

# Myocardial nulling pattern in cardiac amyloidosis on time of inversion scout magnetic resonance imaging sequence - A new observation of temporal variability

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## Abstract

**Context:** The pattern of myocardial nulling in the inversion scout sequence [time of inversion scout (TIS)] of cardiac magnetic resonance imaging (MRI) is an accurate tool to detect cardiac amyloidosis. The pattern of nulling of myocardium and blood at varying times post gadolinium injection and its relationship with left ventricular mass (LVM) in amyloidosis have not been described previously. **Aims:** The aim is to study the nulling pattern of myocardium and blood at varying times in TIS and assess its relationship with LVM and late gadolinium enhancement (LGE) in amyloidosis. **Materials and Methods:** This was a retrospective study of 109 patients with clinical suspicion of cardiac amyloidosis who underwent MRI. Of these, 30 had MRI features of amyloidosis. The nulling pattern was assessed at 5 (TIS<sub>5min</sub>) and 10 (TIS<sub>10min</sub>) minutes (min) post contrast injection. Nulling pattern was also assessed at 3min (TIS<sub>3min</sub>) in four patients and 7min (TIS<sub>7min</sub>) in five patients. Myocardial mass index was calculated. Mann-Whitney *U* test was done to assess statistical difference in the myocardial mass index between patients with and without reversed nulling pattern (RNP) at TIS<sub>5min</sub>. **Results:** RNP was observed in 58% at TIS<sub>5min</sub> and 89.6% at TIS<sub>10min</sub>. Myocardial mass index was significantly higher in patients with RNP at TIS<sub>5min</sub> [mean = 94.87 g/m<sup>2</sup>; standard deviation (SD) = 17.63] when compared with patients with normal pattern (mean = 77.61 g/m<sup>2</sup>; SD = 17.21) (*U* = 18; *P* = 0.0351). **Conclusion:** In cardiac amyloidosis, TIS sequence shows temporal variability in nulling pattern. Earlier onset of reverse nulling pattern shows a trend toward more LVM and possibly more severe amyloid load.

**Key words:** Amyloidosis; cardiac; magnetic resonance imaging; TI scout

## Introduction

Amyloidosis refers to a diverse group of hereditary or acquired disorders characterized by extracellular deposition

of insoluble proteins which results in organ dysfunction.<sup>[1]</sup> Cardiac involvement is an important contributory factor

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to poorer outcome in amyloidosis.<sup>[2]</sup> Myocardial mass, ventricular wall thickness, interatrial septal thickness, diastolic function, and myocardial late gadolinium enhancement (LGE) are all described surrogate markers of increased cardiac amyloid load.<sup>[3]</sup> Magnetic resonance imaging (MRI) is the best available modality for assessment of myocardial structure and function. Time of inversion scout (TIS) sequence, which is done routinely before LGE imaging to choose nulling time of myocardium, shows nulling of myocardium before or coincident with blood pool in cardiac amyloidosis with 77% sensitivity and 96% specificity.<sup>[4]</sup> Previous studies have advocated performing TIS and LGE imaging at times varying from 5 to 15min after contrast injection in suspected amyloidosis.<sup>[3,5-7]</sup> We hypothesize that early reversal of nulling pattern in inversion scout sequence predicts higher myocardial amyloid load. In this study, we highlight the behavior of myocardium and blood pool on the TIS sequence at various time periods post gadolinium injection in amyloidosis and explore the possibility of assessing severity of amyloid deposition with TIS sequence.

