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Markedly Increased Volume of Distribution of Gadolinium in Cardiac Amyloidosis Demonstrated by T_1 mapping

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Abstract

Purpose—To perform myocardial T_1 mapping pre and post gadolinium (Gd) administration and determine the volume of distribution of Gd (Vd_{Gd}) in patients with cardiac amyloidosis to assess extracellular space expansion from amyloid protein deposition.

Materials and Methods—T_1 mapping was performed before contrast and 20 minutes following bolus administration of 0.15 mmol/kg of gadopentetate dimeglumine (Magnevist) in 5 subjects with cardiac amyloidosis and in 8 healthy volunteers using previously validated 3-5 MOLLI pulse sequence. The partition coefficient (λ) and Vd_{Gd} were determined and compared between groups.

Results—Before contrast the T_1 of the blood and myocardium are longer in amyloidosis as compared to controls (1665 ms vs 1509 ms; p=0.03 and 1144 ms vs 963 ms; p<0.001, respectively). Post contrast blood T_1 was also significantly longer in amyloidosis (486 ms vs 408 ms p=0.003) with a trend towards shorter T_1 in the myocardium (503 ms vs 544 ms p=0.15). The Vd_{Gd} was 83% higher in amyloidosis than in controls (0.51 vs 0.28 p=0.005).

Conclusion—Myocardial Vd_{Gd} is markedly increased in cardiac amyloidosis reflecting the increased extracellular space occupied by amyloid proteins. The pre-contrast T_1 of blood and myocardium are increased in amyloidosis extending diagnostic utility in patients who cannot receive Gd.

Keywords

T_1 mapping; Volume of Distribution; Cardiac MRI; Amyloidosis; Modified Look-Locker

Introduction

Amyloidosis is a systemic clinical disorder characterized by extracellular deposition of insoluble fibrillar proteins in multiple organ systems. Light chain amyloidosis (AL), the most common form of amyloidosis in developed countries, affects the heart in up to 90% of patients resulting in a restrictive cardiomyopathy. Fifty percent of AL patients first present with symptoms of diastolic heart failure.(1) Cardiac involvement in AL is a poor prognostic factor(2) and is the cause of death in a majority of AL patients.(3)

Cardiac magnetic resonance imaging (CMR) has shown promise in evaluating cardiac amyloidosis and other cardiomyopathies.(4) Amyloidosis has been associated with diffuse subendocardial delayed enhancement (DE).(5) Global DE is associated with greater

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interstitial amyloid deposition in endomyocardial biopsy (EMB)(6), and is a more accurate non-invasive diagnostic test for cardiac amyloidosis than EKG or transthoracic echocardiogram (TTE) when validated by EMB.(7) Global DE on CMR is also a stronger predictor of 1 year mortality than morphologic characteristics derived by EKG or TTE.(7) However, when the T_1 of the myocardium is similar to that of the blood pool the diagnosis can sometimes be uncertain by conventional DE imaging. Alternatively, T_1 times have been studied for both diagnostic and prognostic uses. Individuals with confirmed or suspected amyloidosis have shorter post-contrast T_1 times in both subendocardial and subepicardial tissues compared to healthy controls.(5) Additionally, small T_1 differences between subepicardial and subendocardial tissues have been linked to poor prognosis.(8) Post contrast T_1 measurements have been useful, but they are affected by multiple factors such as the dose and type of Gd contrast used, timing after gadolinium (Gd) administration, and renal clearance. Quantification of the extracellular volume (ECV) has been used to eliminate part of these dependencies in studying other diffuse fibrotic diseases. Modified Look Locker Inversion (MOLLI) and other T_1 mapping pulse sequences have been used to evaluate multiple cardiac pathologies characterized by diffuse fibrosis to generate T_1 maps of the heart in order to determine the partition coefficient (λ) and volume of distribution of Gd (Vd_{Gd}).(9-11) There has been limited application of these techniques for studying extracellular protein deposition of cardiac amyloidosis *in vivo*.(12) The purpose of this study was to use a modified MOLLI T_1 mapping technique(13) before and after gadolinium administration to determine λ and Vd_{Gd} in patients with suspected amyloidosis and to compare these values to those of normal subjects. We hypothesize that these parameters will be markedly elevated in amyloidosis due to the expansion of the extracellular space and will thus provide a quantitative assessment of cardiac amyloidosis.

