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Native T1 mapping in diffuse myocardial diseases using 3-Tesla MRI: An institutional experience

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Abstract

Aims: Newer cardiac magnetic resonance techniques like native T1 mapping are being used increasingly as an adjunct to diagnose myocardial diseases with fibrosis. However, its full clinical utility has not been tested extensively, especially in the Indian population. The purpose of this study was to find native T1 values in healthy individuals without cardiac disease in our 3-Tesla MRI system and examine whether native myocardial T1 values can be used to differentiate between normal and diffuse myocardial disease groups. **Subjects and Methods:** After approval from the institutional ethics committee, native T1 mapping was performed in 12 healthy individuals without cardiac disease who served as controls and in 26 patients with diffuse myocardial diseases (acute myocarditis (n = 5), hypertrophic cardiomyopathy (HCM) (n = 8), nonischemic dilated cardiomyopathy (DCM) (n = 7), restrictive cardiomyopathy (RCM) due to amyloidosis (n = 6)) in a 3-Tesla MRI system in short axis slices and four-chamber view using a modified Look-Locker inversion recovery sequence. The mean native T1 values and standard deviations were calculated for control and disease groups and compared. The ability of native myocardial T1 mapping to differentiate between normal and diffuse myocardial disease groups was assessed. One-way ANOVA with Tukey's Post-Hoc test was used to find significant difference in the multivariate analysis and Chi-Square test was used to find the significance in categorical data. **Results:** The native T1 values for the healthy group in our 3-Tesla MRI system was 1186.47 ± 45.67 ms. The mean T1 values of the groups acute myocarditis (1418.68 ± 8.62 ms), HCM (1355.86 ± 44.67 ms), nonischemic DCM (1341.31 ± 41.48 ms), and RCM due to amyloidosis (1370.37 ± 90.14 ms) were significantly higher (P = 0.0005) than that of the healthy control group. **Conclusion:** Native myocardial T1 mapping is a promising tool for differentiating between healthy and diffuse myocardial disease groups.

Key words: Cardiac magnetic resonance; cardiomyopathy; diffuse myocardial disease; modified look-locker inversion recovery; native T1 mapping

Introduction

Various myocardial diseases result in diffuse myocardial fibrosis in which there is a significant increase in the amount of collagen in the extracellular matrix.[1-3] Myocardial fibrosis is the major cause of myocardial dysfunction, leading to

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myocardial remodeling with resultant poor outcomes and increased mortality.[4-6]

Recent advances have led to numerous strategies aimed at stopping or reversing myocardial fibrosis.[7,8] Thus, early identification of diffuse myocardial fibrosis is important for optimization of therapeutic approaches. The only available method for assessment of myocardial fibrosis used to be invasive endomyocardial biopsy. However, this technique is invasive with the risk of serious complications and is also prone to sampling error.[9,10]

Recent technical developments in cardiac magnetic resonance (CMR) have made non-invasive assessment of the myocardium a possibility.[11] Currently, late gadolinium enhancement (LGE) imaging is the primary tool for detection of focal myocardial fibrosis or scars.[12] Myocardial fibrosis detected by CMR has been shown to be a major independent predictive factor of adverse cardiac outcome in recent clinical studies.[13-16] However, the identification and characterization of the LGE patterns is subjective, being susceptible to inter- and intraobserver variations. Diffuse myocardial fibrosis may not be detected, as normal myocardium is needed as reference to contrast with late gadolinium enhancement. LGE imaging is also contraindicated in those patients with renal dysfunction as it involves intravenous administration of gadolinium-based contrast agents[12] and also has the potential risk of nephrogenic systemic fibrosis. To overcome these limitations, novel MRI techniques have been developed, including native T1 mapping, which allows the direct quantification of tissue-specific longitudinal (T1) relaxation times.

The aim of the present study was to identify normative native T1 value in our 3-Tesla MRI system and to investigate whether native myocardial T1 values can be used to differentiate between normal and diffuse myocardial disease groups in clinical settings. No studies have yet been done on native T1 mapping in the Indian population. Moreover, we measured native T1 values in three short axis slices and a four-chamber view to get a more representative value, compared to majority of the previous studies in which native T1 value measurement was taken in a single mid-ventricular short axis slice.