## Materials and Methods

Patients with suspected amyloidosis referred to the Radiology department for cardiac MRI from January 2010 to July 2017 were identified from the RIS-PACS database using the search term “amyloidosis.” The cardiac MRI findings and clinical charts of these patients were reviewed. Those patients who had amyloid deposition on endomyocardial biopsy, amyloid deposition in other tissues on biopsy along with MRI features consistent with cardiac amyloidosis, and plasma cell dyscrasia on serum electrophoresis along with MRI features consistent with cardiac amyloidosis were considered as confirmed cases of cardiac amyloidosis. Those patients who had clinical suspicion of amyloidosis based on echocardiography or urine Bence Jones protein positivity and typical MRI features of cardiac amyloidosis without biopsy or electrophoresis confirmation were considered as likely cases of cardiac amyloidosis.<sup>[8-10]</sup> Patients who had an alternate diagnosis based on clinical or imaging findings and patients who had proven plasma cell dyscrasia without MRI features of cardiac involvement were excluded from our study. All patients except one were normotensive. The patient with hypertension was on regular treatment. None of the patients had valvular heart disease. Serum creatinine was within normal limits in all patients.

Cardiac MRI studies were performed on 1.5T scanners (Siemens Avanto or Siemens Avanto Fit, Siemens healthcare, Erlangen, Germany) using dedicated multichannel cardiac coils. Our cardiac MRI protocol consisted of axial, four-chamber, two-chamber, three-chamber, and short axis cine steady-state free precession images and late enhancement imaging following bolus injection of gadolinium-based contrast agent (gadopentetate dimeglumine, Magnevist;

Bayer Healthcare Pharmaceuticals, New Jersey, USA) at a dose of 0.1 mmol/kg. Short-axis TIS sequences were performed at mid cavity level at 5 (TIS<sub>5min</sub>) and 10 (TIS<sub>10min</sub>) min following contrast injection. Short-axis TIS sequences were additionally performed at 3min (TIS<sub>3min</sub>) in four patients and 7min (TIS<sub>7min</sub>) in five patients of our study. The acquisition parameters for the TIS sequence were as follows: 1.18 ms time to echo, 23.8 ms repetition time, 50° flip angle, 8 mm slice thickness, 340 mm field of view, and 170 × 118 matrix. Time of inversion was done at different times starting from 87.5 ms with sequential increase of 22.5 ms up to ~1100 ms. The average time of acquisition of TIS sequence was ~15–20 s.

Left ventricular mass (LVM) and left ventricular function (LVF) were calculated using proprietary “Argus” software (Siemens Healthcare, Erlangen, Germany). Endocardial contours were manually drawn in end diastole and end systole and epicardial contours in end diastole using the pencil tool. The trabeculae and papillary muscles were included as part of the left ventricular cavity. Indexed end diastolic volume (EDVI), indexed end systolic volume (ESVI), indexed LVM, and the pattern of LGE of myocardium were assessed. Based on the pattern of LGE, patients were categorized into two groups, one with global subendocardial enhancement involving not more than one-third of the myocardial thickness (Group A) and the other with subendocardial enhancement involving more than one-third of wall thickness of myocardial wall or transmural enhancement (Group B).

The temporal pattern of myocardial nulling was noted with respect to blood in the TIS images. In each of the TIS image series, the possible outcomes were (1) blood nulls before myocardium, (2) blood nulls coincident with myocardium, and (3) blood nulls after myocardium. The last nulling pattern is named as reversed nulling pattern (RNP). These patterns are represented in Figure 1.

Furthermore, patients were subdivided into two groups based on whether RNP was seen in TIS<sub>5min</sub> or not (Groups 1 and 2, respectively). The mean and standard deviation of myocardial mass index of these two groups were calculated. The presence of any difference in the myocardial mass index between these two groups was assessed by Mann–Whitney *U* test with a *P* value of <0.05 being considered significant. The presence of any significant difference in extent of LGE between groups 1 and 2 was assessed by Fisher’s exact test.

