Stress Perfusion Imaging Of The Celiac Axis Using Turboflash MRI

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Citation

R Tello, G Hartnell, T Hill, A Cerel, J Finn, M Kamalesh, M Cohen, S Lewis. *Stress Perfusion Imaging Of The Celiac Axis Using Turboflash MRI*. The Internet Journal of Radiology. 1999 Volume 1 Number 2.

Abstract

The purpose of this study was to evaluate the ability of cardiac gated Turbo-FLASH MRI to measure the effect of Dipyridamole (DP) on perfusion of the stomach, spleen and liver in patients undergoing DP stress and to establish reproducibility of this technique for the eventual application in screening for mesenteric ischemia, which was briefly evaluated at the splenic flexure of the colon in this work. Turbo-FLASH can provide adequate time and spatial resolution in intra-abdominal perfusion MRI with reproducible changes in hepatic, splenic and gastric perfusion during DP stress. The changes in organ perfusion after DP appear to be intrinsic to the vascular effects of DP and may have clinical importance. Sample size calculation indicates that a controlled study with 165 normals and 165 subjects will be necessary to detect a 20% difference in perfusion between the groups with a power of 0.8.

Portions of this work were funded by a 1992 RSNA research resident award. Portions of this work have been presented at the ARRS 1994, New Orleans LO.

AWARDED with 1994 ARRS PRESIDENTS AWARD

INTRODUCTION

Bowel ischemia or infarction is a difficult problem because of its many clinical presentations and its association with high morbidity and mortality rates (approaching 95%)[1]. Reduced blood flow to the intestine may result from generalized poor perfusion (as in shock or severe left ventricular failure), isolated reduction of blood flow (from occlusion of mesenteric arterial or venous structures), and arterial spasm [1]. The distribution of ischemic regions in the bowel is often sporadic and non-invasive diagnosis can be complicated by collateral communication between the celiac, superior mesenteric and inferior mesenteric arteries. The special case of chronic intestinal ischemia where at least two of these vessels must be compromised can occur in patients with aortoiliac atherosclerotic occlusive disease. Although this is usually asymptomatic, approximately 5% of these patients will have significant mesenteric occlusive disease and are thus at risk for bowel infarction [1].

The purpose of this study was to evaluate the ability of rapid MRI to measure intra-abdominal organ flow and the effects of Dipyridamole on these organs in patients undergoing Dipyridamole stress. It is feasible that if rapid MRI can measure these effects then perfusion MRI may be a viable means to screen, despite a potential high false positive rate, for mesenteric ischemia in at risk patients. This work concentrated on evaluating the perfusion of the organs perfused by the celiac axis with rapid MRI during first pass Gd-DTPA administration and to determine if a consistent relationship exists between the measured perfusion before and after Dipyridamole in the stomach, spleen and liver, the splenic flexure of the colon was included as a representative of mesenteric ischemia. The primary impetus for examination of the celiac axis rather than the bowel perfused by the mesenteric arteries is that it is more common to find single vessel disease in the celiac artery [2]. Thus if celiac perfusion were to be abnormal in a given individual the patient could go directly to invasive angiography. Hence, stress perfusion evaluation of the celiac axis and mesenteric vessels could be used as a minimally invasive screening test to identify patients at higher risk for mesenteric occlusive disease. If the technique can thus be validated the option of using this same technique in evaluating the perfusion of the bowel fed by the SMA and IMA may become feasible as rapid MRI acquires the spatial resolution to evaluate bowel wall perfusion at critical perfusion areas.