Subjects and Methods

This was a prospective single center study conducted for a period of 12 months from June 2017 to May 2018. After approval from the institutional ethics committee in April 2017, 26 consecutive subjects with various diffuse myocardial disease (15 females, 11 males, mean age 38.3 ± 13.7 years) referred for CMR were primarily included in this study. The various diffuse myocardial diseases were acute myocarditis (n = 5), hypertrophic cardiomyopathy (HCM) (n = 8), nonischemic dilated cardiomyopathy (DCM) (n = 7), and RCM due to amyloidosis (n = 6). Cases of myocardial infarction sent for viability assessment were not included in the study, as it was not a diffuse myocardial disease. The patients were assigned these diagnoses by experienced cardiologists in accordance to established diagnostic criteria[17-20] using available clinical information (medical history, ECG, laboratory tests, and echocardiography) and the CMR results (except native T1 mapping).

12 healthy volunteers (4 females, 5 males, mean age 39.9 ± 14.6 years) who were nonsmokers, had no history of cardiac disease, hypertension, family history of cardiomyopathy or sudden death, had a normal 12-lead ECG and ECHO and no other comorbidities were taken as controls after obtaining informed consent. Persons with orthopnea, claustrophobia, MRI non-compatible devices were excluded from the study.

CMR imaging

All CMR scans were performed in a 3-Tesla MRI system (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany). A standardized CMR protocol was used which included the following sequences: T2 HASTE axial, True FISP cine images in four chamber, two chamber, three chamber, and short axis views. T2 STIR axial and PSIR postcontrast images were done in selected cases. Native T1 mapping was performed in all cases using a modified Look-Locker inversion recovery (MOLLI) sequence in short axis slices through the apex, mid-ventricle and base, and in the four-chamber view.

Retrospective ECG gating was used for cine True FISP images and prospective ECG gating for other sequences. For cine imaging, steady-state free precession images were acquired in standard long and short axis views (TR 39 ms, TE 1.4 ms, matrix 139 × 208, field of view 420 × 380 mm^2, flip angle 57°, bandwidth 962 Hz/pixel, slice thickness 6 mm). The parameters for native T1 mapping MOLLI sequence were as follows:

- For RR interval >700 ms, TR 280 ms, TE 1.12 ms, matrix 256 × 144, field of view 360 × 306 mm^2, flip angle 35°, bandwidth 1085 Hz/pixel, slice thickness 8 mm.
- For RR interval <700 ms, TR 272 ms, TE 1.2 ms, matrix 195 × 132, field of view 360 × 307 mm^2, flip angle 35°, bandwidth 1085 Hz/pixel, slice thickness 5 mm.

Image analysis

CMR studies were evaluated, and the mean native myocardial T1 value was obtained from region of interest (ROI) drawn in the anterior, septal, inferior, and lateral walls in each of the three short axis slices. Native T1 was also measured in the septal and lateral walls in the four-chamber view to confirm the diffuse involvement of myocardium. However, these values were not included in calculation of the mean values [Figure 1]. A minimum

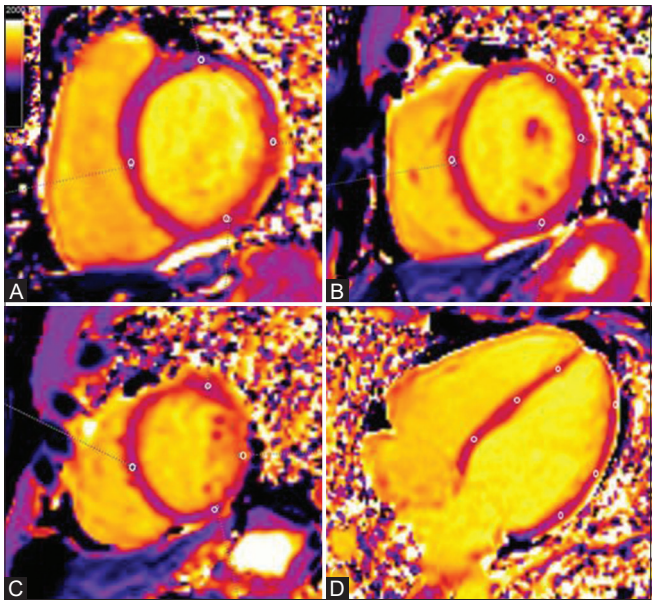

Figure 1 (A-D): (A-D) Short axis slices through the base (A), mid-ventricle (B), base (C) with ROI drawn in the anterior, septal, inferior, and lateral walls for native T1 value measurement. Four chamber view (D) with ROI drawn in the septal and lateral walls at base, mid-ventricle, and apex levels

