Published in final edited form as:

Int J Cardiovasc Imaging. 2013 January ; 29(1): 103–112. doi:10.1007/s10554-012-0042-4.

Utility of the inversion scout sequence (TI scout) in diagnosing myocardial amyloid infiltration

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Abstract

To evaluate the utility of inversion scout (TI-scout) obtained during cardiac magnetic resonance imaging (CMR) in diagnosing myocardial amyloid infiltration. A retrospective analysis of CMR exams in 39 patients (24 males, age range 29–77 years) was performed. Imaging was performed on a 1.5T system, and included steady state cine, post contrast TI-scout and delayed enhancement images. Evaluations included studies in 13 patients with myocardial amyloidosis and 26 patients without myocardial amyloidosis. To characterize abnormal nulling, the time to myocardial nulling on the TI scout was compared to the null times of the blood pool and spleen for each scan. The sensitivity and specificity of different tissue nulling abnormalities for myocardial amyloidosis were computed. The null times of tissues in 18/26 (69 %) patients in the non-amyloid group followed a consistent order with the blood pool null time preceding the myocardial nulling which was equal to that of splenic nulling (Type 1 pattern). This order differed in all 13 patients with myocardial amyloidosis described as three non-mutually exclusive nulling categories: 10 patients had myocardial null time preceding or coincident with blood pool (Type 2 pattern); in 11 patients myocardial null time was non-coincident with splenic nulling (Type 3 pattern); and in 8 patients myocardial null time was non-coincident with both blood pool AND splenic nulling (Type 4 pattern). While no patient exhibited Type 4 nulling pattern in the non-amyloid group, 1/26 patient had a Type 2 and 7/26 patients had a Type 3 nulling pattern. A sensitivity of 100 % was obtained when either Type 2 OR Type 3 nulling was present while a specificity of 100 % was obtained when both Type 2 AND Type 3 nulling were present together (Type 4 pattern). Our study demonstrates that the pattern of nulling on the TI scout sequence CMR has potential diagnostic utility for the presence of myocardial amyloidosis. The temporal pattern of myocardial, blood pool and splenic nulling needs to be carefully evaluated on the TI scout sequence and could prove useful in other infiltrative cardiomyopathies.

Keywords

Cardiac; Magnetic resonance imaging; Amyloidosis

Introduction

Amyloid infiltration of the myocardium is known to have a very poor prognosis [1]. The current gold standard for diagnosis of myocardial amyloidosis is an endomyocardial biopsy, which is an invasive procedure.

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Conflict of interest None.

A diffuse granular or sparkling appearance with left ventricular hypertrophy may be observed on echocardiography, and low voltage peaks on ECG have also been described with myocardial amyloidosis but with lower specificity [2]. Though echocardiography was thought of as the gold standard for non-invasive test of choice in the diagnosis of cardiac amyloidosis in the past, recent studies have shown that delayed enhancement CMR (DE-CMR) with its ability to evaluate myocardial infiltration using DE is the test of choice, not only when there are typical features of cardiac amyloidosis like diffuse subendocardial enhancement, but also features such as patchy focal enhancement and suboptimal nulling, when the myocardium is not significantly thickened [3].

DE-CMR, has its own challenges especially in patients who are unable to comply with optimal breath-hold resulting in poor quality of DE images, especially if DE-CMR protocol uses the magnitude and phase sensitive inversion recovery sequences instead of the single shot non-breath hold images. Frequently, myocardial amyloidosis results in difficulty in obtaining an optimal null time on TI scout and therefore suboptimal DE images [4]. Not infrequently, many myocardial amyloidosis patients also have large pleural and pericardial effusions, with artifacts on the DE sequence. Rarely, differentiation between infarct and myocardial amyloidosis using DE-CMR in a typical coronary arterial territory may also be difficult. We observed that on the inversion scout (TI scout) sequence, which is part of a routine post contrast cardiac MRI study, the inversion time of abnormal myocardium showed a distinct temporal order of nulling in relation to spleen and blood on the inversion scout image in normal individuals. While abnormal nulling of the blood pool has been noticed by other investigators, the pattern and temporal order of the nulling has not been investigated [5]. Thus, we explored the possibility of using the abnormality in temporal nulling on a TI scout sequence as an additional tool for diagnosing myocardial amyloidosis.

