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Improved Quantification of Myocardial Blood Flow using HYPR Reconstruction

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Abstract

Purpose—To improve quantification of myocardial blood flow using a fast T_1 mapping technique using highly constrained back projection reconstruction (HYPR) accelerated acquisition.

Methods—A major source of error in the measurement of myocardial blood flow (MBF) using MRI is the nonlinear relationship between image signal intensity and contrast agent (CA) concentration. HYPR accelerated radial acquisition was used to generate pixel-wise T_1 maps with a temporal resolution of one heartbeat. HYPR produces images with a temporal footprint of 40 ms and 4 images within 188 ms. T_1 values were converted into CA concentrations by the known linear relationship between CA concentration and T_1 . The T_1 mapping technique was used to quantify MBF on 10 healthy subjects and compared with MBF found using image signal intensity and MBF reported in previous literature.

Results—The MBF measured using the proposed method is more consistent with that previously reported in the literature and significantly lower ($P=0.002$) than that calculated using image signal intensity (1.11 ± 0.27 ml/min/g compared to 1.88 ± 0.45 ml/min/g respectively).

Conclusion—We developed a fast T_1 mapping method for myocardial blood flow quantification using radial sampling and HYPR. Further validation is required to determine its clinical value in assessing myocardial perfusion deficit in coronary artery disease.

Keywords

MR studies; coronary artery disease; myocardial perfusion; myocardial blood flow quantification; radial acquisition

Introduction

MR myocardial perfusion imaging is a promising noninvasive technique used for the diagnosis of cardiovascular ischemic disease (1–3). Highly constrained back projection reconstruction (HYPR) has been proposed for accelerating acquisition of myocardial perfusion MRI (4, 5). Compared to conventional Cartesian imaging with parallel imaging, HYPR accelerating imaging has been shown to yield 3–5 fold acceleration, with improved signal to noise ratio (SNR), cardiac coverage, and robustness to motion.

Despite the promise of accelerated imaging, one limitation of MR perfusion imaging is the inability to accurately measure myocardial blood flow (MBF). Accurate measurement of MBF relies on the linearity of image signal intensity to contrast agent (CA) concentration. Unfortunately, signal intensity does not scale linearly with CA concentration due to long saturation recovery (SR) times and/or high CA concentrations required for adequate contrast to noise ratio in the myocardium. This nonlinearity is especially evident in the arterial input function (AIF), where the peak signal is truncated.

Two methods have been proposed to measure the true untruncated AIF. The “dual bolus” method uses two separate scans; the first scan utilizing a dilute bolus of CA, followed by a second scan using a normal dose bolus (6). The dilute bolus is used to estimate the AIF while the normal bolus is used for myocardial signal. This method is logistically demanding (increased setup and scan time) and requires that physiological conditions remain constant between the two scans (7). The second method, the “dual sequence” method, acquires a short TI, low resolution image used to capture the AIF in conjunction with long TI, high resolution images for the myocardial signal during each cardiac cycle (8). The dual sequence method only captures the true AIF from a single cardiac phase, limiting its accuracy for MBF measured from different phases (9). The dual sequence method is also susceptible to T_2^* effects (10).

An alternative method which directly measures CA concentration using fast T_1 mapping has been previously proposed (10–12). The T_1 FARM method proposed by McKenzie *et al* involved creating a T_1 map over two heartbeats by acquiring a steady state image during the first heartbeat followed by an image acquired after an inversion recovery preparation in the next heartbeat (11). Almost a decade later, fast radial T_1 mapping using a saturation recovery (SR) preparation was proposed by Kholmovski *et al* (10). The method utilizes an accelerated radial acquisition to estimate CA concentrations during every cardiac cycle. HYPR uniquely accommodates the fast T_1 mapping method due to short temporal windows achievable by HYPR reconstruction. Compared to previous work, the addition of HYPR reconstruction produces higher resolution and images are reconstructed from fewer projections. The reduced number of projections produces shorter temporal footprint, increased number of images (samples of the longitudinal relaxation), and shorter total acquisition time. The purpose of this study is to measure the true AIF using T_1 mapping for HYPR accelerated radial imaging.