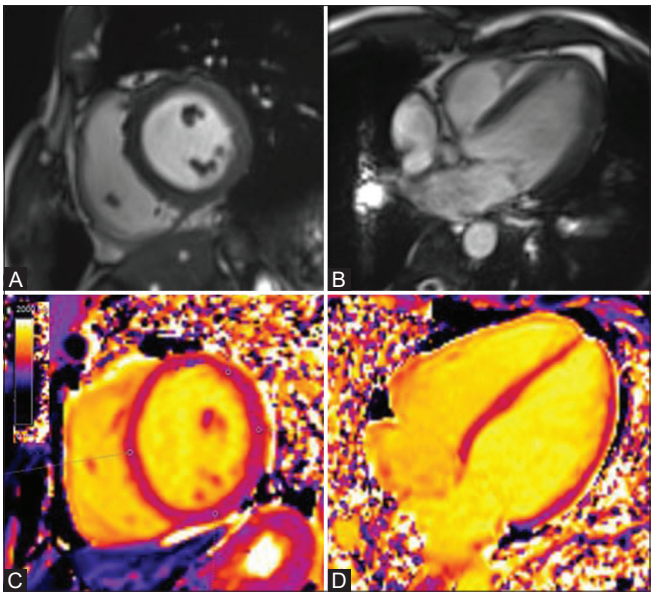

Figure 2 (A-D): (A-D) True FISP short axis mid-ventricle slice (A), four chamber view (B), native T1 map short axis mid-ventricle slice (C), and four chamber view (D) of a normal control with measured native T1 ranging from 1143 to 1192 ms

circular ROI of 20 pixels was used for short axis slices, and manual curved ROI was drawn for four-chamber slices. Care was taken to ensure that the ROI does not include blood or epicardial fat and to avoid partial volume artifacts. Postprocessing and analysis was done on syngo. via VA30 version, which was provided along with the MRI scanner (Original Equipment Manufacturer).

Statistical analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. Frequency analysis and percentage analysis were used for categorical variables, and the mean and standard deviation were used for continuous variables to describe about the data. One-way ANOVA with Tukey's Post-Hoc test was used to find significant difference in the multivariate analysis, and Chi-Square test was used to find the significance in categorical data. In all the above statistical tools, the probability value 0.05 was considered as significant level.

Results

Twelve healthy individuals without cardiac disease (31.6%) who served as controls, 5 patients (13.1%) with acute myocarditis, 8 patients (21%) with HCM, 7 patients (18.4%) with nonischemic DCM and 6 patients (15.8%) with RCM were included in this study. The native myocardial T1 value ranged between 1108.83 and 1261.91 ms in the group of subjects with healthy hearts with a mean of 1186.47 ± 45.67 ms [Figure 2]. The native T1 value of patients with diffuse diseased myocardium ranged between1266.25 and 1428.16 ms**.** The mean native T1 value of each of the groups were: acute myocarditis 1418.68 ± 8.62, HCM 1355.86 ± 44.67, nonischemic DCM 1341.31 ± 41.48, and RCM due to amyloidosis 1370.37 ± 90.14 ms. The highest T1 values were observed in the myocarditis group. The mean native T1 values were significantly higher in diffuse myocardial disease groups compared to normal group. Subgroup analysis revealed a significant difference in the mean native T1 value between the group of subjects with healthy hearts and the groups of patients suffering from acute myocarditis (P = 0.0005), HCM ($P = 0.0005$), nonischemic DCM (P = 0.0005), and RCM due to amyloidosis ($P = 0.0005$) [Figures 3-7].

Discussion

This study aimed at finding normative native T1 values in our 3-Tesla MRI system and to examine whether native myocardial T1 value could be used to differentiate between normal and diffuse myocardial disease groups. The results of this study show that the native myocardial T1 relaxation time allows differentiating normal and diffuse myocardial disease groups.

