Mapping the Future of Cardiac MR Imaging: Case-based Review of T1 and T2 Mapping Techniques[1]

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Abbreviations: AL = amyloid light-chain, ECV = extracellular volume fraction, LGE = late gadolinium enhancement, LL = Look-Locker, MOLLI = modified Look-Locker inversion-recovery, PSIR = phase-sensitive inversion-recovery, ShMOLLI = shortened modified Look-Locker inversion-recovery, SSFP = steady-state free precession, TI = inversion time

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Discuss the role of myocardial mapping as a diagnostic and prognostic tool to quantify disease and improve detection of diffuse abnormalities.
- Describe the basic methods of myocardial T1 and T2 mapping and the advantages and limitations of each technique.
- Recognize findings of common cardiac diseases on T1 and T2 maps and correlate them with findings on traditional cardiac MR images.

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TEACHING POINTS

See last page

Cardiac magnetic resonance (MR) imaging has grown over the past several decades into a validated, noninvasive diagnostic imaging tool with a pivotal role in cardiac morphologic and functional assessment and tissue characterization. With traditional cardiac MR imaging sequences, assessment of various pathologic conditions ranging from ischemic and nonischemic cardiomyopathy to cardiac involvement in systemic diseases (eg, amyloidosis and sarcoidosis) is possible; however, these sequences are most useful in focal myocardial disease, and image interpretation relies on subjective qualitative analysis of signal intensity. Newer T1 and T2 myocardial mapping techniques offer a quantitative assessment of the myocardium (by using T1 and T2 relaxation times), which can be helpful in focal disease, and demonstrate special utility in the evaluation of diffuse myocardial disease (eg, edema and fibrosis). Altered T1 and T2 relaxation times in disease states can be compared with published ranges of normal relaxation times in healthy patients. In conjunction with traditional cardiac MR imaging sequences, T1 and T2 mapping can limit the interpatient and interstudy variability that are common with qualitative analysis and may provide clinical markers for long-term follow-up.

Introduction

Clinical application of cardiac magnetic resonance (MR) imaging has grown rapidly over the past several decades (1,2), and many clinical and experimental studies have validated cardiac MR imaging as a useful noninvasive tool in the diagnosis and management of cardiovascular disease (3). Cardiac MR imaging now plays a pivotal role in cardiac morphologic and functional assessment and tissue characterization, allowing evaluation of various pathologic conditions ranging from myocardial infarction and ischemic or nonischemic cardiomyopathy to cardiac involvement in systemic diseases such as amyloidosis and sarcoidosis (4). This article discusses the use of myocardial mapping as a quantitative adjunct to currently accepted qualitative cardiac MR imaging techniques. The benefits, limitations, and applications of T1 and T2 mapping are reviewed by describing how these sequences can be used to characterize various cardiac diseases and by comparing images obtained with tissue mapping to those obtained with more commonly performed MR imaging sequences.

Traditional Qualitative Cardiac MR Imaging

Until recently, cardiac MR imaging has relied primarily on a qualitative characterization of the myocardium through visual analysis of signal intensity with various nonenhanced sequences (eg, T2 weighting for edema) and use of contrast material–enhanced sequences to identify characteristic enhancement patterns. Typically, gadolinium chelates have been the contrast agent of choice. Gadolinium accumulates in the abnormally increased extracellular space that is often seen in injured or diseased myocardium. By using a contrast-enhanced T1-weighted inversion-recovery sequence (to null normal myocardium), the signal difference between normal myocardium and focal fibrosis can be significantly increased (2,5). The resulting shortening of T1 relaxation times at delayed phase imaging enables detection of various cardiac diseases that show characteristic patterns on late gadolinium-enhanced (LGE) MR images (6). However, identification and characterization of enhancement patterns is subjective (4) and susceptible to the inter- and intraobserver variations common to qualitative analysis.

Teaching Point

Traditional LGE MR images are most useful for evaluation of focal diseases, where normal myocardium can be used as a standard of reference and a pattern of enhancement can be detected. Diffuse fibrosis may go undetected on qualitative images if gadolinium uptake is uniform (7).

