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Evaluation of MOLLI and arrhythmia-insensitive-rapid (AIR) cardiac T1 mapping pulse sequences in cardiomyopathy patients

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Disclosures None

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Abstract

Objective—To compare performance of arrhythmia insensitive rapid (AIR) and Modified Look-Locker inversion recovery (MOLLI) T1 mapping in patients with cardiomyopathies.

Methods—In 58 patients referred for clinical cardiac MRI at 1.5T, we compared MOLLI and AIR native and post-contrast T1 measurements. Two readers independently analyzed myocardial and blood T1 values. Agreement between techniques, inter-reader agreement per technique, and intra-scan agreement per technique were evaluated.

Results—MOLLI and AIR T1 values were strongly correlated ($r^2=0.98$), however statistically significantly different T1 values were derived (bias 80ms, pooled data, $p < 0.01$). Both techniques demonstrated high repeatability (MOLLI, $r^2 = 1.00$ and coefficient of repeatability (CR) =72 ms; AIR, $r^2 = 0.99$ and CR =184.2 ms) and produced high inter-reader agreement (MOLLI, $r^2 = 1.00$ and CR =51.7 ms; AIR, $r^2 = 0.99$ and CR =183.5 ms).

Conclusions—AIR and MOLLI sequences produced significantly different T1 values in a diverse patient cohort.

Keywords

MRI; cardiac; T1 mapping; arrhythmia insensitive rapid; MOLLI

Introduction

Cardiomyopathy is an umbrella term encompassing a heterogeneous group of diseases of the myocardium that may lead to heart failure and ultimately death [1, 2]. A common pathological end-point for many cardiomyopathies is the accumulation of interstitial collagen, leading to expansion of the extracellular volume (ECV) and fibrosis formation. Fibrosis can develop diffusely and focally and cause contractile dysfunction [3-8]. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is the gold standard for imaging of focal fibrosis [9, 10]. However, it is ill-suited for imaging diffuse interstitial fibrosis, since it relies on difference in contrast agent washout kinetics between normal and scarred myocardium [11].

ECV mapping derived from native and post-contrast T1 mapping, in the absence of myocardial edema, has been associated with diffuse myocardial fibrosis [11-17]. Cardiac T1 mapping can be accomplished in a variety of ways following preparation by inversion or saturation recovery, or a combination of preparations, which vary in accuracy, precision and reproducibility [18]. A common theme limiting their application is sensitivity to heart rate and rhythm. The most widely used and commercially available method of cardiac T1

mapping is Modified Look-Locker inversion recovery (MOLLI) [19]. While MOLLI has been reported to be highly precise, its accuracy is dependent on cardiac rhythm, heart rate, magnetization effects [20], and T2 effects [21]. Furthermore, MOLLI requires a prolonged breath hold, which can be difficult for sick patients with limited breath-hold capacity.

To overcome such limitations, an arrhythmia insensitive rapid (AIR) cardiac T1 mapping pulse sequence has been developed [22, 23], based on a transmit radiofrequency field (B1+)-insensitive saturation recovery (SR) pulse. Briefly, AIR acquires two single-shot images (over 2-3 heart beats, dependent on heart rate) and calculates T1 using the Bloch equation, describing SR with one proton density (PD) weighted image and one T1 weighted image, as previously described [22, 23]. Because AIR uses a SR pulse, it is inherently insensitive to heart rate and rhythm. Furthermore, AIR is more adaptable for rapid T1 mapping, because it acquires only two images. These two features of AIR – arrhythmia insensitivity and rapid imaging - broaden its clinical application to patients who are too sick for long breath-holds and/or have irregular heart rhythm. Evaluation of the AIR sequence has incorporated animals and healthy volunteers to date, with limited clinical experience.

The primary purpose of this study was to compare T1 values derived from AIR and MOLLI cardiac T1 mapping pulse sequences in patients with known or suspected cardiomyopathy. Secondary objectives were to assess inter-observer variability and intra-scan repeatability of each sequence in the same clinical cohort.

