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Automated T_2^* Measurements Using Supplementary Field Mapping to Assess Cardiac Iron Content

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Abstract

Purpose—To develop and evaluate an algorithm that automatically identifies high-susceptibility areas and excludes them from T_2^* measurements in the left ventricle (LV) for myocardial iron measurements.

Materials and Methods—An autoregressive moving average (ARMA) model is implemented on multi-gradient echo scans of 24 patients (age range 3 to 45 years, 10 male/14 female). Voxels with relatively high susceptibility (>3 Hz/mm) are flagged and deselected from the T_2^* calculations for iron quantification. The mean, standard deviation, and coefficient of variation (CoV) of the ARMA-defined region are compared to the CoV of four distinct regions of the LV and the entire LV using a Student's t-test ($\alpha=0.05$).

Results—The CoV of T_2^* values obtained by the ARMA method are comparable with that in the interventricular septum (IS), where susceptibility was the lowest (CoV=0.31). The ARMA method provides a greater area ($51.9 \pm 13.7\%$ of the LV) to measure T_2^* than that using the IS alone ($21.1 \pm 3.4\%$, $p<0.0001$). Areas where low susceptibility are measured corroborate with areas reported in previous studies that investigated T_2^* variations throughout the LV.

Conclusion—An automated method to measure T_2^* relaxation in the LV with minimal effects from susceptibility has been developed. Variability is reduced while covering more regions for cardiac T_2^* calculation.

Keywords

cardiac MR; iron overload; T_2^* mapping; susceptibility; multi-gradient echo (mGRE); autoregressive moving average (ARMA) modeling

INTRODUCTION

Hematological conditions such as β -thalassemia major and sickle cell disease often require chronic blood transfusions for disease management. However, multiple transfusions result in an excessive accumulation of iron, which can be deposited in organs such as the heart, liver, and pancreas (1-3). Iron overload in the heart can lead to life-threatening conditions such as arrhythmias and cardiomyopathy (4). Hepatic iron concentration and serum ferritin levels in peripheral blood do not accurately predict the presence of high amounts of iron in the heart (5). Therefore, direct measurements of myocardial iron, either by invasive biopsy or

preferably by noninvasive means, are necessary to monitor cardiac iron deposition in patients receiving chronic blood transfusions.

One method to noninvasively measure cardiac iron is T_2^* mapping of the mid-papillary short axis of the left ventricle (LV) (5-10). Anderson et al. showed that at 1.5 T, patients with T_2^* values of 20 ms or less in the LV are at high risk of developing iron-induced cardiac complications (5). Typically, T_2^* measurements are made in a region of interest (ROI) in the interventricular septum (IS) to avoid T_2^* -lowering susceptibility effects from lung, liver, and epicardial fat. T_2^* measurements in other regions of the heart are more variable, and thereby less reliable, because of these susceptibility effects (11-14). This limits the areas within which T_2^* values can be accurately measured, since T_2^* values in high-susceptibility areas have cumulative effects of both susceptibility and iron deposition. Susceptibility effects from various regions in and around the heart can project to the IS, further causing increased variation in T_2^* measurements (15). In addition, intra- and interobserver variability in the ROI selection can affect the reproducibility of T_2^* measurements (16).

In this study, we implemented and evaluated an automated method that incorporates an autoregressive moving average (ARMA) model of the complex signal from a multi-gradient echo (mGRE) acquisition (17) to map the field and T_2^* of the whole left ventricle. Previous work demonstrated that this method could be used to quantify susceptibility due to iron in the liver (18). In this work, by using the field map areas of high susceptibility caused by factors such as air-tissue interfaces, deoxygenated blood in the cardiac veins, and epicardial fat can be automatically identified. Only areas of the LV minimally affected by anatomy-related susceptibility effects were used to reduce the variability in T_2^* measurements for cardiac iron assessment. Susceptibility effects were also measured at different regions of the heart to directly identify areas of high susceptibility that can affect cardiac T_2^* measurements.