Materials and Methods

The study population consisted of five consecutive individuals (68.6 ± 9.4 years)who were referred by a cardiologist for a clinically ordered CMR study due to a high clinical suspicion of cardiac amyloidosis and/or biopsy proven amyloidosis (Table 1) as part of their diagnostic evaluation who also underwent T_1 mapping for research. Patients underwent a standard clinical CMR study which included steady-state free precession (SSFP) cine images to evaluate myocardial function, and post-contrast inversion recovery imaging to assess late gadolinium enhancement (LGE). All patients were in normal sinus rhythm during their CMR examination, and had a GFR>30 ml/min (per institutional policy). Studies were performed on a 1.5T MR scanner (Magnetom Avanto, Siemens Healthcare) between January and October of 2011, and data was retrospectively analyzed. Eight normal volunteers aged 50.6 ± 9.9 years were scanned for comparison. The normal subjects had a hematocrit (Hct) drawn at the time of the CMR study. The most recent clinical Hct was recorded for the suspected cardiac amyloidosis subjects. This study was approved by our institutional review board.

T_1 mapping was performed before and approximately 20 minutes following bolus administration of 0.15 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer Healthcare). T_1 mapping was performed on a mid-ventricular short axis slice with a 3-5 MOLLI pulse sequence consisting of two inversion pulses separated by 3 heart beats.(14) The first inversion pulse was followed by 3 images taken over 3 heart beats, and the second pulse by 5 images taken over 5 heart beats for a total of 8 images over 11 heartbeats. Typical MOLLI sequence parameters included: TE/TR/FA 1.1 ms/2.5ms/35°, FOV= 340 × 272, resolution 1.8mm × 1.8mm, slice thickness 8mm. Calculation of T_1 maps was performed using an in-house custom MATLAB (MathWorks Natwick, MA, USA) program, where a T_1 map was created by performing a pixel by pixel non-linear-squares fit using the Levenberg-Marquardt algorithm. For data analysis the endocardial and epicardial borders of the left

ventricular myocardium were manually segmented so that the entire myocardium was used to determine the mean myocardial T_1 relaxation times. Additionally, the myocardium was divided into 6 equal-angular segments defined by manual localization of the center of the LV cavity and the superior right ventricular insertion site to assess regional variability in λ and Vd_{Gd}. The T_1 of blood was determined by selecting a region of interest within the left ventricular cavity. The ROI was drawn in the same location for all subjects.(14). Using these T_1 relaxation times and assuming fast water exchange, both λ and Vd_{Gd} were calculated by equations 1 and 2, respectively (10):

$$\lambda = \frac{R_{1myo\ post} - R_{1myo\ pre}}{R_{1LVC\ post} - R_{1LVC\ pre}} \quad [1]$$

$$Vd_{Gd} = \left(\frac{1 - Hct}{100}\right) * \lambda \quad [2]$$

where R1 is the relaxation rate ($1/T_1$) of the myocardium and LV cavity pre and post contrast.

The F-test of equality of variances was used to check for equal variance in pre and post contrast T_1 times, λ, and Vd_{Gd} between amyloidosis subjects and normal subjects. Unpaired student t-tests between groups were used to compare the mean values for amyloidosis vs normal subjects. All statistical calculations were performed in Excel. A p-value less than 0.05 was considered to be statistically significant.

Results

Table 1 shows the clinical information for the subjects with suspected amyloidosis. Four of the five subjects had an independent diagnostic test to confirm amyloidosis: Four had tissue biopsies and one had elevated blood light chain proteins and is currently being treated clinically for amyloidosis. The cardiac function parameters are shown in table 2. All of the patients had late gadolinium enhancement in a pattern consistent with amyloidosis. The suspected amyloidosis subjects had an average Hct of 34.1 ± 5.7 and an average heart rate of 83 ± 11 BPM. The normal subjects had an average heart rate of 67 ± 10 BPM and an average Hct of 37.2 ± 3.6.