METHODS

PATIENTS

Ten subjects (9 males, 1 female) originally referred for evaluation of myocardial ischemia under stress but with no signs or symptoms of mesenteric ischemia, and normal myocardial perfusion studies, were examined using TurboFLASH MRI during bolus injection of Gd-DTPA . The mean age was 57.2 years (range 31-77 yr.) with a mean weight of 81.1 kg (range 60-125 kg). The described protocol was submitted and approved by the institutional review board committee at our institution. Criteria for inclusion in the study included: 1) the ability to safely undergo pharmacologic stress, 2) no unstable angina, 3) no contra-indication to MR imaging, and 4) the ability to give informed consent. 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. 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 body coil. Preliminary resting MR images were obtained during the administration of 0.04 mmol/kg gadopentate dimeglumine (Gd-DTPA, Magnevist, Berlex, Montvale, NJ.). No subject suffered complications from the examination, and none required premature aminophylline reversal, but 100 mg aminophylline IV was administered routinely after all studies were completed. Of the ten subjects examined 3 were diabetic. 1 subject (male, 60 yrs old) with known mesenteric ischemia (stenosis at origin of SMA) was also examined as a representative case to evaluate for differences in response to DP stress compared to the control group. Though the control group does not constitute a totally normal population, it is a group of similar subjects for preliminary data on organ perfusion.

IMAGING 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 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 liver and spleen at 1.0T, tissue contrast is similar to a standard inversion-recovery sequence with an infinite TR. The inversion time (TI) was selected to obtain the greatest nulling of the signal from nonenhanced liver and spleen.

During contrast administration organs perfused by Gd-DTPA will produce nonzero signal. Low flip angle ECG gated MR imaging with predominantly Tl-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, similar to the technique reported by van Rugge [3], with the Turbo-FLASH technique was the basic acquisition technique [4] using a double oblique angulation to image the liver, spleen, stomach and left ventricle was used so that intravascular and parenchymal enhancement could be measured. 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 an 4500 MRI Pulse oximeter (In-vivo medical instruments, Winter Park, FL). Two minutes later an additional 0.04 mmol/kg gadopentate dimeglumine (Magnevist, Berlex, Montvale, NJ.) was given by bolus technique. Stress MRI images were therein obtained with the same technique and angulation.

TurboFLASH images were obtained with a double oblique method [8]. Imaging parameters included a bandwidth of 350 Hz/pixel, a repetition time (TR) of 12 msec, and an echo time (TE) of 6 msec. The flip angle was 12°. A. Representative image is demonstrated in figure 1. An inversion time of 100 msec was selected. Since the mean of hepatic and splenic T1 relaxation time at 1.0 T is approximately 500 msec[5,6], the null point thus calculates to 333 msec. Because the net imaging time was 380 msec, the central views in k space, were acquired at 290 msec (100+(380/2)), within the theoretical null point for the mean value of these organs. The images obtained were 10 mm thick and 64 X 128 interpolated to 256 x 256 with a 35-cm field of view (FOV). After the intravenous bolus of 0.04 mmol/kg of gadopentate dimeglumine, imaging was begun immediately so that 20-30 images were obtained at the same level every 3-4 seconds with voxel size of 1.37 x 1.37 x 10 mm. All images were prospectively triggered from the R wave of the cardiac cycle, and all were obtained within 380 msec during the R-R interval. The subjects were instructed to breathe quietly and to stop breathing during each brief acquisition which provided reproducible slice positioning. A relationship between signal intensity and contrast concentration [7] and thus perfusion has been shown by

others using similar MR techniques [8].

Figure 1

Figure 1: Representative double oblique image including liver, spleen, stomach (arrow), and right and left ventricular chambers