Materials and Methods

Patient Cohort

This was a single center retrospective cross-sectional study, with the requirement for informed consent waived by our institutional ethics committee. The target population was adult patients >18 years presenting for CMR to evaluate known or suspected cardiomyopathy involving the left ventricle (LV), where T1 mapping is routinely performed. Patients were excluded if LGE imaging was not obtained, they had acute renal impairment, or chronic kidney disease with $\text{eGFR} < 30 \text{ ml/min/1.73m}^2$. A total of 72 patients were scanned over an eight month period in 2015, 58 of whom met inclusion criteria. Reasons for exclusion included; incomplete scan protocol (n=9), poor image quality from respiratory motion artifact (n=5). Of note, three patients included in the final cohort had heart rates >100 beats per minute (bpm), and two separate patients were in documented atrial fibrillation (AF) at the time of scanning. Patient characteristics and clinical referral details are summarized in Table 1.

Image Acquisition

Imaging was performed on a whole-body 1.5T scanner (Avanto, Siemens Healthcare, Erlangen, Germany), with a 6-channel body phased array coil anteriorly and spine coils posteriorly automatically selected by the system. Both MOLLI and AIR T1 mapping acquisitions were performed in a short axis plane at mid-ventricular level, with breath-holding at end-expiration. AIR and MOLLI were performed in random order prior to contrast administration and again at 5 minutes post administration of 0.2 mmol/kg

gadoterate meglumine (Dotarem®, Guerbet, Villepinte, France). In a cohort of initial patients (n=14), both sequences were performed twice, both pre and post-contrast, during the same examination, to assess intra-scan reliability. Phase-sensitive inversion-recovery (PSIR) late gadolinium enhanced imaging was performed at approximately 8 minutes after administration of contrast agent as part of the clinical protocol.

AIR acquisitions were acquired with a trigger delay of 600ms, and T1-weighted and proton density (PD) images were acquired with T1 calculated from the ratio of both acquired sequences [22]. MOLLI was performed as previously described by Kellman et al [19, 24]. Other sequence parameters for both AIR and MOLLI are presented in Table 2.

Image Analysis

For MOLLI, a T1 map was automatically generated by the scanner. T1 maps for AIR images were processed by a radiologist with 4 years' experience with MRI (XX, anonymized for review), using customized software in MATLAB (R2009a, MathWorks, Inc, Natick, MA, USA). The same radiologist performed subjective image quality assessment of AIR and MOLLI derived T1 maps, to determine diagnostic versus non-diagnostic image quality. Myocardial and blood pool T1 segmentation of AIR- and MOLLI-derived T1 maps was performed independently in random order by two independent readers (cardiologists YY and ZZ with 2 and 1 years' experience with cardiac MRI, respectively), blinded to patient presentation and identity, using a customized Matlab tool to calculate blood and myocardial T1 value. Areas of LGE (identified by readers on PSIR imaging available at the time of segmentation) were excluded, and blood pool regions of interest were selected to exclude papillary muscles and trabeculations.

Statistical Analysis

Continuous variables were summarized using mean and standard deviation (SD). Mean native T1 and post-contrast T1 values were compared using a paired t-test. Bland-Altman and linear regression analyses were used to assess: (a) inter-technique agreement, (b) inter-reader agreement for each technique, and (c) intra-scan repeatability of each technique. Additionally, we calculated the coefficient of repeatability (CR), which is defined as $1.95 \times$ standard deviation of the difference. To avoid confusion with terminology, we note that CR increases with variability in repeated measurements (i.e., lower agreement). For all analyses, $p < 0.05$ was considered significant unless adjustment for multiple comparisons was applied. All analyses were performed using Stata version 14 (StataCorp, College Station, Texas, USA).

Results

Figure 1 shows representative image quality of T1 maps produced by MOLLI and AIR in a patient.

Both MOLLI and AIR T1 mapping pulse sequences produced significantly different mean native myocardial T1, native blood T1, post-contrast myocardial T1, and post-contrast blood T1 values ($p < 0.0001$) Table 3. This led to a positive bias of 80.0 ms in the Bland-Altman analysis (Fig. 2). As shown in Figure 3, both MOLLI ($r^2 = 1.00$ and $CR = 51.7$ ms) and AIR

($r^2 = 0.99$ and $CR = 183.5$ ms) pulse sequences produced high inter-reader agreement for the entire cohort. Both MOLLI ($r^2 = 1.00$ and $CR = 72$ ms) and AIR ($r^2 = 0.99$ and $CR = 184.2$ ms) pulse sequences produced high intra-scan repeatability in the subgroup of patients where both sequences were acquired twice, with results presented in Figure 4.

Two patients were in atrial fibrillation at the time of examination, with statistical under-powering precluding subgroup analysis of the impact of arrhythmia on derived values. Subjectively, the overall quality of T1 maps was similar between the patients in atrial fibrillation (Figure 5) and sinus rhythm (Figure 1).