Methods

Fast T_1 mapping operates under the framework that T_1 values can be rapidly measured within a single heartbeat by sampling the longitudinal relaxation process following a SR magnetization preparation during a first-pass perfusion exam. The signal following an SR preparation and gradient echo (GRE) acquisition for a Cartesian trajectory can be modeled by the following equation (13):

$$S = \rho \left[\left(1 - e^{-TI/T_1} \right) (E \cos(\alpha))^{n-1} + (1 - E) \frac{1 - (E \cos(\alpha))^{n-1}}{1 - E \cos(\alpha)} \right] \quad (\text{Eq. 1})$$

where ρ includes contributions from proton density, T_2^* relaxation, and coil sensitivity variations; $E = e^{-ES/T_1}$; α = flip angle; n = number of imaging RF pulses applied before acquiring the center line of k-space; TI = delay time; and ES = echo spacing. The T_1 can be found by varying either TI , α , or n while holding the rest of the parameters constant.

Unlike Cartesian imaging, radial imaging has no well-defined k-space center line because all projections pass through the center of k-space. However, it has been shown that the signal intensity can be reasonably approximated by the time required to reach the center of the acquisition window (10). Consequently, the signal intensity of the radial acquisition can be approximately described by the number of projections acquired before the center of the acquisition window.

One assumption made by Eq. 1 is that there is no residual magnetization following the SR preparation. Residual magnetization will result in errors in the T_1 estimation. To minimize this error, a composite pulse train preparation as described in Kim *et al* is used (14). In short, the SR preparation used is a combination of three 90° rectangular pulses with crusher gradients interleaved between each 90° pulse. The expected error caused by residual magnetization is under 5% at a T_1 value of 50 ms.

T_1 and ρ were found on a pixel-wise basis by solving a nonlinear least squares problem using the sampled images (I_k , $k = 1, 2, 3, 4$) and known acquisition parameters. To improve condition of the fit, the initial guess and bounds of T_1 values were adaptively modified according to signal intensity of the final image of the series (I_4). The initial guess for T_1 values was found using single point T_1 measurements (15). Bounds were then set to be 20% greater and less than the initial guess. This boundary was set to correspond with the error in T_1 calculations associated with single point T_1 measurements (15).

To improve the SNR of T_1 maps, spatial and temporal constraints were incorporated. First, both ρ and T_1 are constrained to vary slowly through time. This constraint has been applied to accelerated image reconstruction for myocardial perfusion imaging (16). Second, T_1 is constrained to be spatially smooth (minimize the total variation). The total variation constraint has been previously applied to denoise medical images with great success (17).

The T_1 values can then be converted to CA concentration using Eq. [2] and the known relaxivity of gadolinium-based (Gd) CA ($\gamma = 3.9 \text{ mM}^{-1}\text{s}^{-1}$) (18).

$$\frac{1}{T_1} = \frac{1}{T_{1baseline}} + \gamma [Gd] \quad (\text{Eq. 2})$$

$T_{1baseline}$ is the pre-contrast T_1 values. γ is the relaxivity of Gd. $[Gd]$ is the concentration of Gd. The baseline T_1 can be found using pre-contrast images where the first five precontrast data points were averaged together to produce the baseline T_1 value.

Acquisition and Reconstruction of Radial Perfusion Data

To measure T_1 using an SR preparation, each image must be acquired with a short temporal footprint (<60 ms) to adequately capture the shape of T_1 relaxation (10). HYPR accelerated radial imaging is uniquely suited for this application due to the short temporal footprint achievable. A segmented radial acquisition is used to minimize the temporal footprint during each R-R. Data collected during each R-R is highly undersampled. The HYPR reconstruction uses an iterative process which a composite reference image constructed from data acquired from multiple heartbeats (8 in this work) is used to constrain the reconstruction of images of individual R-Rs (5). The advantage of this method is that it minimizes undersampling streak artifacts while preserving high SNR and high resolution images using a small number of projections per cardiac cycle. Because the reconstruction of the individual frames depends on a composite image constructed from multiple heartbeats, breathing artifacts may corrupt multiple frames. To limit this, all scans are acquired during a breath hold.