## Results

A total of 30 patients (mean age 56.4 years, males = 23 and females = 7) were included in our study. The LVF, LVM, and TIS characteristics of our patients are summarized in Table 1. Twelve patients were confirmed cases (patients 1–12 in Table 1) and 18 patients were likely

Time of inversion (milliseconds)	99.5	124.5	147	172	219.5	267
Normal nulling pattern						
Coincident nulling pattern						
Reversed nulling pattern						

**Figure 1:** Representative images from inversion scout sequence showing normal nulling pattern (blood nulling before myocardium) in the second row, coincident nulling pattern (blood nulling at the same time as myocardium) in the third row, and reversed nulling pattern (myocardium nulling before blood) in the fourth row. The inversion time is mentioned in the first row

cases of amyloidosis (patients 13–30 in Table 1). All the 30 patients had global subendocardial or global transmural enhancement on LGE. Of the 12 patients with confirmed amyloidosis, 3 had endomyocardial biopsy and 9 had plasma cell dyscrasia on serum electrophoresis or bone marrow biopsy.

The mean and standard deviation of EDVI, ESVI, and ejection fraction of the patients were  $68.8 \pm 22.8$  mL/m<sup>2</sup>,  $39.8 \pm 17.6$  mL/m<sup>2</sup>, and  $43.7 \pm 10.9\%$ , respectively. Global subendocardial enhancement involving up to one-third of wall thickness was the most common pattern observed ( $n = 22$ , 73.3%). The rest ( $n = 8$ , 26.7%) showed global subendocardial enhancement more than one-third of wall thickness or transmural enhancement.

TIS<sub>10min</sub> was done in all 30 patients and TIS<sub>5min</sub> was done in 19 patients. TIS<sub>3min</sub> and TIS<sub>7min</sub> were done in four and five patients respectively. The distribution of nulling pattern in our study is given in Table 2. We observed that the nulling pattern in an individual patient can evolve depending on the time elapsed post contrast injection, which was best represented by patient number 10. In this patient, blood nulled before myocardium at TIS<sub>3min</sub>, blood and myocardial nulling were coincident at TIS<sub>5min</sub> and myocardial nulling preceded blood (RNP) at TIS<sub>7min</sub> and TIS<sub>10min</sub>. Of the four patients with TIS<sub>3min</sub>, three had normal nulling pattern and one had reverse nulling pattern (25%). All the patients with TIS<sub>7min</sub> had reverse nulling pattern (100%). Group 1, in whom RNP was seen in TIS<sub>5min</sub> ( $n = 11$ ), had mean myocardial mass index of  $94.87 \pm 17.63$  g/m<sup>2</sup>, while those in Group 2 in whom RNP was not seen ( $n = 7$ ) had mean myocardial mass index of  $77.61 \pm 17.21$  g/m<sup>2</sup>. Group 1 had significantly

higher myocardial mass index than Group 2 with a *U*-value of 18 ( $P = 0.035$ ) as calculated by Mann–Whitney *U*-test. No statistically significant difference was seen in the extent of global late enhancement between Groups 1 and 2 on Fisher’s exact test ( $P = 0.536$ ). No statistically significant difference was seen in indexed myocardial mass in the two categories of extent of late enhancement (Groups A and B) on Mann–Whitney *U* test, although the mean indexed myocardial mass was higher in Group B ( $P = 0.054$ ).

### Discussion

The common types of systemic amyloidosis based on the chemical structure of deposited proteins are AL, AA, ATTR, and Ab<sub>2</sub>M. AL type is the most common subtype. The AL subtype, seen in the setting of plasma cell dyscrasias or monoclonal gammopathy of unknown significance (MGUS), and the ATTR subtype, caused by mutations on gene encoding transthyretin cause cardiomyopathy. The AA subtype associated with chronic systemic inflammatory disorders and the Ab<sub>2</sub>M subtype which occurs in patients with long-standing end-stage renal failure on hemodialysis usually do not affect the heart.<sup>[11]</sup>

Cardiac involvement in amyloidosis causes biventricular diastolic dysfunction and atrial dilation due to myocardial amyloid infiltration. At late stages, it progresses to systolic dysfunction. Amyloid can act as a substrate for arrhythmia. Most patients have associated pleural and pericardial effusions. Clinical manifestations include exercise intolerance, palpitations, and syncope. Electrocardiogram shows low-voltage complexes, despite ventricular wall thickening. Echocardiography shows ventricular