Native T1 mapping is a relatively new MR technique that allows for quantification of tissue-specific longitudinal (T1) relaxation times based on which parametric color maps can be generated for easy regional and interpatient comparisons. This technique does not require contrast administration. It is useful in detecting diffuse myocardial diseases, in addition to focal pathologies.[21,22] Elevated native T1 values are seen with increase in the extracellular space as in diffuse or focal fibrosis seen in various cardiomyopathies, as well as in interstitial deposition of amyloid protein and

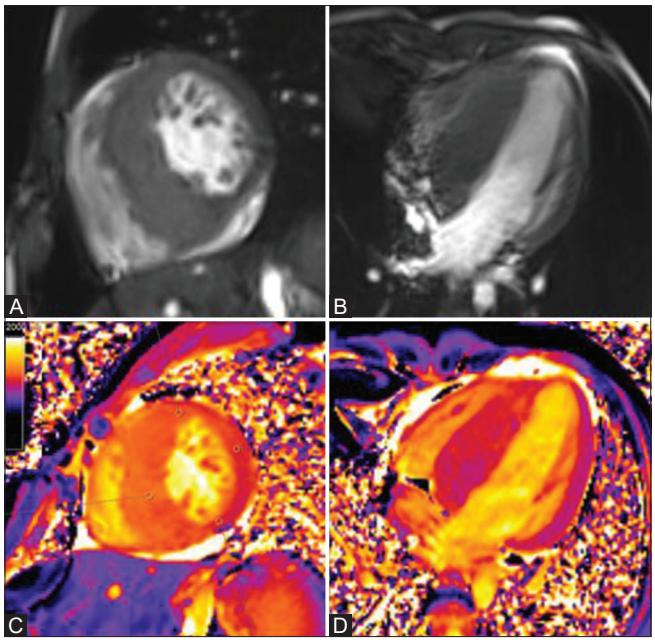

Figure 3 (A-D): (A-D) True FISP short axis mid-ventricle slice (A) and four chamber view (B) in a case of HCM showing asymmetrical hypertrophy of interventricular septum. Native T1 map short axis mid-ventricle slice (C) and four chamber view (D) of the same patient shows increased native T1 values ranging from 1275 to 1389 ms

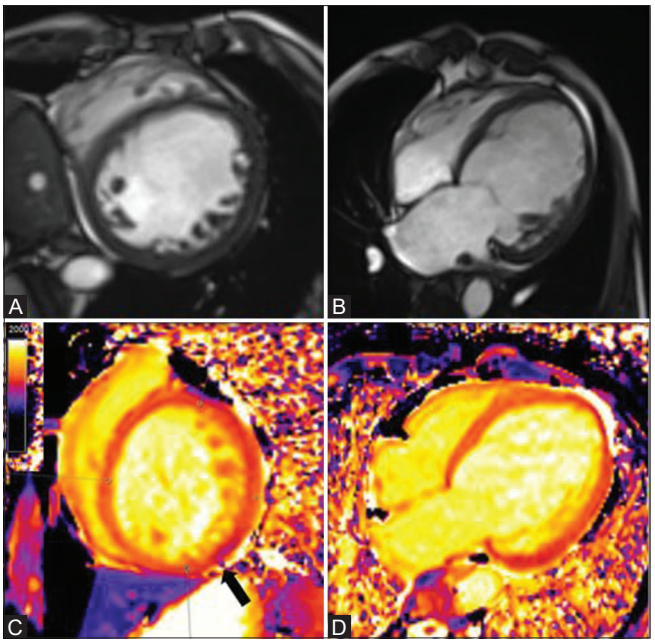

Figure 4 (A-D): (A-D) True FISP short axis mid-ventricle slice (A) and four chamber view (B) in a case of nonischemic DCM showing dilated left atrium and left ventricle. Native T1 map short axis mid-ventricle slice (C) and four chamber view (D) of the same patient shows increased native T1 values ranging from 1339 to 1377 ms