Materials and methods

Study subjects, inclusion/exclusion criteria

A retrospective analysis was conducted on 39 consecutive patients evaluated between June 2006 and July 2009 (24 males, age range 29–77 years). The study was approved by the institutional review board. The indications included multiple myeloma (27 patients), ischemic heart disease (9 patients), and suspected left to right shunt (3 patients). Exclusion criteria included poor quality exam, insufficient clinical data, or non-administration of contrast. No patients were excluded based on these criteria. Four patients had multiple exams, and only the first one was included in this analysis.

Amyloid group

This group had 13 patients who were positive on chart review for myocardial amyloidosis. Of these 13 patients, an endomyocardial biopsy was performed in 6, all being positive for myocardial amyloidosis. The remaining 7 patients were diagnosed with myocardial amyloidosis based on clinical criteria (patients with multiple myeloma or monoclonal gammopathy of unknown significance with any one of the following: clinical symptoms of arrhythmia or congestive heart failure, lambda light chain levels high in serum or end-organ involvement such as proteinuria or peripheral neuropathy) and DE-CMR findings of myocardial amyloidosis with global subendocardial delayed enhancement in a non-territorial distribution (Fig. 1).

Non amyloid group

This group of 26 patients consisted of multiple myeloma (14 patients) as well as patients with non-myeloma indications (12 patients). All myeloma patients in this group were negative for myocardial amyloidosis based on clinical and DE-CMR criteria discussed

above (14 patients), with 4 patients having a negative endomyocardial biopsy. None of the non-myeloma patients underwent an endomyocardial biopsy but all had CMR which was negative for myocardial infiltrative disease based on normal nulling of the myocardium on the 10 min delayed post-contrast phase sensitive inversion recovery sequences (Fig. 1).

MRI technique

All imaging was performed on a 1.5-T scanner (Siemens 1.5T Avanto, Erlangen, Germany). All acquisitions were obtained during breath-hold in expiration and retrospective ECG gating. Routine sequences included cine and static steady-state free precession, dark blood T1 and T2, TI scout 10 min after gadolinium injection followed by delayed hyper-enhancement PSIR sequence. The TI scout gradient echo sequence had the following parameters: 8 mm thick, mid ventricle level, TR 20 ms (ms), TE 1.24 ms, flip angle 50°, generated using 20 ms increments from 85 to 795 ms. The inversion time used for the delayed hyper-enhancement was the time to complete nulling of the signal of the myocardium on the inversion scout (TI scout) sequence. DE-CMR was performed using 2D phase sensitive inversion recovery (PSIR) Turbo FLASH sequence (TR/TE 700/5.4 ms; flip angle 25°; slice thickness 6–8 mm).

Image interpretation

Two cardiac MRI radiologists who worked in consensus analyzed the TI scout images. The images were viewed on the commercial cardiac workstation (Argus viewer, version VA50C, Siemens Medical Solutions, Erlangen, Germany) and PACS (Sectra, Philips, Netherlands). The readers were not aware of the final clinical diagnosis at the time of the review. The temporal order of nulling of the contrasted blood pool, myocardium and spleen were recorded in each case from the TI scout sequence. The individual TI times were not recorded. Normal temporal nulling order was classified as Type 1 if blood pool nulling was followed by myocardial nulling, and splenic nulling was coincident with myocardial nulling (Fig. 2). Abnormal nulling was classified as Type 2, 3 or 4. Type 2 nulling was defined as myocardial null time preceding or coinciding with the blood pool (Fig. 3), and Type 3 as myocardial nulling non-coincident with the splenic nulling (Fig. 4). A Type 4 pattern was present if both Type 2 AND Type 3 nulling was seen (i.e., when the myocardium nulled before or at the null time of the blood and the myocardial nulling was non-coincident with the splenic nulling, Fig. 5). The abnormal nulling Types 2, 3 and 4 were non-mutually exclusive categories since some patients exhibited more than one pattern. These patterns were also studied using signal intensity graphs plotted across all the images of the TI scout sequence over regions of interest (ROI) placed over the blood pool, the myocardium and the spleen (Fig. 6).