T_1 maps were successfully obtained in all of the subjects. Figure 1 shows T_1 maps from a representative normal subject and all of the subjects with suspected cardiac amyloidosis before (top row) and 20 minutes after (bottom row) Gd bolus. There was less image contrast between the myocardium and left ventricle in the T_1 maps of the amyloidosis patients compared to the T_1 maps of the normal subjects. The T_1 relaxation times pre and post contrast for the amyloidosis subjects and normal subjects as well as λ and Vd_{Gd} are detailed in Table 3. The amyloidosis subjects had longer pre-contrast T_1 relaxation times of the myocardium ($p<0.001$) and LVC ($p=0.025$) than the normal subjects. Twenty minutes after injecting the Gd bolus, the amyloidosis subjects had a longer T_1 relaxation time in the LVC compared to the normals ($p=0.003$). There was a trend towards a lower T_1 relaxation time in the myocardium post contrast in the subjects with amyloidosis ($p=0.15$). The amyloidosis subjects had a smaller difference in post contrast myocardium and LVC T_1 relaxation times ($\Delta T1_{post}$) than the normal subjects, 17.1±54.3ms vs 136.1 ± 18.4 ms ($p = 0.006$). Additionally, the amyloidosis subjects had a greater difference between post and pre-contrast relaxation rates ($\Delta R_1 = 1/T_{1post} - 1/T_{1pre}$) in the myocardium than the normal subjects, 1.1 s^{-1} vs 0.81 s^{-1} ($p = 0.008$) resulting in a larger numerator for equation 1. Conversely, the

amyloidosis subjects had a smaller ΔR1 for the LVC than the normal subjects, $1.5 \times s^{-1}$ vs $1.8\ s^{-1}$ ($p = 0.007$) resulting in a smaller denominator for equation 1. Both of these differences favor an increase in the partition coefficient and Vd_{Gd} for the amyloidosis subjects.

The mean partition coefficient (λ) of the amyloidosis subjects was 76% higher than that of the normal subjects (0.78±0.18 vs 0.44±0.01; p=0.014), and the mean Vd_{Gd} was 83% greater in amyloidosis subjects than normals (0.51±0.09 vs 0.28±0.01; p=0.005). When analyzed on a segmental basis the standard deviation of λ ranged from 0.02 to 0.13 with a mean of 0.063±0.045), and the standard deviation of Vd_{Gd} ranged from 0.01 to 0.07 with a mean of 0.041±0.026). The regional variability in λ and Vd_{Gd}, as characterized by the segmental SD of the respective parameters divided by their mean values ranged from 2% to 13% with a mean of 7.7±4%.

Discussion

The major finding of this study was the markedly increased partition coefficient, λ, and volume of distribution, $Vd_{Gd,}$ of the myocardium in subjects with amyloidosis as compared to the normal subjects. The λ and Vd_{Gd} were both 1.8 fold higher in the amyloidosis subjects than the normal volunteers. The Vd_{Gd} would be expected to more accurately reflect the extracellular volume fraction since it includes a correction for differences in Hct. One clinical advantage of utilizing the Vd_{Gd} rather than post contrast T_1 mapping is that the Vd_{Gd} should be largely independent of contrast dose, time of post-contrast imaging, clearance of gadolinium, and the presence of significant anemia. Furthermore, the differences in pre and post contrast T_1 relaxation times of the myocardium and blood pool seen between amyloidosis subjects and normal subjects should result in an amplification of the magnitude of difference in λ and Vd_{Gd}. These T_1 differences result in both an increase in ΔR_{1myo} (numerator of equation 1) and a decrease in ΔR_{1LVC} (denominator of equation 1) in amyloidosis subjects which will increase λ and Vd_{Gd} in these subjects as compared to normal subjects. Recently, an increased Vd_{Gd} was used to diagnostically differentiate amyloidosis from hypertension induced hypertrophy in a single case report(15) in which the Vd_{Gd} was 0.49, similar to that found in the present study.

This study demonstrated that pre-contrast T_1 relaxation times in amyloidosis subjects are statistically higher in both the myocardium and LVC as compared to normal volunteers. On average, the amyloidosis subjects' myocardial T_1 relaxation times pre contrast were 181 msec, or 19%, longer compared to normal subjects. Further investigation of the long myocardium pre-contrast T_1 relaxation times is required as even pre-contrast T_1 mapping of the myocardium may provide important information in patients with suspected cardiac amyloidosis. This is important since many patients with suspected amyloidosis have abnormal renal function and may not be candidates to receive gadolinium. Similarly, the amyloidosis subjects had pre-contrast LVC T_1 relaxation times that were 156 msec, or 10%, greater on average than the normal subject The reason for the increased T_1 in the blood pool is not clear but could be related to lower hematocrit or some other abnormality in amyloidosis.