MATERIALS AND METHODS

Patient Demographics and MR Imaging

This retrospective study was approved by the local institutional review board. MR exams from individuals with suspected transfusional iron overload (10 male/14 female, 18.0 ± 11.4 years (Range: 3 to 45 years)) were retrieved from the institution's diagnostic imaging PACS system and evaluated in Matlab (MathWorks, Natick, MA). Patients underwent a diagnostic cardiac mGRE scan to monitor for possible iron loading in the heart due to their transfusion history and/or increasing serum ferritin levels. Diagnoses for these patients included sickle cell disease (n=10), β -thalassemia major (n=7), sideroblastic anemia (n=1) and congenital dyserythropoietic anemia (n=1). Five patients have received at least one bone marrow transplant for the following conditions: acute leukemia (n=2), Hodgkin's lymphoma (n=1), aplastic anemia (n=1), and red cell aplasia (n=1). After obtaining informed consent from patients, MRI scans were conducted on 1.5T whole-body scanners (Avanto and Symphony, Siemens, Malvern, PA) with a phased-array body coil. An electrocardiogram-gated, single breath-hold technique was used to obtain mid-papillary short-axis mGRE images at the end of the diastole. Echo times ranged from 1.5 ms to 21.3 ms, and were used in increments of 1.8 ms (echo train length=12). Other imaging parameters were as follows: flip angle 35° , slice thickness 8 mm, matrix size 135×128 , and variable field of view ($300\text{--}400\text{ mm}^2$), depending on patient size. The acquisition was divided into 15 heart beats with 9 segments in each heart beat with a variable TR, between 600 and 1200ms, depending on the heart rate. Total acquisition time ranged from 18 to 21 s.

Automated Identification of High-Susceptibility Regions in the Heart

The proton resonant frequency (PRF), T_2^* value, and amplitude of multiple peaks (i.e. water and bulk methylene in epicardial fat), were calculated using an ARMA model on the mGRE acquisition as described in previous work (17,18). With this algorithm, the mGRE signal in each voxel is expressed as a rational polynomial after utilizing a z -transform. The algorithm then iteratively approximates the coefficients of the polynomial where the poles correspond to the PRF and T_2^* of each peak – thereby providing separate values for water and fat (i.e. epicardial fat). The amplitude of each peak was calculated using Cauchy's residue theorem and the water PRF was used for the field map.

To identify an appropriate threshold for the field map gradient, simulations using identical MR acquisition parameters were used with T_2^* values ranging from 1 to 50 ms. For the simulation, effects of field gradient in the z -direction was simulated to determine its effect on T_2^* values, since this typically gives the greatest effects on T_2^* . This, in turn, will give a worst-case scenario on field inhomogeneity effects on T_2^* . Given the water amplitude, ρ , the effect of the signal, $s(t)$, due to a PRF gradient, G , can be described as

$$s(t) = \rho e^{\left(i2\pi f - \frac{1}{T_2^*}\right)t} \Delta z \quad \text{sinc}(\gamma G \Delta z t) \quad (1)$$

where f is the PRF, Δz is the length of which the gradient passes, and γ is the gyromagnetic ratio (19,20). A threshold value was chosen based on these simulations which would exclude voxels due to susceptibility effects that can affect T_2^* measurements.

By using the magnitude image at the first TE, an ROI was selected that covered the entire LV. This was the only user interaction needed for the T_2^* calculation. The gradient of the field map was generated by measuring changes in the PRF as the root of the sum of squares of the field changes in the image's x and y coordinates. Based on the results from the simulations, voxels with gradient values above 3.0 Hz/mm were excluded from the T_2^* measurement. Next, the algorithm identified extraneous voxels that are not connected to other voxels (<4 voxels connected together) and omitted them for the T_2^* calculation. Also, voxels with T_2^* values greater than 70 ms (signifying values that are higher than normal myocardial tissue (i.e. blood) (21)) were excluded from the measurement. The remaining area was used for ARMA-based T_2^* measurements. In this ROI, the T_2^* values can be calculated voxel by voxel throughout the LV (Figure 1).