Computer Simulations

Computer simulations were performed to optimize the temporal footprint and the number of samples required to accurately capture the expected range of T_1 values. A Monte Carlo style simulation was performed. The longitudinal magnetization evolution following an SR preparation was simulated using Eq. [1]. The temporal footprint was varied from 25–80 ms. Gaussian noise was added to each sample according to experimental SNR measurements from a typical perfusion scan; the lower the magnetization corresponds with higher level of noise added (SNR = 1–14) (5). T_1 estimation was then performed using the simulated signal. The root mean square error was measured for each estimated T_1 . A range of T_1 s between 25ms to 1500 ms were simulated. Simulations assumed acquisition parameters used for in-vivo scans (TI = 27.6 ms, TR = 2.5 ms, and FA = 10°).

Phantom Studies

Phantom studies were performed to test the validity of this method. T_1 was estimated in 50 ml centrifuge tubes doped with known CA concentration using the proposed method. Vials of water were doped with gadoversetamide (Optimark, Mallinckrodt Inc.) with concentrations ranging from 0–10 mmol/ml. Tubes were placed in a water bath to minimize the difference in magnetic susceptibility between the tubes and the immediate surroundings. Gd concentrations were compared to a reference 2D Cartesian inversion recovery GRE TI scan with ten different TI times (TI = 25, 50, 100, 200, 300, 500, 750, 1000, 1500, 2000). Imaging parameters for the reference scan were $1.7 \times 1.7 \times 8 \text{ mm}^3$ and TR/ES/TE = 5000/2.5/1.4 ms. Acquisition was repeated 10 times to increase SNR.

Human Subject Protocol

Ten healthy volunteers underwent perfusion MRI studies on a Siemens 3T Verio (Siemens Medical Solutions, Erlangen, Germany) system with IRB approval and informed written consent. Studies employed a 12 channel spine and body phased array coils. First pass perfusion scan was performed at rest using a segmented GRE pulse sequence with radial acquisition for T_1 mapping. The scans used a commercially available composite pulse train SR preparation as described previously (14). A single midventricular slice was acquired. Subjects were given a bolus of 0.1 mmol/kg Optimark (gadoverstamide injection, Mallinckrodt Inc, Montana, USA) followed by a 20 ml saline flush at a rate of 4 ml/s. All scans were performed during breath hold and were electrocardiogram triggered with image acquisition set for the quiescent phase of diastole.

Imaging parameters for the radial scan are as follows: FOV = 270 mm²; BW = 744 Hz/pixel; α = 10°; TR/TE = 2.5/1.4 ms; four images acquired consecutively following each SR pulse with TI = 48 ms, 88 ms, 128 ms and 168 ms respectively; spatial resolution = 1.7×1.7×8 mm³, 160 readout points x 128 projections acquired over 8 shots (8-R-R cycles) with 16 projections per shot. The projections were collected in a doubly interleaved manner as describe in Adluru et al, to ensure that changes in contrast was evenly distributed through k-space (19). The four images were collected at the same slice position during the quiescent phase of diastole. The total temporal footprint per cardiac cycle was 188 ms. First-pass perfusion data was acquired over 48 R-R cycles.

Analysis of Data

Segmentation was performed using the freely available Perfusion Imaging Toolkit (Mallinckrodt Institute for Radiology, St. Louis, USA) (20). A region of interest (ROI) was placed in the ventricular blood pool and the myocardium for the AIF and myocardial signal. ROI in the ventricular blood pool was drawn to avoid papillary muscle while maximizing size of ROI to ensure high SNR of the AIF. The ROI in the myocardium was divided into AHA recommended segments (21). Average MBF was measured in each segment. The signal intensity curves were taken from the image with the TI which most closely matches conventional clinical protocol (TI = 128 ms). The signal intensity curves and Gd curves were scaled such that the final four frames of each curve matched signal intensities.

MBFs were found using a linear time invariant model (22) with a model independent deconvolution (23). MBF were found using both signal intensity curves and Gd concentration curves. Paired Student's t-test was performed comparing estimated MBF derived from image signal intensities and the proposed T_1 mapping method. The statistical significance was set at $P=0.05$.

