Kerwin, E. R. McVeigh, and J. L. Prince, "Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging," *Magn Reson Med*, vol. 42, pp. 1048-1060, 1999.
- [7] N. F. Osman, E. R. McVeigh, and J. L. Prince, "Imaging heart motion using harmonic phase MRI," *IEEE Trans Med Imaging*, vol. 19, pp. 186-202, 2000.
- [8] T. Foo, V. Ho, and D. Kraitchman, "Single breath-hold single-phase and CINE 3D acquisition using variable temporal k-space sampling," presented at International Society for Magnetic Resonance in Medicine, Glasgow, Scotland, p. 112, 2001.
- [9] D. Pennell, S. Underwood, C. Manzara, R. Swanton, J. Walker, P. Ell, et al., "Magnetic resonance imaging during dobutamine stress in coronary artery disease," *Am J Cardiol*, vol. 70, pp. 34-40, 1992.
- [10] F. M. Baer, E. Voth, L. Karl, C. A. Schneider, P. Theissen, H. J. Deutsch, et al., "Comparison of dobutamine transepophageal echocardiography and dobutamine magnetic resonance imaging for detection of residual myocardial viability," *Am J Cardiol*, vol. 78, pp. 413-419, 1996.
- [11] F. van Ruge, E. van der Wall, S. Spanjersberg, A. de Roos, N. Matheijssen, A. Zwinderman, et al., "Magnetic resonance imaging during dobutamine stress for detection and localization of coronary artery disease. Quantitative wall motion analysis using a modification of the centerline method," *Circulation*, vol. 90, pp. 127-138, 1994.