**Table 1: Left ventricular parameters and TIS characteristics of our patients with amyloidosis**

No.	Age/sex	EDVI* (mL/m <sup>2</sup> )	EF† (%)	LVMI‡ (g/m <sup>2</sup> )	TIS <sup>§</sup> <sub>5min</sub>	TIS <sub>10min</sub>
1	43/M	61	54	127	NA <sup>  </sup>	M <sup>**</sup>
2	61/F	58	53	43	NA	M
3	53/M	58	50	97	M	M
4	65/M	44	54	72	C <sup>††</sup>	M
5	60/M	55	33	71	C	M
6	50/M	39	40	54	M	M
7	60/F	77	27	108	M	M
8	68/M	51	35	82	NA	M
9	37/M	123	29	87	NA	M
10	41/F	47	38	54	C	M
11	52/M	41	61	103	B <sup>‡‡</sup>	M
12	47/F	NA	NA	NA	M	M
13	76/M	83	34	97	M	M
14	61/M	47	44	90	NA	M
15	43/F	68	29	81	NA	M
16	49/M	56	39	96	B	B
16	62/M	65	35	74	NA	M
18	46/M	54	45	63	NA	M
19	52/M	71	34	91	NA	M
20	59/F	71	51	95	M	M
21	55/M	74	42	100	M	M
22	55/M	84	58	65.5	C	M
23	64/F	77	68	59.6	NA	C
24	58/M	103	25	81.6	B	C
25	60/M	104	48	95.2	M	M
26	65/M	127	44	126.8	M	M
27	63/M	74	39	84	M	M
28	67/M	56	51	100	M	M
29	60/M	87	45	86.5	NA	M
30	82/M	41	61	86.8	M	M

\*End diastolic volume index; †Ejection fraction; ‡Left ventricular mass index; §Time of inversion scout; ||Not available; \*\*Myocardial nulling before blood; ††Coincident nulling of myocardium and blood; ‡‡Blood before myocardium

**Table 2: Nulling pattern on TIS\* in our patients**

TIS	Reversed nulling pattern	Coincident nulling pattern	Normal nulling pattern	Total
TIS <sub>3min</sub>	1	0	3	4
TIS <sub>5min</sub>	12	4	3	19
TIS <sub>7min</sub>	5	0	0	5
TIS <sub>10min</sub>	27	2	1	30

\*Time of inversion scout

hypertrophy and a characteristic speckled appearance of the myocardium. Although echocardiography is well-established as a tool for assessing myocardial structure and function, it falls short in tissue characterization and is operator-dependent.<sup>[12]</sup> MRI gives detailed assessment of the cardiac structure and function and is considered the gold standard.

The LGE sequence shows the characteristic pattern of global subendocardial enhancement in amyloidosis.<sup>[12]</sup> Pandey

*et al.* have showed that RNP at TIS<sub>10min</sub> can be a very useful adjunct to other cardiac MRI sequences in diagnosing cardiac amyloidosis.<sup>[4]</sup> They observed that myocardium nulls before or coincident with the blood pool in patients with amyloidosis in TIS sequence done at 10min post gadolinium injection as opposed to the normal pattern observed in patients with other diagnoses or no cardiac abnormality, where the blood pool nulls before myocardium. The reversal of nulling which is said to be characteristic of amyloidosis happens due to two reasons. One reason is that myocardial amyloid deposition causes increase in extracellular space resulting in gadolinium accumulation and shortening of the myocardial T1 time. The other reason is that systemic amyloid load tends to extract the gadolinium from the blood pool, thus causing relative prolongation of the blood T1 time. This additive two-fold effect essentially causes myocardial T1 to become shorter than blood T1 following gadolinium administration. Thus, early RNP could possibly predict higher myocardial amyloid load and higher systemic amyloid load.