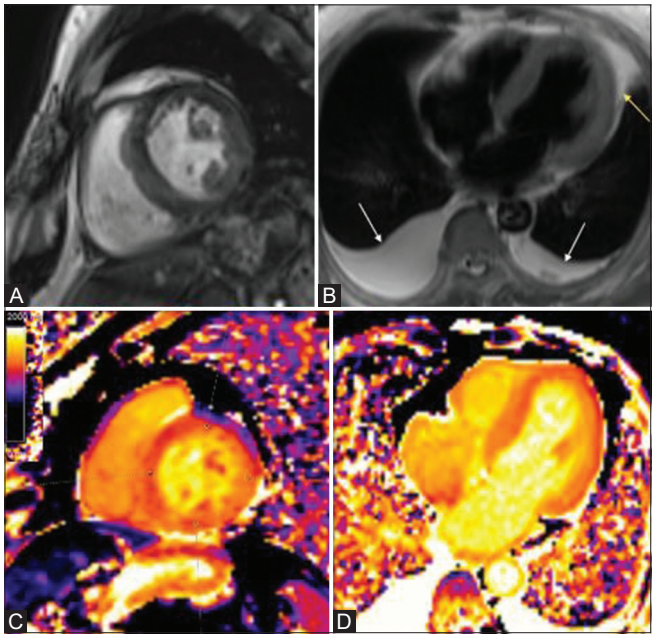

Figure 5 (A-D): (A-D) True FISP short axis mid-ventricle slice (A) and T2 HASTE axial (B) in a case of amyloidosis showing mildly dilated left atrium, bilateral pleural effusions (white arrows in b) and minimal pericardial effusion (yellow arrow in B). Native T1 map short axis mid-ventricle slice (C) and four chamber view (D) of the same patient shows increased native T1 values ranging from 1351 to 1422 ms

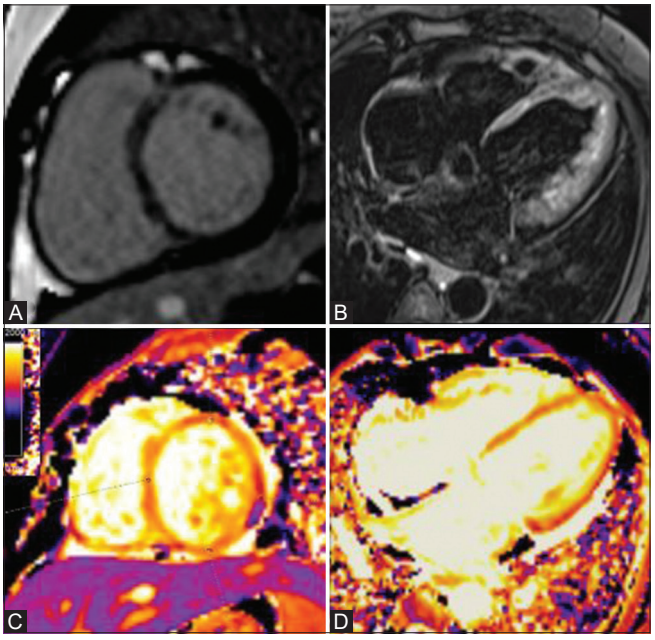

Figure 6 (A-D): (A-D) PSIR postcontrast images short axis mid-ventricle slice (A) shows patchy mid myocardial enhancement in the anteroseptal and inferoseptal walls of left ventricle, and STIR axial image (B) shows patchy STIR hyperintensity in the left ventricle wall in a case of acute myocarditis. Native T1 map short axis mid-ventricle slice (C) and four chamber view (D) of the same patient shows increased native T1 values ranging from 1372 to 1448 ms

in edema seen in acute myocarditis,[20,23-26] whereas they are decreased in iron accumulation, and intracellular fat deposition like in Anderson–Fabry disease.[23,27] Previous studies have demonstrated the ability of native T1 mapping to detect myocardial involvement in the subclinical stage of disease.[28-31] Native T1 mapping is thus a technique which noninvasively samples the myocardium, making it a promising alternative to invasive myocardial biopsy and

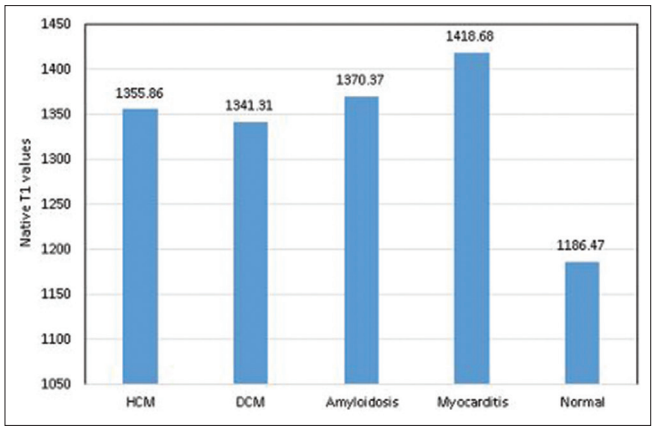

Figure 7: Bar chart showing mean native T1 values among study groups

LGE imaging. Postcontrast T1 mapping can also be done after administration of intravenous Gadolinium-based contrast agent and is sensitive in detection of diffuse myocardial fibrosis. However, it is subject to variations caused by multiple factors such as concentration, volume, clearance rate, injected dose and the type of the administered contrast, body composition, time of measurement and haematocrit,[32,33] and therefore, interpretation should not be done in isolation.