Coefficient of Variation and Regional Analysis

The mean and standard deviation (SD) of T_2^* values in the whole LV, IS, and ARMA-defined ROIs were calculated for each patient. Mean values were used since the skewness and kurtosis of the T_2^* measurements were low (<-0.6), thereby supporting the use of parametric statistical methods (22). For each of the 3 ROIs (LV, IS, and ARMA), the coefficient of variation (CoV) was calculated and compared individually by a paired Student's t -test ($\alpha = 0.05$). The total area of the LV, IS, and ARMA-defined region was also recorded.

To investigate susceptibility effects in distinct areas of the LV, the LV was divided into four 90° quadrants – the IS, anterior wall (AW), lateral free wall (LFW), and posterior/inferior wall (PIW) (Figure 2) – as done in the study by Yamamura et al. (8). The mean, SD, and CoV of T_2^* values were recorded for each region, in addition to the T_2^* calculated by the ARMA model for each region (whole region vs. low-susceptibility areas). Each area excluded from T_2^* measurement due to field gradients above the threshold was also recorded.

RESULTS

A field gradient of 3 Hz/mm was chosen for the threshold to remove voxels that may be decreased due to susceptibility effects. As shown in figure 3, voxels with gradients to the right of the white dashed line was thresholded out. It can be noted on the surface plot that susceptibility affects longer T_2^* values more strongly in comparison to short T_2^* tissues, which are generally seen in iron overload.

Table 1 gives the mean T_2^* measurements of the 24 patients in the entire LV, IS, and ARMA-defined regions. There was no statistically significant difference in the mean T_2^* values between the IS and ARMA regions ($p=0.32$). To visually demonstrate this, a Bland-Altman plot of the IS and ARMA mean T_2^* values is shown in figure 4. The population mean T_2^* of the entire LV was lower than that of the IS and ARMA ($p<0.01$). In all cases, the mean ARMA T_2^* measurement was higher than the LV T_2^* measurement ($p=0.03$). The T_2^* values calculated by the ARMA model ranged from 15.8 to 41.2 ms (mean, 32.6 ms; SD, 6.6 ms).

The mean IS ROI area was $21.1 \pm 3.4\%$ of the total LV area. Compared with the IS area, the mean area for ARMA-based T_2^* measurements was $51.9 \pm 13.7\%$ ($p<0.0001$) of the LV area. Although on average the area for the ARMA-defined region was significantly higher than that for the IS, the CoV of T_2^* measurements between the IS and ARMA did not significantly differ from that of the IS. The CoV of T_2^* measurements by ARMA was 19% lower than the CoV of T_2^* measurements in the entire LV ($p<0.0001$).

In evaluating the four regions of the LV, there were areas where susceptibility was consistently high in our patient cohort regardless of iron-overload status. Table 2 displays which areas were used for ARMA-defined T_2^* measurements. The IS contained the least voxels with gradients above the threshold signifying that it had the least susceptibility. The lateral free wall had the greatest area of susceptibility with $73.1 \pm 24.8\%$ of the voxels excluded for T_2^* measurements. Of all the accepted voxels (< 3 Hz/mm gradient), 46.6 % of voxels came from the IS, 38.1 % came from the anterior wall, 15.3% came from the posterior/inferior wall and 18.1% came from the lateral free wall. Figure 5 shows an example where the ARMA model identified areas of low susceptibility, which was mostly in the IS. In each of the four regions, the ARMA model decreased the CoV ($p<0.01$) demonstrating more precise measurements in the ROI using ARMA compared to ROIs of the entire region.

Except in one patient, the implementation of the ARMA model did not change the indication of low risk of complications (>20 ms) to high-risk of complications (<20 ms) from iron overload or vice versa. The patient that was an exception had a subcutaneous port in the left chest wall, which led to increased susceptibility in the IS (Figure 6). The LV for the patient was 16.3 ± 11.1 ms and the IS T_2^* was 14.7 ± 10.7 ms. The ARMA model was used to identify the area of high susceptibility and exclude it from the T_2^* measurement. By using the threshold, a T_2^* of 23.5 ± 6.7 ms was calculated by the ARMA model, and the uncertainty of the measurement placed the 95% confidence interval at the level where the patient would be determined to be at higher than normal risk of cardiac complications. In the Bland-Altman plot in figure 4 this patient was marked by an arrow, which demonstrates the wide variation between the T_2^* measurements in this patient.