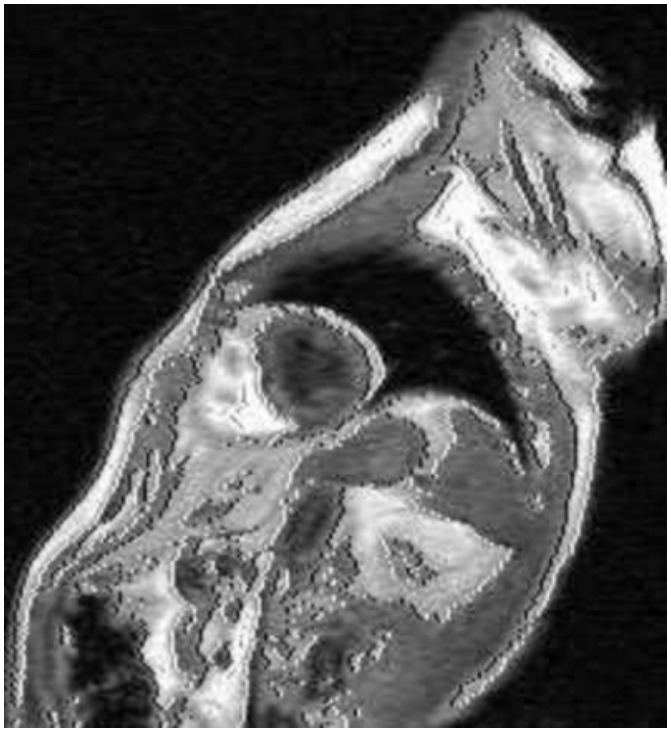
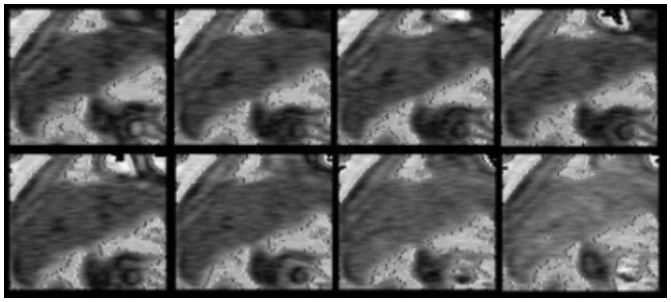


Figure 2

Figure 2: Representative sequential images of the liver during Gd-DTPA administration



ANALYSIS OF MR DATA

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 for the pectoral muscle, left hepatic lobe, and spleen. Gastric wall enhancement was measured using a curved line of 30 pixels along the fundus, enhancement of the splenic flexure of the colon was measured using a circular ROI encompassing the flexure and its contents. Once the ROI was placed for a particular measurement on the baseline image, it was kept constant in position and size with respect to the organ position with adjustments made to compensate for respiratory induced organ motion within the field of view for the subsequent images. All signal-intensity measurements on MR images were standardized to (divided by) the signal intensity of the epicardial fat (which was chosen due to its location within the magnetic isocenter) ; and logarithmic scaling was calculated by -Log (SI(t)/SI(0)) (representative curves are shown in figure 1). Note that SI(0) is the standardized value of signal intensity before gadolinium administration. The linearity of this transformation for the dose and imaging protocol used has been established when evaluating cardiac output elsewhere [8]. Analysis of plateau signal enhancement of each organ was then performed using Microsoft Excel V4.0 (Microsoft, WA) and student's T-test was used to calculate significance [9] , the rise portion of the time-signal curves was analyzed using linear regression and Chow's analysis [10] and comparison between all organs and within each organ before and after stress was performed. The quality of the timing of the study was rated by observing the timing of the intravascular enhancement within the left ventricular chamber, with peak enhancement occurring within 30 seconds of injection.

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. 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 [5,8,11]. None of the patients had any known or documentable liver disease based on biochemistry and scout MRI images

MR ANALYSIS

Analysis of intravascular enhancement demonstrated that peak left ventricular enhancement occurred within 30 sec (range: 20-30 sec) of Gd-DTPA administration and that less than 10% residual signal enhancement was present in all subjects prior to administration of the second bolus of Gd-

DTPA, based on first scan just prior to second injection. Normalizing with respect to the resting muscle perfusion (defined as 1) the plateau relative perfusion values are demonstrated in table 1. The pectoral muscle perfusion was chosen for normalization due to its non-significant enhancement during the bolus Gd-DTPA injection. Each patient signal analysis was performed and percentages calculated on an individual basis with statistical analysis performed on the group as a whole. The effects of changing inversion time between patients were not specifically investigated but signal nulling appeared consistent between patients.

Table 1: Relative perfusion before and after Dipyridamole administration where 1.0 is defined as resting perfusion of pectoral muscle at rest. Value in parentheses represents increase rather than decrease in perfusion.