Results

Simulations

Figure 1 shows the results from the computer simulation. T_1 estimation errors were substantially reduced by increasing number of samples acquired and decreasing the number of projections acquired per image (decreasing the temporal footprint). T_1 errors increase

with decreasing T_1 . Root mean square error reach above 20% for extremely long (>1500 ms) and extremely short (<50 ms) T_1 values.

Phantom Studies

Gd concentration estimates from the phantom are shown in Figure 2. The proposed method gave similar CA values as the reference multiple TI inversion recovery method; $Gd_{test} = 0.98 Gd_{ref} - 0.20$, $r^2 = 0.99$, where Gd_{test} is the CA concentration found using the T_1 mapping technique and Gd_{ref} is the CA concentration found using the reference technique.

Human Studies

Figure 3 shows a comparison of images of each TI. All images have excellent image quality and myocardial delineation. On average, there is a $3 \pm 2\%$ difference in septal and lateral myocardial wall image signal intensity. Total temporal footprint per cardiac cycle was held to 188 ms. It was found that there is on average a 13% change in myocardial area between the first (TI = 48 ms) and the fourth image (TI = 168 ms).

Figure 4 shows comparison of curves derived from image signal intensities and CA concentrations. The AIF found using the T_1 mapping method yield a 78% increase in peak amplitude on average compared to AIFs measured directly from the image signal intensities. The mean MBF found using the image signal intensities was 1.88 ± 0.45 ml/min/g. The mean MBF found using CA concentration curves was 1.11 ± 0.27 ml/min/g, which was significantly different from MBF estimates found using the image signal intensities ($P=0.002$). Figure 5 shows a pixel-wise and segmented MBF map of the myocardium. For pixel-wise approach, there is an average standard deviation of 0.08 ml/min/g in the myocardium for all studies. For the AHA segmented approach, there is an average standard deviation of 0.03 ml/min/g.

Discussion

In this work we develop a fast T_1 mapping method to quantify MBF using radial imaging and HYPR reconstruction. CA concentration maps were found using the T_1 maps. MBF found using the CA concentration curves were found to be significantly different from those found from signal intensity curves ($P=0.002$) and comparable to MBF reported by previous literature.

The HYPR technique has been shown to have several advantages over traditional Cartesian imaging: higher resolution, improved SNR, and greater cardiac coverage (5). Moreover, Sharif et al. have recently shown that radial first-pass perfusion imaging reduces the prevalence and extent of subendocardial dark-rim artifacts (24–26). Improved spatial resolution, higher SNR and reduced level of dark rim artifact allows for better visualization of subendocardial deficits, potentially increasing the sensitivity in detecting disease (27). Improved cardiac coverage is desired because extent of deficits have been shown to be closely linked with prognosis (28). HYPR accelerated imaging has been shown to have high sensitivity and moderate specificity for the detection of coronary artery disease (4).

Compared to previously published fast T_1 mapping methods, the HYPR reconstruction used in this work is capable of producing images of higher resolution ($1.7 \times 1.7 \text{ mm}^2$ compared to $2.0 \times 2.0 \text{ mm}^2$) and shorter temporal footprint (40 ms compared to 60 ms). The shorter temporal footprint allows for increased number of samples (4 compared to 3) during a shorter acquisition window (188 ms vs 210 ms), reducing T_1 estimation error by improving the condition of the fit. The shorter acquisition time also improves robustness to cardiac motion, which may cause errors in T_1 estimation. Motion artifacts are especially a cause for concern for the pixel-wise T_1 mapping approach taken in this work. Furthermore, images of different TIs do not share any information with each other. Sharing information across different TIs may result in the sharp edges of the images becoming blurred due both cardiac motion and inherently different contrast of each projection (29).