Statistical methods

The associations of myocardial nulling patterns with myocardial amyloidosis as determined by biopsy/clinical diagnosis and DE-CMR were investigated using Chi-square tests. To assess the diagnostic performance of different nulling types, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and corresponding exact binomial 95 % confidence intervals were computed. Competing nulling types were compared in terms of sensitivity and specificity using the exact McNemar's test for paired data.

Results

Patient characteristics

Table 1 summarizes the cardiac MRI parameters of left ventricular ejection fraction, myocardial mass, and presence of biopsy proven amyloid in myocardium and other tissues

in both the amyloid and non-amyloid groups. The amyloid group had significantly higher median myocardial mass as compared to the non-amyloid group (79 vs. 57, $p = 0.022$), and there was a trend for a higher left ventricular ejection fraction (65 vs. 58, $p = 0.097$). Amyloid in non-cardiac anatomical regions was only found in two patients (8 %) in the non-amyloid group as compared to eight patients (62 %) in the amyloid group ($p = 0.001$); however, this may reflect a selection bias as all patients were not tested for all anatomical regions.

Pattern of nulling on TI scout sequence

Type 1 nulling pattern was seen in 18 of 39 patients. No patients with myocardial amyloidosis demonstrated Type 1 nulling. Type 2 pattern (loss of normal temporal nulling pattern between the blood pool and myocardium) was seen in 11 patients and Type 3 pattern (spleen-myocardial non-coincidental nulling) in 18 patients. Type 4 pattern (both Type 2 AND 3) was seen in 8 patients.

Association of myocardial nulling patterns on TI scout with cardiac amyloidosis

The performance of myocardial nulling patterns on the TI scout sequence in diagnosing myocardial amyloidosis as determined by DHE-MRI and cardiac biopsy/clinical diagnosis is summarized in Table 2 and Fig. 7. Type 1 nulling was associated with a lower risk of myocardial amyloidosis and Types 2–4 were associated with a higher risk (all $p < 0.05$).

Type 2 nulling had a sensitivity of 77 % (95 % CI: 46–95 %) and Type 3 nulling had a sensitivity of 85 % (95 % CI: 55–98 %) and were not significantly different from each other ($p = 0.65$). The Type 4 nulling (Type 2 and 3 nulling pattern) had a sensitivity of 62 % (95 % CI: 32–86 %). If Type 2 OR Type 3 nulling is present the sensitivity was 100 % (95 % CI: 75–100 %) but the improvement was not significantly better than Type 2 ($p = 0.25$) or Type 3 ($p = 0.50$) individually, given the denominator of 13 subjects.

When the TI scout nulling was correlated with myocardial amyloid diagnosis, Type 2 nulling yielded significantly better specificity than Type 3 nulling [96 % (95 % CI: 80–100 %) vs. 73 % (95 % CI: 52–88), $p = 0.034$]. The specificity was the highest for Type 4 nulling [100 % (95 % CI: 87–100 %)], which was significantly better than Type 3 nulling ($p = 0.016$), but not Type 2 nulling ($p = 1.000$).

In our population, which included patients with non-amyloid indications, the positive predictive value was good in Type 4 [100 % (95 % CI: 63–100 %)] and Type 2 [91 % (95 % CI: 59–100 %)], and the negative predictive value was good when groups Type 2 OR Type 3 nulling were present [100 % (95 % CI: 82–100 %)].

Discussion

The focus of our study is to detect myocardial amyloidosis using CMR TI scout sequence. The role of the temporal order of nulling of tissues (myocardium, blood pool and spleen) to diagnose myocardial amyloidosis has not been studied to the best of our knowledge. Our study shows that analysis of the TI scout sequence with specific attention to the order of temporal nulling between myocardium, blood pool, and spleen can be used to predict the presence of myocardial amyloidosis. Patients with myocardial amyloid infiltration null the myocardium before that of the blood pool and/or non-coincidentally with the spleen as compared to non-amyloid patients who have a predictable order of nulling with blood pool at shorter times than the myocardium. The myocardium and spleen null coincidentally in most non-amyloid patients.