Native T1 mapping together with postcontrast T1 mapping allows for the calculation of the proportion of contrast agent in the blood pool versus that in the myocardium. If the hematocrit value is known, quantification of the proportion of extracellular volume (interstitium and extracellular matrix) fraction (ECV) of the myocardium is possible using a specific formula.[34] An increased ECV, akin to increased native T1 value, is also a marker of fibrosis. ECV maps can also be generated on a pixel-wise basis, similar to parametric native T1 maps.[35]

Although native myocardial T1 relaxation time is a true tissue parameter, it varies with magnetic field strength (1.5-Tesla versus 3-Tesla units), equipment manufacturer, and the type of mapping sequence used.[23,36] These factors must be taken into consideration when comparing results between different studies, and thus a direct comparison of our study and previous studies is not possible.

There are numerous techniques which have been described for native T1 mapping, which are based on inversion recovery, saturation recovery, or a combination of both techniques. These include MOLLI, shortened modified Look-Locker inversion recovery (ShMOLLI), saturation recovery single-shot acquisition (SASHA), and saturation pulse prepared heart-rate-independent inversion recovery (SAPPHIRE).[23,31,37-39] The most commonly used and the most evaluated method for T1 mapping is MOLLI. It uses 17 heartbeats with acquisition of 3-3-5 images and an interval of three heartbeats for recovery in between acquisitions. It has high signal-to-noise ratio, good reproducibility, and high sensitivity. However, it is dependent on heart rate and has low specificity as it underestimates T1 values due to dependence on various factors including magnetization transfer, magnetic field inhomogeneities, and T2 relaxation time. Since it requires a 17 heartbeat breath hold, it is difficult to perform in sick patients. ShMOLLI, a modification of the MOLLI technique, was devised to overcome this drawback and requires only a nine heartbeat breath hold. It is also independent of heart rate and is more accurate in T1 estimation but has a comparably low signal-to-noise ratio, is more prone for artifacts and causes systematic T1 value underestimation like MOLLI. Multislice interleaved T1 (STONE) is a MOLLI-like technique, which improves spatial coverage. SASHA, which is based on saturation recovery sequence, is more accurate, and is not susceptible to bias from T1, T2, magnetization transfer, or magnetic field heterogeneities. However, it has reduced T1 precision compared with Look-Locker techniques such as MOLLI. The SAPPHIRE sequence has the advantages of both of inversion recovery techniques and saturation recovery techniques with resultant T1 values similar to SASHA and precision in between MOLLI and SASHA.[23,40] A study comparing the accuracy, precision, and reproducibility of the four T1 mapping sequences in phantoms and healthy subjects showed that SASHA and SAPPHIRE had higher accuracy, lower precision, and similar reproducibility compared with MOLLI and ShMOLLI for T1 measurement.[41] Newer 3D techniques have been developed which allow for greater spatial coverage, intrinsic higher signal-to-noise ratio with the potential to characterize the thinner right ventricle and atria.[40]

Native T1 mapping technique also has certain inherent drawbacks, which have to be addressed before a large-scale application for clinical decision-making can be recommended. Postprocessing and analysis of the T1 map can also introduce bias, errors, and loss of precision. These include contamination of native T1 values by adjacent tissue, especially at interfaces between myocardium with blood and fat and in those conditions with thin myocardial walls like DCM. Adequate spatial resolution, slice thickness, and careful slice orientation should be ensured to avoid partial volume effects.[21] Although some organizations like the Society for Cardiovascular Magnetic Resonance (SCMR) have published guidelines and consensus statements[21] regarding scan planning, acquisition, interpretation, postprocessing and quality control for native T1 mapping, they have not come into widespread use and variability with regards to these still exists from center to center.