Our study shows that the nulling pattern in TIS in amyloidosis is time-dependent and is likely related to the load of amyloid deposition. This also explains the practical difficulties and variability of findings in TIS and LGE in patients with cardiac amyloidosis. We observed RNP in 90% of patients at 10min, whereas the corresponding figure was 58% at 5min. Thus, RNP was more accurate at TIS<sub>10min</sub> to diagnose amyloidosis when compared with TIS<sub>5min</sub>. As the routine cardiac MRI protocols are different in different institutions with regard to the timing of the TIS and delayed enhancement sequences, this temporal variability assumes importance. It is important to note that in three of our patients (patient no. 16, 23, and 24 in Table 1) in the likely amyloidosis group, RNP was not observed at even 10min. Interestingly, patient no. 22 showed evolution from normal nulling pattern at 5min to coincident nulling at 10min. This raises possibility that RNP could occur at a time later than 10min in these patients and requires further investigation by more delayed TIS sequences done at 15 or even 20min after contrast injection.

Increased myocardial load in amyloidosis correlates with poor survival.<sup>[13]</sup> Left ventricular myocardial mass, wall thickness, LGE, N-terminal pro-brain natriuretic peptide, and cardiac troponins are prognostic markers for predicting survival in cardiac amyloidosis.<sup>[10,14-20]</sup> Our results show statistically significant increased LVM in patients with early RNP compared with those with late RNP. Gadolinium kinetics are altered in amyloidosis, and lower difference between the subendocardial T1 and subepicardial T1 in amyloidosis has been shown to correlate with worse prognosis.<sup>[15]</sup> White *et al.* used TIS sequences at 5–10min after contrast injection to assess the ability of qualitative assessment of T1 of the myocardium with respect to blood pool in predicting mortality.<sup>[21]</sup> They qualitatively assessed

T1 by observing the nulling pattern based on the concept that T1 is proportional to the nulling time, that is, the earlier the nulling, the shorter the T1. They observed that the presence of diffuse enhancement by visual assessment of myocardial T1 was a strong predictor of mortality. They performed TIS sequence at a single time point post contrast injection in each patient, unlike our study where multiple time periods post contrast injection were studied. Our study did not show statistically significant difference in the extent of LGE in those with early RNP compared with those with late RNP. This is likely related to the absence of patients without late enhancement and small number of total patients in our study. The three patients in our study with amyloidosis based on endomyocardial biopsy had subendocardial enhancement up to one-third of wall thickness.

Another recent development in assessing myocardial amyloid deposition is T1 mapping using cardiac MRI. In amyloidosis, myocardial T1 is prolonged. T1 mapping has been shown to accurately diagnose and prognosticate cardiac amyloidosis.<sup>[22,23]</sup> This was not evaluated in our study. The important difference between T1 mapping and temporal variability of nulling pattern is that variability of nulling pattern is influenced by both myocardial and systemic amyloid load, while myocardial T1 is solely a myocardial property. Moreover, we did not correlate our results with other modalities such as serum amyloid P component scintigraphy<sup>[24]</sup> which reflects systemic amyloid load. N-terminal pro-brain natriuretic peptide and cardiac troponins were not assessed. This study was limited by small sample size for TIS<sub>3min</sub> and TIS<sub>7min</sub>. One of our patients did not have optimal short-axis cine stack of images and LVF was not calculated. Endomyocardial biopsy was not done in the majority of our patients. However, endomyocardial biopsy is an invasive procedure with its own attendant risks and can be associated with pitfalls due to sampling errors.<sup>[25]</sup> The ability of early RNP to predict survival requires further research with prospective study and larger sample size.

## Conclusion

The nulling pattern of myocardium and blood pool in cardiac amyloidosis shows temporal variability with earlier onset of reverse nulling pattern in TIS sequence showing trend toward more LVM and possibly more severe amyloid load. Performing TIS sequence at multiple time points post contrast injection may provide prognostic information in patients with cardiac amyloidosis; however, this requires validation with a prospective study having larger sample size. Although TIS images are advisable at multiple time points, 10min or later images rather than the earlier images would be more useful to diagnose cardiac amyloidosis based on RNP.

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## Conflicts of interest

There are no conflicts of interest.

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