Normal subjects (n=10)

Figure 3

Organ	Resting Mean perfusion±SI	Stress Mean perfusion±SD	Percent Reduction	P value
Muscle	1.00±0.14	0.23±0.09	75±13%	P<0.01
Liver	5.86±1.10	2.26±0.32	61±11%	p<0.01
Stomach	6.95±0.84	1.83±0.46	74±8%	p<0.01
Spleen	6.60±0.84	4.30±0.54	35±14%	p<0.01
Colon	0.58±0.22	1.44±0.24	(250±48%)	p<0.01

In subject with mesenteric ischemia

Figure 4

Organ	Resting Mean perfusion±SI	Stress Mean perfusion±SD	Percent Reduction
Muscle	1.00	1.0*	0% *
Liver	4.05	3.17*	22% *
Stomach	7.92	2.58	67%
Spleen	15.9 *	5.45	66% *
Colon	6.9 *	2.15 *	69% *

Note * indicates P<0.01 with respect to similar parameter in 'normal cohort'. This demonstrates the difference in response to DP in the control group and the subject with mesenteric ischemia. Since pectoral muscle perfusion is defined as the baseline, the relative lack of change in perfusion in the ischemia subject may be due to lack of statistical power to detect a physiologic change.

EFFECT OF DIPYRIDAMOLE

First pass analysis after Dipyridamole of liver, stomach and splenic perfusion demonstrated rapid enhancement while the pectoral muscle demonstrated minimal enhancement. This was reproducible among all 10 subjects with normalized perfusion values consistent and distinctly different among each organ during the resting state. Performing linear regression on the normalized signal during the rapid intravascular phase, demonstrated statistically significant difference in organ perfusion (P<0.01), with statistically significant depression of liver and splenic perfusion by 61% (P<0.01) and 35% (P<0.01)respectively with a decrease in gastric perfusion by 74% (P<0.01) by paired T-test and Chow's Test for difference between sets of coefficients in linear regressions [10]. These relative changes are shown in table 1. In the subject with mesenteric ischemia the celiac axis changes were comparable however, while in the normal subjects there was effective shunting from the celiac axis to the splenic flexure of the colon, in the subject with mesenteric ischemia there was discordant diminution of perfusion to the colon as shown in table 1.

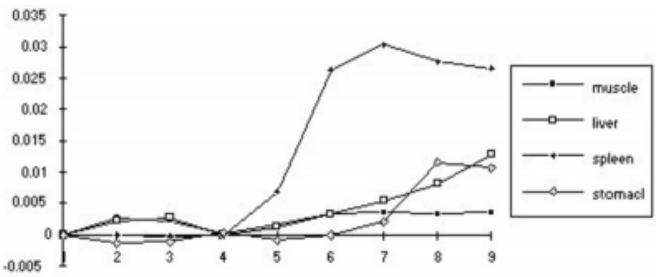
DISCUSSION

Assessing global mesenteric blood flow by determining flow in the mesenteric arteries requires measurement in at least three separate vessels [12]. This is time-consuming and may not be practical, particularly in patients with mesenteric ischemia who may have numerous collateral vessels; consequently noninvasive assessment of organ perfusion may be of utility in the diagnosis of mesenteric ischemia. Significant work has been done to look at cine phase contrast MRA which has been able to demonstrate surgically correctable proximal disease in the mesenteric vessels, however these have been limited to evaluation of proximal locations [13, 14]. Dipyridamole is known to antagonize cellular adenosine uptake and thus inactivation which results in increased concentration of extra cellular adenosine [15]. The decrease in blood pressure observed during Dipyridamole infusion is the result of peripheral vasodilatation and the heart rate increase is a compensatory mechanism for the fall in peripheral resistance. Consequently in the mesentery assessment of perfusion could theoretically be made by evaluating the resulting regional perfusion response to a Dipyridamole challenge as is currently exemplified by Dipyridamole stress scintigraphy of the myocardium, since any perfusion changes would represent regional perfusion effects of Dipyridamole, rather than global changes due to changing cardiac output.