Recent studies have attempted to quantify the amount of fibrotic myocardium by using signal intensity thresholds (usually set 2–6 standard deviations higher than for normal myocardium), but these methods are also limited if no normal myocardium is available as a reference (8,9). Moreover, patient and respiratory motion, tachycardia, and cardiac arrhythmia can compromise analysis of signal intensity and extent of disease (10–12). In contrast, myocardial mapping techniques allow signal quantification by using standardized, reproducible T1 and T2 values (in milliseconds), which appears to be more robust than qualitative assessment of signal intensity (13–17).

Quantitative Myocardial Mapping

Nonenhanced T1 Mapping

All tissues have inherent T1 (ie, longitudinal or spin-lattice) relaxation times that are based on a composite of their cellular and interstitial components (eg, water, protein, fat, and iron content). At a fixed magnetic field strength and in the absence of exogenous contrast agent (eg, gadolinium chelate), the native T1 value of normal tissue falls within a predictable range (eg, at 1.5 T, normal myocardium has a T1 relaxation time of 940–1000 msec) (18).

Teaching Point

Whereas qualitative sequences rely on the use of arbitrary signal intensity scales for T1 and T2 values that have interpatient and interimage variability, myocardial mapping offers the potential to produce images that have standardized, reproducible scales similar to the attenuation values used at computed tomography (13).

Mapping sequences employ different techniques (described in the following sections) to acquire a series of images at various inversion times, from which a T1 recovery curve is derived. The result is a T1 map, a parametric image that displays the T1 relaxation values pixel by pixel (Figs 1, 2). These maps are commonly displayed using color to aid in visual interpretation. Regions of interest can be drawn to assess a larger area of the myocardium.

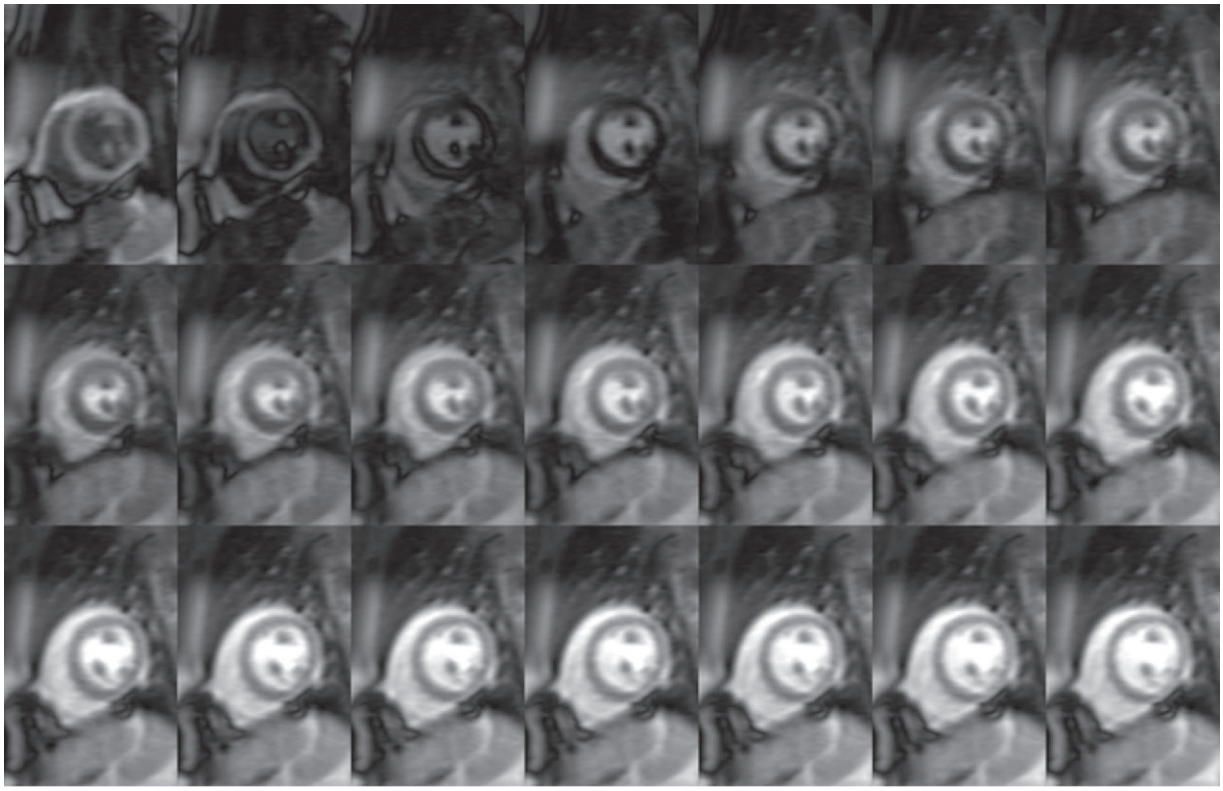
Native myocardial T1 relaxation times vary by magnetic field strength (3-T magnets result in longer native T1 times), equipment manufacturer, and the type of mapping sequence used. Several recent publications have reported "normal" T1 ranges for healthy subjects; these ranges are discussed later in the article. By providing a reproducible standard of T1 and T2 values, myocardial mapping may reduce interpretation variability and error related to subjective analysis and image artifact. Quantitative tissue characterization with mapping may also be better suited for longitudinal assessment of patients with cardiac disease than the arbitrary scale used at traditional cardiac MR imaging (19).