DISCUSSION

We used the ARMA model and magnitude/phase information from a short-axis mGRE acquisition to generate field maps and T_2^* maps without adding imaging time, since the field map was derived and calculated directly from the mGRE acquisition. By using the field

map data, areas of high susceptibility were automatically identified and excluded from the analysis in an effort to deliver a more precise estimate of T_2^* in the myocardium. The procedure needed minimal user interaction: the user only outlines the LV, and the T_2^* is automatically calculated in areas where susceptibility from various sources is relatively minimal. In addition, the user could further define a more restrictive ROI (i.e. lower threshold) based on the region preselected by the algorithm as an area of low susceptibility.

Iron itself induces a susceptibility effect that is reflected by a reduction in T_2^* values and a possible increase in the field gradient. However, it was found in this study that the correlation between the median field gradient across the heart and the T_2^* of the tissue was very low ($R^2=0.069$). Certain regions of the LV showed the same susceptibility effects independent of the LV or IS T_2^* , supporting that the susceptibility effects measured are from the geometry and/or anatomy of the heart. Therefore, in our opinion, the majority of voxels excluded for high susceptibility are due to the cardiac geometry and/or anatomy and not excessive iron in different regions the heart.

It is also important to note that susceptibility is an added effect. Therefore, measuring the T_2^* in these high-susceptibility areas may lead to overestimation of the amount of iron present in the myocardium. Meloni et al. (14) suggested that this may be negligible in the case of patients with severe iron overload. In severe cardiac iron overload, there can be a gradient of iron concentration along the transmural layers of the myocardium (5,23). This could cause an increased susceptibility effect across the myocardial wall. Given that none of our patients had severe iron overload ($T_2^* < 10$ ms) we could not assess the algorithm under these conditions. As it is done with superparamagnetic iron oxide (SPIO)-labeled cells (24) or in the liver (18), it may be possible in these cases to measure the susceptibility across the septum using the ARMA-generated field map as an additional measurement to the T_2^* measurement for iron assessment (6).

In this study, a conservative 3 Hz/mm threshold was used to remove areas of high susceptibility while maintaining a large area to make T_2^* measurements. While the gradient effects lower T_2^* tissues less, this threshold was chosen to assure that higher T_2^* values (>20 ms) will not be adversely affected. We found that the variation in T_2^* measurements was significantly lower when a 3 Hz/mm threshold was used than when measuring the T_2^* of the entire LV. While this simulation used the prescribed acquisition from this study, it is important to note that decreased spatial resolution and increased slice thickness can increase the field gradients' effect on T_2^* measurements. It is typically assumed that the greatest effect on T_2^* is from the through-plane field gradient (19,20). Since the PRF measurement is an average over the entire voxel and the greatest dimension was through-plane, this simulation is a reasonable estimation to determine the threshold.

In this study, the LFW had the most voxels excluded from the T_2^* evaluation. Yamamura et al. (13) have reported the lowest T_2^* values in the posterior/inferior and anterior walls of the heart, which in our study had slightly fewer areas of high susceptibility on average than the LFW did. While the mean values show that the LFW had the highest area of excluded voxels, this was not the case in every patient as seen in the large standard deviation in Table 2. In eight cases, the AW or PIW had the most voxels excluded due to susceptibility. In addition, in published reports (13,14) the variations in T_2^* values are used as a marker for susceptibility. The fact that we are directly measuring the field and not T_2^* variations may indicate why there are some differences. It is important to note that all these studies, including this study, agree that the IS exhibits the least susceptibility.