Intravenous administration of Gd-DTPA improves in vivo MR imaging of lesions with very low toxicity [16,17]. The pharmacokinetics of Gd-DTPA are similar to iodinated contrast media and identical to Tc99m-DTPA [18]. Thus the resting Gd-DTPA perfusion imaging of the mesenteric organs should manifest similar kinetics as in other radiographic studies, which is substantiated by figure 3. More recent investigation of Gd-DTPA as a 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 [3, 19]. However, Gd-DTPA is limited as a marker of steady state perfusion because of its rapid equilibration within the extracellular fluid space and rapid elimination by renal excretion. Thus as a minimum rapid imaging during first pass kinetics may be applicable in evaluating mesenteric perfusion. The dominant etiology for differential tissue enhancement is probably due to greater blood flow to and greater blood volume in viable tissue, whereas differential enhancement in ischemic and infarcted tissue may be due to increased extra cellular space and resulting increased permeability of the damaged cell membrane in the infarcted tissue. Hence the ability to measure rapid first pass kinetics of Gd-DTPA has the potential to provide an index of end organ perfusion. We recognize that localized ischemia is not likely to be detected by either this or PC based techniques, but this technique is more likely to become applied for localized disease as the temporal and spatial resolution of MR improves.

Figure 5

Figure 3: Representative resting time signal analysis curves of stomach, liver, spleen, and pectoral muscle as calculated by -Log (SI(t)/SI(0)) during Gd-DTPA administration, horizontal axis represents image number, with images every 3-4 seconds. Horizontal axis represents sequential image number after peak left ventricular enhancement (note that this accounts for R-R patient variability)



Since the use of Dipyridamole stress MRI with Gd-DTPA administration to evaluate for myocardial ischemia appears to be valid [4] it was our hypothesis that this same methodology could be applied to assess ischemia in other organs. In a qualitative manner it is plausible to identify several categories of factors that regulate normal perfusion in the mesentery. In particular it has been postulated that local vasoactive substances and intrinsic properties of mesenteric vascular smooth muscle play an active role in development of ischemia. This has been substantiated by the observation that a majority of patients with ischemia are on cardiac glycosides at the onset of the ischemic state, and research on conscious normal human subjects given Oabain have had splanchnic flow reduced by 30-40% within 30 minutes[20]. The similarity of mechanistic action between Oabain and Dipyridamole on cyclic AMP and the relative similar depression of mesenteric flow in these experiments and celiac axis perfusion in our work appear to support the hypothesis that Dipyridamole may be a valid stressor for evaluation of mesenteric ischemia and that these effects can be measured with cardiac gated Turbo-FLASH MRI.

Teleologically the rational for adenosine mediated decreased perfusion in the liver has been shown in rats. The vasoconstrictive effects of adenosine in rat liver have been potentiated by Dipyridamole. The evidence is supported by the decreased toxicity of hepatotoxins in rats given Dipyridamole which may be due to shunting away from the liver [21,22]; however, with active vasoconstriction, Dipyridamole may not potentiate ischemia any further. Experimental work has shown that when mesenteric ischemia is induced reversal with Prostaglandin E or papaverine can return mesenteric flow to baseline measures [23]. Consequently in an ischemic patient our work predicts that the mesentery would exhibit a blunted response to Dipyridamole stress, which could indicate a baseline vasoconstricted state, and that subsequent administration of papaverine or Prostaglandin E2 could alleviate the ischemia. It is thereby logical that celiac axis vasoconstriction at the end organs would result in shunting to the colon and other mesenteric organs, however in mesenteric ischemia shunting to the mesentery would not only be limited, but as the subject in this work shows, might even be precipitated if the mesentery is critically perfused, thereby causing the patient to complain of abdominal pain during DP stress, a phenomena not unusual in clinical nuclear medicine departments (personal communication TC Hill).

In conclusion, at the dosage used 1)Turbo-FLASH can provide adequate time and spatial resolution in celiac axis perfusion imaging, 2) Dipyridamole stress testing of the celiac axis is reproducible and corroborates previous

invasive human and animal experiments on the mesenteric and celiac axis perfusion effects of adenosine, and 3) lack of shunting to the mesentery during DP stress may be the hallmark of mesenteric ischemia and would warrant further animal and human studies perhaps with phase contrast MRI correlation. Sample size calculation indicates that a controlled study with 165 normals and 165 subjects will be necessary to detect a 20% difference in perfusion between the groups with a power of 0.8.

ACKNOWLEDGMENT

Jessie Chai for editorial assistance, Melvin Clouse for unceasing departmental support of this project and underwriting MRI costs and Joanne Volpe for technical assistance. Portions of this work were funded by a 1992 RSNA research resident award. Partial support from PHS grant RR 05591 and NIH grant CA 09536.

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