Myocardial disease affects the cellular and extracellular composition of myocardial tissue, thereby altering the native T1 and T2 signals. In general, a prolonged native myocardial T1 signal is encountered in various disease states that result in edema or fibrosis, and in amyloid deposition. Shortening of the native T1 relaxation time can be seen with siderosis, Anderson-Fabry disease, and fat deposition, although these diseases are less commonly encountered in routine practice (20–23). Examples of specific diseases are discussed later in this article.

Contrast-enhanced T1 Mapping

The use of gadolinium-based contrast agents shortens the native T1 relaxation time of myocardium by several hundred milliseconds. Areas with a disproportionate accumulation of contrast material (eg, fibrosis) will therefore exhibit shorter T1 relaxation times than normal myocardium (21–23) when using contrast-enhanced T1 mapping sequences. Whereas nonenhanced T1 map values are a native property of the myocardium, contrast-enhanced T1 map values are variable and highly dependent on *(a)* variable weight-based

Figure 1. T1 mapping with a Look-Locker (LL) MR imaging sequence in a healthy 34-year-old man with normal myocardium. **(a)** LL (inversion time [TI] scout) image series performed at 1.5 T shows 21 images acquired at a fixed location (short-axis, midventricle) at different TIs ranging from 75 msec (top left) to 695 msec (bottom right), with a 30-msec increase in TI between images. The images were obtained after administration of gadolinium-based contrast agent. Note the variation in chamber size as images are acquired throughout the cardiac cycle without electrocardiographic gating, which is one of the limitations of this technique. **(b)** T1 map displays a color scale of the uniform T1 values of the myocardium. Note that the endocardial and epicardial borders are somewhat indistinct because of motion and misregistration. (Scale is in milliseconds.) **(c)** Graph of a multiparameter curve-fitting analysis of a selected pixel in the interventricular septum shows how each value is used to derive the contrast-enhanced T1 value (299 msec) for this pixel.



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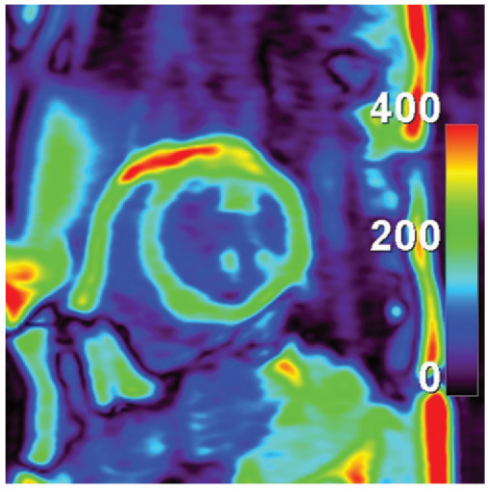