Myocardial amyloid involvement is the cause of death in approximately half of patients with AL-amyloidosis [6, 7]. Once congestive heart failure occurs, the median survival is 6 months in untreated patients [1]. The most effective way to slow down progression of the disease is by administering high-dose chemotherapy [8]. Therefore, timely diagnosis and monitoring of cardiac involvement during therapy is advisable. Endomyocardial biopsy is a gold standard but has its own limitations including ventricular free-wall perforation up to 0.4 %, arrhythmia 0.5–1.0 %, conduction disorders 0.2–0.4 % [9]. Biopsy also has a potential for sampling error. It is therefore not a practical tool for monitoring the disease process. Clinical diagnosis is often based on a combination of the multiple criteria such as presence of arrhythmia, ECG voltage abnormalities, congestive heart failure, high lambda light chain levels in serum, other end-organ deposition of amyloid, proteinuria, and peripheral neuropathy.

The literature enumerates several diagnostic features of myocardial amyloidosis on MRI such as increased interatrial and interventricular septum thickness, elevated T1 and T2 relaxation times, and diffuse post contrast enhancement [4, 10–13].

DE-CMR is the most powerful non-invasive tool to detect myocardial amyloidosis [11]. The concept of DE-CMR is that the signal from the normal myocardium can be completely nulled about 5–30 min after contrast administration using specialized pulse sequence and differential enhancement patterns between abnormal myocardium which retains contrast and normal nulled myocardium can be studied. In order to find the optimal myocardial null time to obtain DE CMR images, the traditional method has been to use an inversion scout (TI scout) sequence where multiple frames of a midventricular section are acquired, each with a different TI. Along with the myocardium, the TI scout sequence also demonstrates nulling of other tissues like the blood pool, spleen, and liver. The normal myocardium nulls at about 200–300 ms at 10 min in a 1.5 Tesla scanner.

In a typical patient with myocardial amyloidosis, on DE-CMR obtained using the above technique, diffuse subendocardial or transmural hyperenhancement of the myocardium in a non coronary distribution in association with ventricular wall thickening can be expected [14]. According to some studies, myocardial amyloidosis can be diagnosed with high sensitivity and specificity (93 and 95 % respectively) using DE-CMR if this imaging appearance is seen [11]. This pattern is unlike myocardial infarction that shows subendocardial or transmural DE in coronary distribution and various non-ischemic myocarditis/cardiomyopathies (sarcoidosis, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, chagas disease etc.) that show intramural and/or epicardial distribution [7]. The exact mechanism of this diffuse subendocardial DE in myocardial amyloidosis is not well known. It could be due to nonfibrotic interstitial widening due to amyloid. Whatever be the underlying mechanism, it should be noted that this typical global subendocardial DE pattern, although specific, was not found to be sensitive and was seen in only about 69 % of amyloid patients in one study [4].

Another limitation in amyloid imaging is selecting an optimal TI time using the TI-scout sequence. Since the deposition of the abnormal protein starts in the endocardium and spreads through the myocardium in a transmural fashion, using the traditional TI-scout approach invariably leads to incorrect TI selection due to the heterogeneous appearance of the myocardium. In such situations, the enhancement pattern may be incorrectly dismissed as a technical failure of myocardial signal suppression on the inversion recovery gradient-echo T1-weighted pulse sequence commonly used for DE imaging.

One of the ways to overcome these limitations is to study the temporal order of nulling on a TI scout sequence, which should not be affected by these changes in the myocardium.

In our study, we observed that the temporal order of nulling was different for patients with myocardial amyloidosis and was often more easy to appreciate than selecting a single null time. The TI scout sequence demonstrated a consistent temporal order of nulling of the blood pool, myocardium and spleen in a normal subject (Type 1 nulling pattern, Fig. 2). The blood pool nulls first followed closely by the normal myocardium. The splenic nulling coincides the myocardial nulling. This observation was the basis of our study.