In general, quantitative analysis find the MBF in large ROIs. This is done to increase MBF estimation accuracy by increasing the SNR of myocardial tissue curves and to reduce the effect of motion artifacts. Averaging the signal in an ROI reduces sensitivity to small, subendocardial perfusion deficits, which may reduce sensitivity to CAD (30). Subendocardial deficits or gradients in MBF have also been shown to be novel biomarkers for certain diseases (31, 32). The high SNR images produced by HYPR reconstruction allows for pixel-wise MBF estimate with only a slight increase in MBF inhomogeneity (as shown in figure 5). Another limitation for pixel-wise MBF measurements is respiratory motion may cause errors in MBF measurements due to misregistration between pixels. Respiratory motion is minimized by careful manual motion correction and breath holds.

Traditional T_1 mapping methods require a large range of TI times (50–1000ms) to accurately fit a large range of T_1 s (300–1600ms) (33). The proposed method uses only TI times of 48ms–168ms. The expected range of T_1 values during first pass imaging is relatively short (50–400 ms) (15, 34). For this range, it was found that the T_1 error is less than 10%. For longer and shorter T_1 's, the estimation accuracy decreases due to poor conditioning (high noise sensitivity) of the fit. Using Eq. [2], it can be shown that even large errors pre-contrast T_1 values have minimal impact on the measured MBF. A 50% error in baseline T_1 value results in a 3% error in peak CA concentration and consequently a ~3% error in final MBF measurement (7).

Study Limitations

One limitation of this work is precise registration of the four images acquired during each cardiac cycle is required to produce a pixel-wise T_1 map. Cardiac motion hinders the ability to do pixel-wise T_1 mapping because of misregistration of pixels between the first (TI=48 ms) and fourth (TI=168 ms) image. As such, the method is currently limited to a single slice acquired during the quiescent period of diastole, during which cardiac motion is minimized. To apply this method during systole, as required by a typical clinical exam, motion compensation is required.

Another limitation of this study is the lack of direct validation. While the MBF values derived from the CA concentrations found in this study falls within the range of rest MBF for healthy subjects as reported by previous studies (35), direct validation with an established gold standard is still needed. Because ischemic disease necessitates reduced CA

concentrations in the myocardium and longer T_1 values compared to healthy myocardium, the range of T_1 values in the myocardium may fall outside of the range of the expected range of T_1 values. This can possibly result in poor fit conditioning and increased T_1 errors. Errors in T_1 measurement may reduce sensitivity to disease, whether due to poor delineation of size or severity of deficit. Patient studies are required to validate if disease can be identified and diagnosed.

Conclusion

The radial fast T_1 mapping technique is a technique that is highly compatible with HYPR perfusion imaging. MBF found using T_1 maps are significantly different than those found using signal intensities due to signal nonlinearities. Decreased temporal footprint may allow for increased CA dosages, thus improving contrast to noise ratio. This method offers a simple, single scan, single acquisition method to measure the true AIF using HYPR accelerated radial perfusion scans.

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Figure 1.

a) Simulation of T_1 estimation percent errors caused by noise with respect to number of samples and sampling interval. Results are shown for $T_1 = 50$ ms. The sampling interval depends on TR and number of projections acquired during each cardiac cycle. For all cases, increasing number of samples decreases errors. Conversely, decreasing the sampling interval decreases errors. The circle depicts the parameters used for this study. b) The percent error by T_1 values for the parameters used in this study (4 samples, sample interval of 40 ms). T_1 error increases with decreasing T_1 .

Figure 2.

Comparison of Gd estimates comparing the proposed method with a reference method (IR GRE with multiple TIs). Gd estimates using the proposed method have a high correlation with the reference method.

Figure 3.

(a) Comparison of radial images of different TI times. Radial images show progression of T_1 recovery. Each image shows high SNR and minimal streaking (b) Evolution of signal intensities through radially sampled images from a single pixel (marked in white). The black line represents the fitted line used to derive T_1 values.

Figure 4.

(a) AIF and (b) myocardial tissue curves taken from (i) image signal intensities, and (ii) Gd concentration maps derived from the accelerated radial scan. There is a clear increase in peak enhancement using the Gd concentration maps in the AIF.

Figure 5.

(a) Example of pixel-wise measure of MBF. (b) MBF can be averaged and displayed in standard AHA segments.