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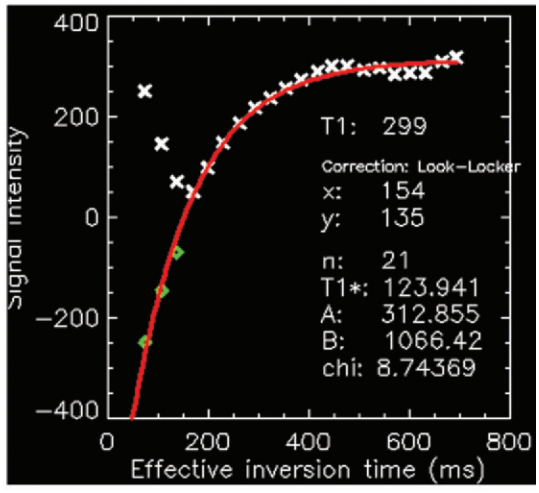
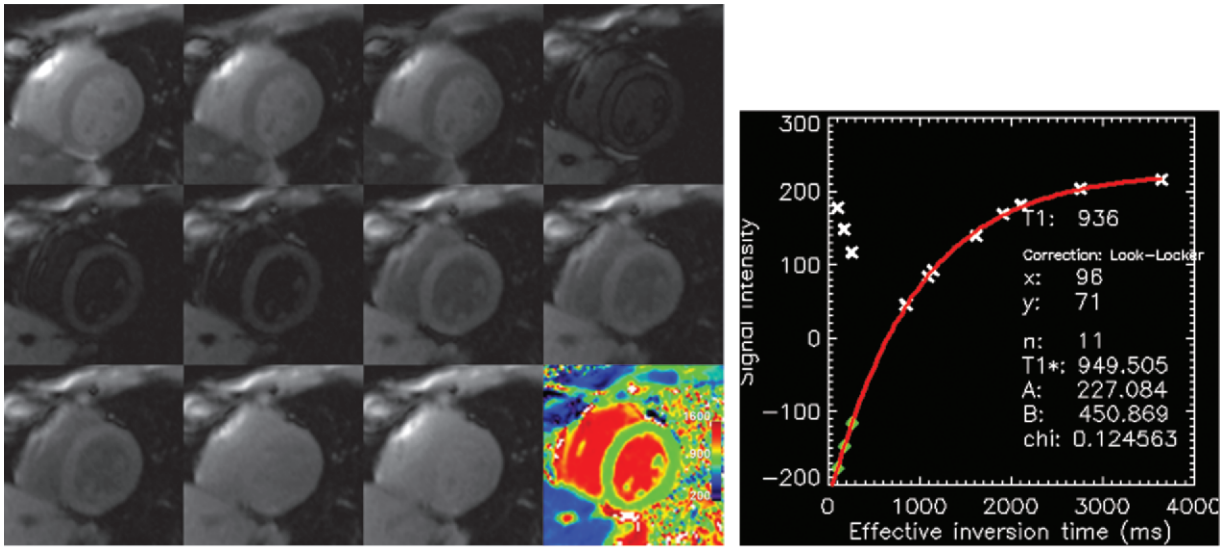


c.

contrast agent dosing, *(b)* the exact time elapsed after contrast agent administration before images are acquired, *(c)* renal clearance of the contrast agent, and *(d)* displacement of contrast material by the hematocrit (3,24). Thus, nonenhanced T1 mapping is less variable (within the same patient and across patients) than contrast-enhanced T1 mapping because of the variability in the exact time of image acquisition with contrast-enhanced mapping (18).



a. b.

Figure 2. T1 mapping with a modified LL inversion-recovery (MOLLI) MR imaging sequence in a healthy patient. **(a)** Images from a nonenhanced MOLLI series at 1.5 T were obtained during one breath hold at the same time point in diastole, resulting in less misregistration than with an LL sequence. Inset shows the resultant native T1 map. (Scale is in milliseconds.) **(b)** Graph of a curve-fitting analysis for a single pixel in the interventricular septum shows a normal nonenhanced T1 value of 936 msec.

T1 Mapping Technique

LL Sequence

Most modern MR imaging units already include the ability to perform a sequence that can be used for T1 mapping, called the LL sequence (also known as the TI scout) (25,26). For routine LGE MR images, the patient is initially injected with 0.1–0.2 mmol/kg of gadolinium-based contrast agent, and, after 6–8 minutes, a series of approximately 20 images is acquired at variable inversion-recovery times (the LL sequence) (Fig 1). The supervising technologist or imager uses this series to select the inversion time that most effectively nulls normal myocardial signal (typically 200–300 msec). At traditional cardiac MR imaging, after the appropriate inversion time is selected, the scout images are usually disregarded. However, these images can be loaded into postprocessing software to create a pixel map of T1 values (a T1 map) generated by the curve fitting of all images in a sequence. The LL sequence is limited by heart rate variability and acquisition during different phases of the cardiac cycle, a process that has been previously detailed (27). Therefore, contouring of the epicardial and endocardial boundaries is limited by partial volume effects (28).