Post-contrast T_1 relaxation times of the blood pool in amyloidosis subjects was also increased compared to the normal subjects. This may be related to differences in blood properties between normal subjects and subjects with amyloidosis, but may also reflect differences in the clearance of gadolinium from the blood pool. Maceira et al described similar increased rates of Gd clearance in amyloidosis subjects in their study.(5)

There was a trend towards decreased post contrast T_1 relaxation times in the myocardium of the amyloidosis subjects as compared to the normal subjects. Given the greater extracellular volume caused by the amyloidosis disease process, shorter T_1 relaxation times in the myocardium would be expected due to the increased volume of distribution for gadolinium. The lack of a difference could be explained by both the time the images were taken post-contrast and the increased rate of gadolinium clearance and the small sample size of this study. Maceira et al also saw a decreasing difference in the post contrast T_1 relaxation times of the myocardium between amyloidosis subjects and normal subjects, particularly starting 12 minutes after Gd administration.(5) However, the post contrast T_1 maps for our study were taken 20 minutes after Gd administration. Further investigation of T_1 mapping in amyloidosis should examine the difference in post contrast T_1 relaxation times at earlier time points.

As expected, the difference in T_1 relaxation times between the myocardium and LVC among the amyloidosis subjects was significantly reduced, by a factor of 8, as compared to the normal subjects. This corresponds to the well described difficulty of ‘nulling’ the myocardium in amyloidosis patients post-contrast and is demonstrated by the reduced contrast between the myocardium and LVC seen in amyloidosis subjects in Figure 1. Since the myocardium and blood have similar T_1 relaxation times, they should also have similar signal intensity on T_1-weighted late delayed enhancement images as was noted by Maceria et al.(5)

Our study had some limitations. First, the sample size was small and only patients with a high clinical suspicion of amyloidosis were evaluated, given this small number of subjects, correlation between λ and Vd_{Gd} with clinical parameters and outcomes are not possible. Second, only 4 of the 5 cases had definitive biopsy proven amyloidosis. The patient without a biopsy had elevated light chain proteins with a high clinical suspicion for cardiac amyloidosis. All patients had evidence of LGE in a pattern consistent with CMR evidence of amyloidosis. Third, we only performed T_1 mapping on a single mid-ventricular slice which may reflect the global burden of disease given the diffuse distribution of cardiac amyloidosis. However, regional heterogeneity from base to apex should be explored in further studies to verify this assertion. Fourth, the Vd_{Gd} has been shown to be increased in patients with left ventricular hypertrophy, and this is the major group of patients who would need to be diagnostically differentiated from patients with cardiac amyloidosis. However, the amyloidosis subjects in our study had an average Vd_{Gd} of 0.51 ± 0.09 and the patient in Robbers et al had a Vd_{Gd} of 0.49. In comparison, two separate T_1 mapping studies found the Vd_{Gd} to be 0.31 ± 0.02(16) and 0.34 ± 0.03(17), respectively, in subjects with left ventricular hypertrophy. Differences in pre-contrast T_1 times, which are increased in amyloidosis patients but not in hypertensive patients with left ventricular hypertension, may also help differentiate these two clinical entities. Finally the methodology used in this paper assumes a fast transcytolemmal water exchange limit which may be violated in the setting of myocyte hypertrophy and high gadolinium contrast concentrations.(18) It has been noted that this assumption typically results in a <5% error in Vd_{Gd} measurements for R_1's less than 2 sec^{-1} (T1 of 500 ms).(19) In our study, the shortest post contrast T_1s in the LV cavity ranged from 458ms-507 ms (R_1s of 2-2.2 sec^{-1}) so this assumption should only have a small effect on the results of this study. In future studies, measuring the T_1s at multiple points post contrast will enable verification of this assumption, or provide data to fit a 2 site exchange model.

In conclusion, this study demonstrates markedly increased λ and Vd_{Gd} for subjects with amyloidosis as compared to normal subjects, and the magnitude of this effect is larger than changes in individual T_1 relaxation times. Moreover as Vd_{Gd} reflects the size of the extracellular space, it is largely independent of Gd dose, timing of imaging post contrast,

and renal clearance of gadolinium. Hence, the Vd_{Gd} is capable of facilitating comparisons between studies completed with different protocols, which would be confounded when just looking at post-contrast T_1 parameters. The increased pre-contrast T_1 relaxation times of the myocardium and left ventricle blood pool could also serve as a diagnostic parameter, particularly in patients with suspected cardiac amyloidosis who do not have sufficient renal clearance for gadolinium. As the deposition of amyloid proteins in the heart is progressive and results in expansion of the extracellular space over time, the Vd_{Gd} may be a useful parameter for quantifying the severity of disease and, potentially, monitoring novel therapies for cardiac amyloidosis.