Teixeira *et al.*[36], who compared different cardiovascular magnetic resonance sequences for native myocardial T1 mapping using the same 3-Tesla MRI system (Magnetom

Skyra Siemens Healthcare, Erlangen, Germany) and the same MOLLI sequence used in our study, reported a native T1 value of 1199 ± 28 ms. This value was very close to the value of 1186.47 ± 45.67 ms obtained in our study. Several other studies[25,42-44] using various 3-Tesla scanners and different T1 mapping sequences have also reported native T1 values in healthy controls comparable to our study. Few other studies[17,45-47], also performed using a 3-Tesla scanner and MOLLI technique reported slightly lower normative native T1 values compared to that of our study, ranging from 1,045 ± 23 to 1,070 ± 55 ms. Boomen *et al*.[48] in their systematic review and meta-analysis, which included studies using MOLLI or ShMOLLI techniques, reported a weighted mean T1 value of 1081 ± 45 ms in controls at 3-Tesla. Overall, the mean native myocardial T1 value of 1186.47 ± 45.67 ms for healthy individuals obtained in our study is comparable with those of previous studies. The small differences in reported mean native myocardial T1 values could be explained by differences in the sequences and MR systems used.

Various studies[17,42,43,47] on native T1 values in acute myocarditis reported values ranging from 1179.2 ± 48.3 to 1,203 ± 71 ms, which were significantly higher than those of respective control groups. Few studies[25,45] have also reported significantly longer native T1 values in patients with HCM and DCM compared with control subjects. Boomen *et al*.[48] in their systematic review and meta-analysis on native T1 reference values for nonischemic cardiomyopathies concluded that native T1 mapping can potentially assess myocardial changes in HCM, DCM, and myocarditis compared to controls with a significant increase of the myocardial T1 values for patients with diffusely diseased myocardium compared with controls.

The mean T1 values of the various disease groups in our study, namely, nonischemic DCM (1341.31 ± 41.48 ms), HCM (1355.86 ± 44.67 ms), RCM due to amyloidosis (1370.37 ± 90.14 ms), and acute myocarditis (1418.68 ± 8.62 ms) were also significantly higher than those of healthy controls as reported by previous studies. Thus, it could be concluded that native T1 mapping can be used to differentiate between healthy and diseased hearts. However, our values in patients with diffuse myocardial disease were comparatively higher than those reported in previous studies. These differences could be attributed to more severity or a later stage of disease in our cohort, both of which could result in higher native T1 values. Moreover, compared to previous studies in which native T1 mapping was done only in one mid-ventricular short axis slice, we performed it in three short axis slices and in the four-chamber view. Therefore, the measured mean native myocardial T1 value could be a more representative value of the entire left ventricular myocardium. We also noted significantly elevated native T1 values in those myocardial segments, which did not show LGE in some cases of HCM. This finding suggests that native T1 mapping could detect myocardial involvement in an earlier stage of disease than that detected by LGE, a finding which was also noted in previous studies.[28-31] However, intravenous contrast was not administered to all cases as some had renal dysfunction. Native T1 mapping can thus be useful in those patients with renal failure where intravenous Gadolinium-based contrast is contraindicated, as was the case in some of our subjects.

The higher mean native myocardial T1 value in the HCM and DCM groups can be explained by an increased interstitial space due to replacement fibrosis and reactive interstitial fibrosis, respectively,[23] whereas elevated native T1 value in amyloidosis can be explained by diffuse infiltrative fibrosis due to extracellular deposition of amyloid protein in the myocardium.[26] Myocardial edema in the acute phase of myocarditis[24] results in the high mean native myocardial T1 value in the group of patients suffering from acute myocarditis.

The present study has some limitations. First, the number of patients in the control and different subgroups of diffuse myocardial pathologies in our study is rather small, which is an inherent limitation of this study. The SCMR consensus statement on T1 mapping recommends acquisition of a minimum of 10 normal subject samples for defining normative values.[21] It is also to be reiterated that native T1 value varies with field strength and from system to system due to changes in software versions or scanner type, and thus every center should acquire their own normative native T1 values. Second, only MOLLI sequence was used for native T1 mapping. Thus, the results of this study should be interpreted with caution when compared with studies using other T1 mapping techniques.

In this study, we calculated the native T1 values of normal healthy hearts in our 3-Tesla MRI system. The results of our study also confirmed that native T1 mapping can be used to differentiate between normal groups and those with diffusely diseased myocardium. We were able to readily incorporate native T1 mapping into our existing CMR protocols. This may be considered a pilot study, as no other studies regarding native T1 mapping in the Indian population exists. The findings of this study are comparable with those previous studies on native T1 mapping and reaffirm that these may be extrapolated to the Indian population. However, more multicenter studies are needed before native T1 mapping of the myocardium is incorporated into clinical decision making. More efforts towards setting reference ranges of native T1 values for the various myocardial pathologies and standardization of the acquisition techniques are required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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