MOLLI and ShMOLLI Sequences

MOLLI and shortened modified LL inversion-recovery (ShMOLLI) sequences are newer techniques that have distinct advantages over the LL sequence. With the MOLLI sequence, there are two changes to the standard LL sequence: *(a)* data are acquired at a fixed point in the cardiac cycle over successive heartbeats during a single breath hold (approximately 16–20 seconds), and *(b)* multiple LL image acquisitions are performed at different inversion times and merged into one dataset to facilitate the final analysis (13,18,27) (Fig 2).

In addition to being shorter than standard LL sequences, MOLLI sequences result in less myocardial misregistration because images are acquired at the same time point in the cardiac cycle (18). Motion-correction algorithms have been developed to account for slight interbeat variability and variation in respiration (29). These modifications result in a tighter range of T1 values that have been observed with MOLLI versus with LL sequences (27). ShMOLLI is an even shorter variation that uses sequential inversion-recovery measurements with a single breath hold of only nine heartbeats. Although full recovery of T1 magnetization is not achieved, the implementation of conditional interpretation reconstruction algorithms at imaging can yield accurate measurements (19).

Other Sequences under Investigation

Additional cardiac MR imaging sequences, including saturation recovery single-shot acquisition (SASHA) (30) and saturation pulse prepared heart-rate-independent inversion recovery (SAPPHIRE) sequences (31), are actively being studied but are not commonly used in clinical practice and are beyond the scope of this article.

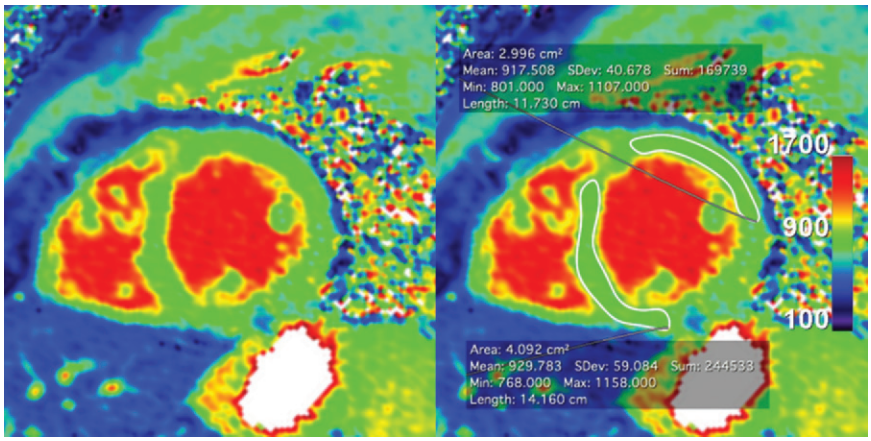


Figure 3. T1 maps obtained with a nonenhanced MOLLI MR imaging sequence at 1.5 T in a 49-year-old man without cardiac disease show normal findings. Note the relatively uniform signal intensity throughout the myocardium. Regions of interest are drawn freehand to ensure that blood pool and epicardial fat are excluded. (Scale is in milliseconds.)

Myocardial Tracing, Inversion Time, and Curve Fitting

Teaching Point

The T1 map is a single image that represents a pixel map of the T1 values generated by curve fitting of all images in a sequence (ie, LL, MOLLI, or ShMOLLI). This image may be generated automatically at the imaging unit; however, open-source software is available for analysis and has been validated for clinical use (32). Off-line post-processing of the T1 or T2 map is completed by manually or semiautomatically tracing the epicardial and endocardial borders with care to avoid the inclusion of epicardial fat and ventricular blood pool contamination. An example of a T1 map with normal values is shown in Figure 3.

T2 Mapping Technique

The T2 relaxation time is altered by the water content in tissue. Myocardial edema has been described in patients with acute myocardial infarction (33), myocarditis (34), stress cardiomyopathy (34), sarcoidosis (35), and cardiac allograft rejection (36). As with traditional T1-weighted sequences, qualitative T2-weighted imaging performed with dark-blood turbo spin-echo sequences (37) has several limitations, including magnetic field heterogeneity from surface coil arrays, stagnant blood flow resulting in increased signal intensity (particularly along the subendocardium), and through-plane motion resulting in signal loss (15,37).