Discussion

In this study, we have evaluated the performance of MOLLI and AIR cardiac T1 mapping pulse sequences in cardiomyopathy patients undergoing clinical MRI at a tertiary referral center. Consistent with a previous pre-clinical study [23], our study in patients showed that MOLLI and AIR produced significantly different T1 values. Also consistent with a previous clinical study [25], MOLLI produced higher repeatability than AIR.

The AIR T1 mapping sequence was developed in response to acknowledged limitations of MOLLI, namely, sensitivity to heart rate and rhythm, and relatively prolonged scan time. AIR, by comparison, is not sensitive to heart rate and rhythm and is clinically attractive, with only 2-3 heart beats required in a single breath hold. Early phantom and animal studies [22, 23] suggest that AIR has the potential to make an important contribution to the noninvasive assessment of diffuse myocardial fibrosis.

As a comparator for the sequence being evaluated, our MOLLI-derived T1 values are in agreement with the reported literature at 1.5T in both healthy subjects and those with known/suspected cardiac disease [26, 27]. Our native myocardial MOLLI mean T1 value (986 ms) compared similarly with mean values published by Reiter et al [27] (984 ms in healthy volunteers at 1.5T) and Rogers et al [28] (952 ms in patients with left ventricular hypertrophy and dilated cardiomyopathy at 1.5T).

Limited studies to date have evaluated the performance of AIR T1 mapping sequence. Fitts et al [22] demonstrated consistently lower native T1 values for MOLLI than AIR with poor agreement between the two. A later study by Hong et al [23] demonstrated significant differences in animal MOLLI and AIR mean T1 values for native/post-contrast myocardium and native blood pool. Our study demonstrates similar findings of significantly lower T1 values for MOLLI compared to AIR for native/ post contrast myocardium and blood pool. These differences in derived T1 values could be explained by MOLLI's recognized under-estimation of myocardial T1, particularly at higher T1 values [20, 21, 29, 30]. The reasons behind such under-estimation have been explored and include the effect of slight T2 weighting (due to steady-state free precession behavior) [30], magnetization transfer (altering the shape of the inversion recovery curve) [20] and dependence on inversion pulse efficiency (with imperfect inversion accounting for up to 4% of error in T1 estimation) [31, 32]. AIR T1 estimation is not influenced by any of the aforementioned variables and has

been shown to be more accurate in reference T1 phantom models compared to MOLLI, suggesting that AIR may more accurately reflect tissue T1 values [18, 22].

MOLLI produced T1 maps with qualitatively greater signal-to-noise ratio (SNR) in comparison to AIR, in keeping with longer acquisition over a greater number of heart beats. MOLLI samples the magnetization recovery curve 8 times acquiring more lines of k-space, in comparison to AIR which samples the curve at 2 time points on the curve. MOLLI's higher SNR is reflected in the narrower confidence intervals and lower co-efficient of variability obtained for T1 values when compared to AIR sequence. In particular, our native AIR T1 values demonstrated greatest variability, where myocardial and blood T1 are relatively long.

Our findings from a clinical cohort contribute to the few preliminary studies of the AIR sequence as a rapid cardiac T1 mapping pulse sequence. On a practical level, the sequence was easily incorporated in CMR workflow and post-processing was efficient. Whilst not subjectively evaluated in our study, we would suggest that AIR might be better tolerated by unwell patients, due to reduced breath-hold requirements.

Our study has several limitations. We had a small sample size of a heterogeneous population, with all data acquired at a single institution on a single scanner. Previous AIR research was performed at 3T magnetic field strength, limiting comparison with our data at 1.5T. Relatively lower achievable SNR at 1.5T likely impacted repeatability of native blood pool and myocardial assessments with AIR. We did not perform repeatability analysis on separate days. Images were acquired at 5 minutes post contrast administration in order to optimize CMR workflow, which does not reflect true equilibrium [33, 34]. Due to the combination of our clinical population and logistics of magnet workflow in a busy academic institution, it was not felt practical to delay T1 mapping acquisitions further until after the LGE acquisition.