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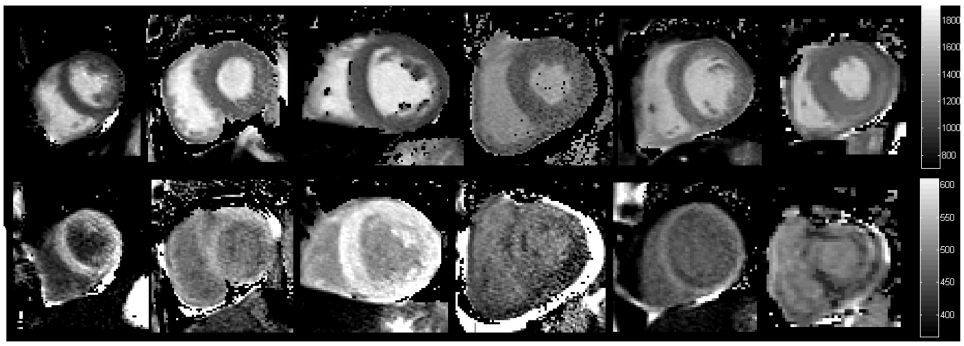

Figure 1.

T_1 maps pre contrast (top row) and post contrast (bottom row) from a normal subject and the 5 subjects with cardiac amyloidosis. The corresponding Vd_{Gd} are 0.29, 0.49, 0.36, 0.55, 0.51, and 0.63, respectively.

Table 1

Clinical information of suspected amyloidosis patients.

Patient	Age	Sex	Hct	HR	BP	GFR	Clinical Information	Additional Tests
1	63	M	29	83	136/70	>60	Low voltage EKG, LVH on echo w/o Hx of HTN, CHF, Hx Renal Amyloid	Renal Biopsy – AL Amyloid
2	71	M	29.9	92	130/80	>60	LVH on echo w/o HTN, weight loss, new CHF	Elevated kappa light chain,
3	68	M	43.2	87	92/58	53	LVH on echo w/o HTN, CHF symptoms, Hx of Myeloma	UPEP+, bone marrow biopsy w/ myeloma
4	58	M	35.2	88	96/60	>60	Low voltage EKG, LVH w/speckle pattern on Echo, diastolic dysfunction, CHF	Cardiac Biopsy – AL Amyloid
5	83	M	33	63	130/68	>60	LVH on echo, abnormal stress echo, CHF	Cardiac Biopsy –AL Amyloid
Mean±SD	68.6±9.4		34.1±5.7	82.6±11.4				

*Hct= Hematocrit values. BP=Blood pressure in mmHg, GFR in mL/min/1.73m^2

Table 2

Functional CMR Parameters from the Amyloidosis Subjects

Patient	LVEF (%)	LVEDV (mL)	LVESV (mL)	LVM (g)	LVMI (g/m^2)
1	60.4	142.92	56.62	83	83.6
2	37.3	253.2	158.8	92	124.7
3	49.4	100.81	51	87	83.7
4	56.4	124.7	54.4	88	104.7
5	44.7	114.1	63.1	63	123.8
Mean±SD	49.6±9.2	147.6±61.3	76.8±46.1	82.6±11.4	104.1±21.3

Table 3

Comparison of amyloidosis patients and normal individuals.

	Amyloidosis (mean±SD)	Normal (mean±SD)	Significance (p-value)	Percent difference
T_1 LV Pre	1665±133	1509±85	0.025	10.3
T_1 Myo Pre	1144±49	963±42	<0.001	18.8
T_1 LV Post	486±18	408±42	0.003	19.2
T_1 Myo Post	503±61	544±36	0.153	7.5
ΔT_1 post	17.1±54.3	136.1 ± 18.4	0.006	800
λ	0.78±0.18	0.44±0.01	0.014*	75.9
Hct	34±5.68	37±3.56	0.249	8.3
Vd_{Gd}	0.51±0.09	0.28±0.01	0.005*	82.6