T2 parametric maps are generated on the basis of a similar principle to that used in T1 mapping, where a series of images is obtained to calculate a T2 decay curve. A T2 preparation pulse is applied to impart T2 signal contrast, and a subsequent readout is performed by using a steady-state free precession (SSFP) sequence that has less sensitivity to turbo spin-echo artifacts (10,15,38). T2 mapping techniques have not yet received the same focus as T1 mapping techniques; thus, a comparison of diagnostic efficacy between the two techniques will be better served in future investigations.

"Normal" T1 and T2 Mapping Values and Limitations

Absolute T1 and T2 values for normal left ventricular myocardium vary across MR imaging systems and manufacturers. Furthermore, several studies have shown that numerous factors can affect the native T1 relaxation time, including the exact sequence used; the magnetic field strength (native T1 values are higher at 3 T than at 1.5 T); the image acquisition plane (eg, two-chamber vs four-chamber); the region of myocardium being sampled; and the patient's heart rate, age, and sex (13,14,27). For example, a study by Piechnik et al (39) of 231 healthy individuals showed an average myocardial T1 relaxation time of 961 msec ± 26 (1.5 T, ShMOLLI) across all subjects; men had an average T1 relaxation time of 947 msec ± 20 and women had an average T1 time of 974 msec ± 25. The sex differences in T1 times were most prominent in the 2nd–5th decades of life, and T1 values decreased with age. Tables 1 and 2 summarize additional values that have been reported in the literature for different imaging sequences and magnet strengths.

Extracellular Volume Fraction

Contrast-enhanced T1 mapping is useful for calculating the extracellular volume fraction (ECV), a measure of the proportion of extracellular space within the myocardium. The ECV has drawn recent interest in the cardiology community, as it has been shown to offer important prognostic information related to cardiac morbidity and mortality (45). Nonenhanced and contrast-enhanced T1 mapping allows evaluation of the proportion of gadolinium-based contrast agent in the blood pool versus in the myocardium. In conjunction with the hematocrit value, mapping enables quantification of the proportion of extracellular

Teaching Point

Table 1: Select Reported Myocardial T1 Relaxation Times in Healthy Subjects

Magnet	Technique	No. of Subjects*	Age (y)	Native T1 (msec)†	Contrast-enhanced T1 (msec)	Authors	Year
1.5 T	LL	14 (8)	38 ± 10.9	1000.4 ± 126	523.3 ± 72.8	Nacif et al (27)	2011
1.5 T	MOLLI	15 (9)	33.1 ± 8.5	982 ± 46	NR	Messroghli et al (13)	2006
1.5 T	MOLLI	10 (7)	35 ± 7	976 ± 46/80	NR	Piechnik et al (19)	2010
1.5 T	MOLLI	14 (8)	38 ± 10.9	1029.4 ± 56.8	462.4 ± 62.2	Nacif et al (27)	2011
1.5 T	MOLLI	13 (7)	38.1 ± 11.1	NR	466 ± 14	Sibley et al (23)	2012
1.5 T	ShMOLLI	10 (7)	35 ± 7	966 ± 48/88	NR	Piechnik et al (19)	2010
1.5 T	ShMOLLI	21 (8)	55 ± 13	944 ± 17	NR	Ferreira et al (40)	2012
1.5 T	ShMOLLI	45 (32)	42 ± 14	941 ± 18	NR	Ferreira et al (41)	2013
1.5 T	ShMOLLI	342 (170)	38 ± 15	962 ± 25	NR	Piechnik et al (14)	2013
1.5 T	ShMOLLI	36 (22)	59 ± 4	958 ± 20	NR	Karamitsos et al (42)	2013
3 T	MOLLI	10 (7)	35 ± 7	1169 ± 45/73	NR	Piechnik et al (19)	2010
3 T	MOLLI	24 (8)	29 ± 6	1159.0 ± 39.2	NR	Liu et al (21)	2012
3 T	MOLLI	60 (30)	48 ± 17	1158.7	411.2	von Knobelsdorff-Brenkenhoff et al (43)	2013
3 T	ShMOLLI	10 (7)	35 ± 7	1166 ± 60/91	NR	Piechnik et al (19)	2010

Note.—NR = not reported.
*Number in parentheses indicates number of male subjects.
†Some values are represented as mean ± standard deviation/mixed standard deviation, as defined by Piechnik et al (19).