We were unable to make a formal assessment of patients with arrhythmia due to the low prevalence in our cohort, with only three patients with a heart rate over 100 bpm and two patients in atrial fibrillation at the time of examination, precluding formal statistical analysis in this subgroup. Hematocrit was not routinely obtained in our clinical cohort, precluding calculation of ECV. We elected not to calculate partition coefficient (λ) because post-contrast imaging was conducted 5 minutes after administration of gadolinium. Further experience in a larger cohort is necessary including more patients with arrhythmia, and with post contrast imaging performed after at least a 15-minute delay.

We conclude that AIR and MOLLI pulse sequences yield significantly different T1 values. Both pulse sequences produce high intra-scan repeatability and inter-reader agreement. Awareness of differences in derived T1 values is important for clinical interpretation of results, with potential diagnostic, monitoring and management implications.

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Figure 1.
Representative native and post-contrast T1 maps as shown. 29 year old male with suspected myocarditis (HR 68 bpm)

Inter-Technique Agreement

Reader #1

Reader #2

Figure 2.

Linear regression and Bland-Altman plots comparing MOLLI and AIR T1 values: as assessed by reader 1 (top row) and reader 2 (bottom row).

Inter-Reader Agreement

Figure 3.
Linear regression and Bland-Altman plots evaluating inter-reader agreement: for MOLLI (top row) and AIR (bottom row). Note that smaller CR represents better agreement.

Intra-Scan Repeatability

Figure 4.

Linear regression and Bland-Altman plots evaluating intra-scan repeatability of both readers combined: for MOLLI (top row) and AIR (bottom row). Note that smaller CR represents better agreement.

Figure 5. Representative native and post-contrast T1 maps of a 54 year old male with suspected dilated cardiomyopathy in atrial fibrillation (HR 110 bpm). Overall, the T1 map quality is similar as shown in Figure 1. Compared with MOLLI, AIR produced higher native and post-contrast T1 values.

Table 1

Patient Characteristics. Continuous variables are presented as mean±standard deviation, patient numbers are provided with percentages in parentheses

Characteristic	Patients (n=58)
Average Age (years)	53±16
Male	35 (60%)
BMI (kg/m ²)	2.2±0.4
Heart rate (bpm)	67±16
Sinus rhythm	56 (96%)
Patients with LGE	19 (32%)
Indication for Cardiac MRI	
Known or suspected hypertrophic / hypertensive heart disease	15 (26%)
Known or suspected dilated cardiomyopathy	15 (26%)
Known or suspected infiltrative disease (i.e. sarcoid, amyloid)	2 (3%)
Known or suspected myocarditis/pericarditis	11 (19%)
Suspected arrhythmogenic ventricular focus	8 (14%)
Valvular disease	1 (2%)
Ischaemia	6 (10%)

BMI=body mass index, BPM=beats per minute, HR=heart rate, LGE=late gadolinium enhancement

Table 2

MRI parameters for arrhythmia-insensitive-rapid (AIR) and Modified Look-Locker inversion recovery (MOLLI)

Parameter	AIR	MOLLI
TR/TE (ms)	2.4/1	2.4/1
Matrix	192 × 144	192 × 144
Slice thickness (mm)	8	8
Flip angle (degrees)	55	35
Field of view (mm)	360 × 270	360 × 270
R (GRAPPA [*])	2	2
Partial Fourier	none	7/8
Total k-space lines	84	72
Band width (Hz/pixel)	930	965
Temporal resolution (ms)	201	173
Acquisition	Single breath hold, 2-3 beats, 2 × single shot images	Single breath hold, 11 beats, 8 × single shot images

^{*} GRAPPA – generalized autocalibrated partially parallel acquisitions [35]

Table 3

Pair-wise t-test statistics comparing the different subgroups of T1 derived from Modified Look-Locker Inversion-recovery (MOLLI) and arrhythmia-insensitive-rapid (AIR) cardiac T1 mapping pulse sequences: native myocardial T1, native blood T1, post-contrast myocardial T1 and post-contrast blood T1. T1 value represents mean $\pm$ standard deviation

Tissue type	MOLLI	AIR	<i>p</i>
Native myocardial T1	985.5 $\pm$ 47.8 ms	1119.7 $\pm$ 55.4 ms	< 0.0001
Native blood T1	1548.8 $\pm$ 94.4 ms	1647.9 $\pm$ 144.2 ms	< 0.0001
Post-contrast myocardial T1	333.0 $\pm$ 43.0 ms	406.2 $\pm$ 43.6 ms	< 0.0001
Post-contrast blood T1	209.6 $\pm$ 35.0 ms	223.7 $\pm$ 33.8 ms	< 0.0001