We observed that in cases with myocardial amyloidosis this temporal order of nulling was altered. The myocardial nulling was either coincident or prior to the blood pool nulling in 3 patients (Type 2 nulling pattern, Fig. 3). This finding was 77 % sensitive and 96 % specific for identification of myocardial amyloidosis. Somewhat similar observations were also made by Mahroholdt et al. who found that TI for myocardial nulling and blood pool nulling were closer together in patients with myocardial amyloidosis than those without [7, 15]. On similar lines, it has also been reported that the difference in TI between subendocardium and blood 4 min after a gadolinium bolus has accuracy for identifying myocardial amyloidosis in 88 % of patients [4]. Our approach of observing the temporal order of null time is much simpler, reproducible, and has comparable accuracy to the reported studies.

Additionally, we observed that the temporal order of the splenic nulling with that of the myocardial nulling can also be used in the diagnosis of myocardial amyloidosis on similar grounds. Using abnormal splenic nulling pattern alone for the diagnosis of myocardial amyloidosis, our sensitivity and specificity were 85 and 73 % respectively (Type 3 nulling pattern, Fig. 4). The addition of the abnormal splenic nulling to abnormal blood nulling (Type 4 nulling pattern, Fig. 5) did increase our *specificity* for diagnosing myocardial amyloidosis to 100 %. This is an important observation as it implies that TI scout Type 4 nulling pattern on its own can rule in myocardial amyloidosis. Correlation of T1 times of spleen therefore needs further evaluation. To the best of our knowledge, this observation has not been reported.

TI scout nulling sequence is also sensitive in detection of myocardial amyloidosis. In our study, abnormal nulling pattern of blood pool, myocardium and spleen (Type 2 OR Type 3 nulling patterns) had 100 % sensitivity for amyloid detection, suggesting the addition of abnormal splenic nulling information to normal blood nulling may be useful.

Some limitations should be noted. The precision of estimates and our ability to definitely statistically differentiate pattern types was affected by small sample sizes, which is a consequence of the rarity of myocardial amyloidosis. Also, given the limited number of patients with cardiac biopsy, the diagnosis of amyloidosis was expanded to include biopsy, clinical indicators, and MRI. Indeed many patients in our study who were included in the amyloidosis group did have biopsy proven amyloidosis in other areas (Table 1). Lack of early TI scout at 5 min/early gadolinium enhancement imaging is another limitation in our study although we were limited by the retrospective review of the scans and the CMR protocol only had post contrast TI scout images at 10 min. There is no clear explanation of this abnormal TI scout nulling pattern seen in patients with myocardial amyloidosis, and the reason for this preferential drop in the blood pool signal after the gadolinium administration (resulting in Type 2 nulling abnormality) in myocardial amyloidosis is not well understood. A possible explanation could be increased contrast extraction from the blood secondary to significant burden of amyloid in the body [4]. Since, this phenomenon was seen in 77 % patients with myocardial amyloidosis and in one of the other fourteen myeloma patients who were part of this study, it may be hypothesized that the presence of myocardial amyloidosis may in itself represent more diffuse amyloid deposition elsewhere and may warrant further evaluation.

In conclusion, we recommend evaluating the temporal pattern of nulling as an adjunct in the diagnosis of myocardial amyloidosis since TI scout is routinely obtained as part of DE-CMR.

Acknowledgments

This project was supported by the Translational Research Institute (TRI), grant **UL1RR029884** through the NIH National Center for Research Resources and National Center for Advancing Translational Sciences.

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Fig. 1.

Four-chamber (top left) and vertical long axis two chamber (*top right*) true-FISP phase sensitive inversion recovery (PSIR) CMR image obtained after 10 min of intravenous gadolinium injection shows normal homogenous nulling of the myocardium in a patient from the control group. 10 min post contrast two-chamber short axis PSIR image (*bottom*) in a biopsy proven case of myocardial amyloidosis shows global subendocardial hyperenhancement (*arrows*)

Fig. 2.