This study shows that there are several sources of susceptibility in and around the heart that do not come from iron deposition. The posterior and middle cardiac veins carry

deoxygenated blood from the myocardium in areas near the PIW and LFW. The deoxygenated hemoglobin in the blood has a well-understood susceptibility effect that can affect T_2^* measurements (25,26). Another major source of susceptibility is the air–tissue interface at the lungs, which is mostly prevalent at the LFW adjacent to the left lung. Other susceptibility sources are epicardial fat (more prominent at the anterior wall along with the great cardiac vein) and foreign bodies, as seen in Fig. 3. Again, these areas were automatically omitted from the T_2^* calculation, which contributed to an overall more precise T_2^* measurements using the ARMA model.

In addition to identifying the areas with the least susceptibility, the ARMA technique can be used as an automated warning of high-susceptibility areas in ROIs. For instance, an ROI can be drawn in the IS. By using the gradient maps generated by ARMA, the area of high susceptibility within the ROI can be detected and identified, which could be particularly useful in patients with susceptibility artifacts arising from the chest wall. Also since multiple chemical shifts can be calculated, epicardial fat can be detected and automatically excluded from the T_2^* calculation.

As mentioned above, one limitation of this study is that there were only two patients with T_2^* values less than 20 ms to demonstrate an increased risk of cardiac complications. No patient had T_2^* values less than 10 ms. Although it is encouraging that the majority of our patients did not have heavy iron loading in the heart, this meant that we were not able to test the algorithm in myocardia with high iron loads. It is interesting to note that the median gradients in the two iron-overloaded patients were not statistically different from those of the other patients. In fact, the highest median gradient was seen in the patient who had the subcutaneous port in the left chest wall. Twenty-one of these 24 patients had iron overload in the liver, which were determined by T_2^* values calibrated to liver iron content (27). In this study, liver R_2^* values ranged from 87 to 595 Hz in addition to two patients with R_2^* values that could not be precisely determined due to severe iron overload ($R_2^* > 1000$ Hz). Excluding these two cases, the mean liver R_2^* was 334 Hz with a standard deviation of 161 Hz. Similar to observations in previous reports (28,29), the two patients with very high liver iron content had a cardiac T_2^* that was normal using both the IS and ARMA T_2^* measurements (Range: 25.9 – 33.1 ms). In terms of abdominal imaging such as for the liver and pancreas, this technique can possibly be used to identify areas of high susceptibility due to air/tissue interfaces (i.e. from gas in bowel) and omit those voxels from the T_2^* calculation. It could particularly be helpful when fat is present in the liver and/or pancreas since multiple chemical shifts (i.e. water and bulk methylene) can be calculated with the ARMA technique (17,18).

Typically, only magnitude data is used for MRI measurements. It is important to note that both magnitude and phase data are needed to make the field measurements using ARMA. This can be done on most MR scanners by using options to output the images either in magnitude/phase or real/imaginary form.

Our future studies will focus on making this approach a fully automated diagnostic reporting tool to identify patients at risk of developing cardiac complications due to iron accumulation. A large study has been conducted to develop fully automated methods to segment the LV for analysis (30). These methods could be incorporated into the ARMA method presented to make the processing fully automated to aid in the standardization of T_2^* measurements in the heart.

In conclusion, an automated method was evaluated for measuring T_2^* relaxation in the heart, in which susceptibility effects are minimized. By using this method, the variation of T_2^* values was found to be comparable with variations in the IS, where susceptibility is the

lowest. At the same time, the method provided, on average, a greater area to measure T_2^* than that using IS alone. Areas in which low susceptibility was directly measured corroborated with areas reported in previous studies that investigated T_2^* variations throughout the LV (8,14). This method could aid the diagnosis of iron overload in the heart while reducing inter-observer and intra-observer variability, since the only user input needed is a rough outline of the entire LV as a starting point for the automated region selection algorithm.

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Figure 1.

Schematic diagram for automated cardiac T_2^* measurements. The magnitude and phase images from the mGRE acquisition are used to generate a field map. The gradient of the field map is calculated to identify areas of susceptibility. A gradient of 3 Hz/mm is used as a threshold for T_2^* calculations. Any voxel above the threshold in the left ventricle (LV) is excluded from the T_2^* calculation. As shown in the figure on the far right, the algorithm can highlight areas of low susceptibility in the LV (highlighted in red).