Type 1 (normal) nulling pattern: sequential TI scout two chamber short axis images are shown at different inversion times. Notice the temporal sequence of nulling of the blood pool, (Bl) at 230 ms, followed by myocardium (m) and spleen (Sp) (252 ms). The myocardium and spleen normally show coincidental nulling

Fig. 3.

Type 2 nulling pattern: sequential TI scout two chamber short axis images are shown at different inversion times. Notice that the nulling of the myocardium (m) (275 ms) precedes the nulling of the blood pool (Bl) and spleen (Sp) at 315 ms

Fig. 4.

Type 3 nulling pattern: sequential TI scout two chamber short axis images are shown at different inversion times. Notice that the blood pool (Bl) and the myocardial (m) nulling occurs earlier at 200 ms than the splenic (Sp) nulling (240 ms)

Fig. 5.

Type 4 nulling pattern: sequential TI scout two chamber short axis images are shown at different inversion times. Notice that the myocardial (m) nulling is patchy but occurs earlier (197–217 ms) than the blood pool (Bl) nulling (260 ms) which is not coincident with the splenic (Sp) nulling (302 ms)

Fig. 6.

Graphical representation of temporal nulling patterns on a TI scout sequence obtained by plotting the mean signal of the region of interest (ROI) in each image of the sequence with ROI placed over myocardium, blood pool and spleen: In Type 1 nulling pattern the blood pool (*dashed line*) nulls earlier than myocardium (*solid line*) and spleen (*dotted line*). Both myocardium and spleen null together. In Type 2 Nulling pattern, myocardial nulling precedes blood pool and splenic nulling. In Type 3 nulling pattern the splenic nulling is non-coincident with either the blood pool or myocardium and in Type 4 nulling all three null at different times

Fig. 7.
Sensitivity and specificity for different nulling types (n=39)

Table 1

Patient characteristics

	All patients N = 39	Myocardial amyloid group N = 13	Non-myocardial amyloid group N = 26
Ejection fraction %, median (range)	62 (9–84)	65 (56–84)	58 (9, 84)
Left ventricular Mass g/cm ² , median (range)	61 (39–139)	79 (51–106)	57 (39–139)
Amyloid biopsy positive ^a , n			
Heart	6	6	0
Non-cardiac sites	10	8	2
Kidney	5	4	1
Liver	3	3	0
Small bowel	2	2	0
Lower bowel	2	2	0
Bone marrow	2	2	0
Soft tumor	2	1	1
Eyelid	1	1	0
Fat	1	1	0

^aNot all patients were tested for all anatomical regions. There were 4 patients who had negative cardiac biopsies and 2 patients who had both negative fat and nerve biopsies (all in non-amyloid group). Some patients had amyloid detected at multiple anatomical sites so the total individual sites do not add up to the number of non-cardiac sites

Table 2

Accuracy measures for different nulling types for diagnosing myocardial amyloidosis (n = 39)

Myocardial nulling	% (n ₁ /n ₂) and 95 % CI			
	Sens	Spec	PPV	NPV
Type 2 (blood abnormality)	76.9 (10/13) 46.2–95.0	96.2 (25/26) 80.4–99.9	90.9 (10/11) 58.7–99.8	89.3 (25/28) 71.8–97.7
Type 3 (spleen abnormality)	84.6 (11/13) 54.6–98.1	73.1 (19/26) 52.2–88.4	61.1 (11/18) 35.8–82.7	90.5 (19/21) 69.6–98.8
Type 4 (blood AND spleen abnormality)	61.5 (8/13) 31.6–86.1	100 (26/26) 86.8–100	100 (8/8) 63.1–100	83.9 (26/31) 66.3–94.6
Type 2 OR 3 (blood OR spleen nulling abnormality) *	100 (13/13) 75.3–100	69.2 (18/26) 48.2–85.7	61.9 (13/21) 38.4–81.9	100 (18/18) 81.5–100

Sens sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value

* Type 2 or 3 is equivalent to not having Type 1 pattern