Figure 2. Division of the myocardium of the LV into the interventricular septum (IS), anterior wall (AW), lateral free wall (LFW), and posterior/inferior wall (PIW) in the mid-papillary short axis.

Figure 3. Surface plot of the effects of field gradients, particularly in the z-direction, on T_2^* values. Due to increased susceptibility effects at higher TE values, the gradients have a larger effect at higher T_2^* values. A threshold of 3 Hz/mm (dashed line) was used to negate field gradient effects over a large range of T_2^* values.

Figure 4.

Bland-Altman plot of the IS and ARMA mean T_2^* values. The mean deviation (solid line) between the two measurements was 0.2 ms with a 95% confidence interval (dashed lines) of -3.2 to 3.6 ms. The point with the arrow corresponds to a patient with a subcutaneous chest port (see figure 6), which lowered the T_2^* in the IS.

Figure 5.

Automated ROI selection using combined T_2^* and susceptibility information. (a) shows a T_2^* map of the left ventricular short axis of a patient with sickle cell disease. In the regular workflow, a relatively thin ROI would be drawn in the intra-ventricular septum, thereby avoiding obvious voxels with signal from blood (high T_2^*) and areas of high susceptibility (i.e., AW and PIW, low T_2^*). (b) The gradient of the corresponding field map generated by the ARMA algorithm shows high susceptibility in portions of the AW, LFW, and the PIW (red circles). (c) Given the information in (b), a final ROI outlined in red was automatically identified by the algorithm circumscribing a large volume in the IS with low susceptibility as a reliable location for precise T_2^* measurements.

Figure 6.

Cardiac iron concentration assessment in a patient with a subcutaneous port in the left chest wall. (a) Circle highlights the susceptibility artifact on the short axis scout image. (b) The proton resonant frequency ranges from 1 to 4 ppm in the anterior and septal regions of the LV, demonstrating high susceptibility presumably from the port. (c) The areas in red are regions of the LV having a field gradient that is below the 3 Hz/mm value, demonstrating the lowest areas of susceptibility. (d) The increased susceptibility detected by the algorithm decreases the T₂* in the same area. Measuring the T₂* in this region may result in overestimation of the amount of iron present, since other sections of the myocardium have T₂* values that reflect normal iron loading.

Table 1

Mean T_2^* measurements of the 24 patients in the entire LV, IS, and ARMA-defined regions

	T_2^* (ms)	CoV	% of LV
LV	28.6 ± 6.0	0.49 ± 0.08	-
IS	$35.1 \pm 10.0^*$	$0.33 \pm 0.13^{**}$	21.1 ± 3.4
ARMA	$32.6 \pm 6.6^*$	$0.31 \pm 0.07^{**}$	$51.9 \pm 13.7^{***}$

Abbreviations

LV Left Ventricle

IS Interventricular Septum

ARMA Autoregressive Moving Average Model Calculation

* Statistically Different from LV T_2^* ($p < 0.05$)

** Statistically Different from LV CoV ($p < 0.001$)

*** Statistically Different from IS % Vol ($p < 0.0001$)

Table 2

ARMA-defined T_2^* measurements in the 4 regions of the left ventricle after susceptibility correction

Region	Percent of Voxels Excluded for Susceptibility	CoV Before Correction	CoV After Correction
IS	27.7 ± 21.0	0.44 ± 0.13	0.25 ± 0.08 ^{**}
AW	40.2 ± 27.7	0.42 ± 0.20	0.26 ± 0.08 [*]
LFW	73.1 ± 24.8	0.65 ± 0.31	0.26 ± 0.12 ^{**}
PIW	56.6 ± 31.2	0.47 ± 0.18	0.25 ± 0.11 [*]

Abbreviations: IS, interventricular septum; AW, anterior wall; LFW, lateral free wall; and PIW, posterior/inferior wall.

^{*}
 $p < 0.01$ when compared before correction.

^{**}
 $p < 0.001$ when compared before correction.