Table 2: Select Reported Myocardial T2 Relaxation Times in Healthy Subjects

Magnet	Technique	No. of Subjects*	Age (y)	Native T2 (msec)	Authors	Year
1.5 T	SSFP multipoint IR	19 (13)	38 ± 17	50 ± 4	Blume et al (16)	2009
1.5 T	Spiral interleaved T2	10 (5)	36 ± 7	54 ± 6.8	Sparrow et al (17)	2009
1.5 T	SSFP	14 (NR)	NR	52.18 ± 3.4	Giri et al (15)	2009
1.5 T	SSFP	21 (13)	28 ± 7	55.5 ± 2.3	Verhaert et al (33)	2011
1.5 T	SSFP	10 (NR)	NR	53.4 ± 6.1	Giri et al (44)	2012
1.5 T	SSFP	14 (NR)	NR	51.5 ± 2.0	Crouser et al (35)	2014
3 T	SSFP	60 (30)	48 ± 17	45.1 (mean)	Von Knobelsdorff-Brenkenhoff et al (43)	2013

Note.—IR = inversion-recovery, NR = not reported.
*Number in parentheses indicates number of male subjects.

(interstitium and extracellular matrix) myocardial volume to cellular (myocyte) volume. An increased ECV is a marker of myocardial remodeling and is most often due to excessive collagen deposition (in the absence of amyloid or edema). Recent analyses have shown that the ECV may be as important as the left ventricular ejection fraction as a marker for cardiac disease severity, indicating vulnerable myocardium with decreased tolerance to ischemia (24,46). Early studies have shown that the ECV is positively correlated with worsened mechanical dysfunction, arrhythmia, and mortality, particularly in patients with diabetes or a history of myocardial infarction (24,46). In a large cohort of 1176 patients who underwent cardiac MR imaging, Wong et al (46) found a higher average ECV in patients with type II diabetes than in those without diabetes (30.2% vs 28.1%, respectively) and reported that a patient's risk for death or hospitalization for heart failure increases as the ECV increases. ECV quantification can be used to identify and characterize diffuse fibrosis or subtle myocardial abnormalities in what may otherwise be a normal-appearing

Table 3: Select Reported ECVs in Healthy Subjects

Magnet	Technique	No. of Subjects*	Age (y)	ECV	Authors	Year
1.5 T	MOLLI	9 (NR)	20–50	0.217–0.262	Wong et al (24)	2012
1.5 T	MOLLI	62 (30)	43.6 ± 17.4	0.254 ± 0.025	Kellman et al (48)	2012
1.5 T	MOLLI	30 (15)	45 ± 13	0.255 ± 0.026	Miller et al (49)	2013
1.5 T	MOLLI	17 (17)	33 ± 8	0.24 ± 0.02	Florian et al (50)	2014
3.0 T	MOLLI	11 (6)	36 ± 13	0.267 ± 0.01	Lee et al (51)	2011
3.0 T	LL	9 (3)	45 ± 11	0.24	Mongeon et al (52)	2012

Note.—NR = not reported.
*Number in parentheses indicates number of male subjects.

cardiac MR imaging study (47). Furthermore, because the ECV represents a ratio of T1 signal intensities, measurements may be more reproducible across different vendors and different acquisition techniques (45).

The ECV is calculated on the basis of nonenhanced and contrast-enhanced T1 map values, using the ratio of the difference in reciprocal values for contrast-enhanced and nonenhanced myocardial T1 and contrast-enhanced and nonenhanced blood pool T1 as follows (21,24):

$$ECV = (1 - HCT) \cdot \frac{\left(\frac{1}{MT1_{post}} - \frac{1}{MT1_{pre}}\right)}{\left(\frac{1}{BT1_{post}} - \frac{1}{BT1_{pre}}\right)},$$

where $BT1_{post}$ = contrast-enhanced blood pool T1, $BT1_{pre}$ = nonenhanced blood pool T1, HCT = hematocrit, $MT1_{post}$ = contrast-enhanced myocardial T1, and $MT1_{pre}$ = nonenhanced myocardial T1. The hematocrit level should be measured at the time of the MR imaging examination because it can affect gadolinium displacement from the blood pool. The reported range of the ECV in healthy subjects is 21%–27%, as noted in the selected studies reported in Table 3. Examples of ECV calculation in healthy and diseased myocardium are provided in Figure 4.

All of the images shown were acquired with an Avanto 1.5-T MR imaging system (Siemens Medical Solutions, Erlangen, Germany). Reference values for this system have been published in several different studies (19,27).

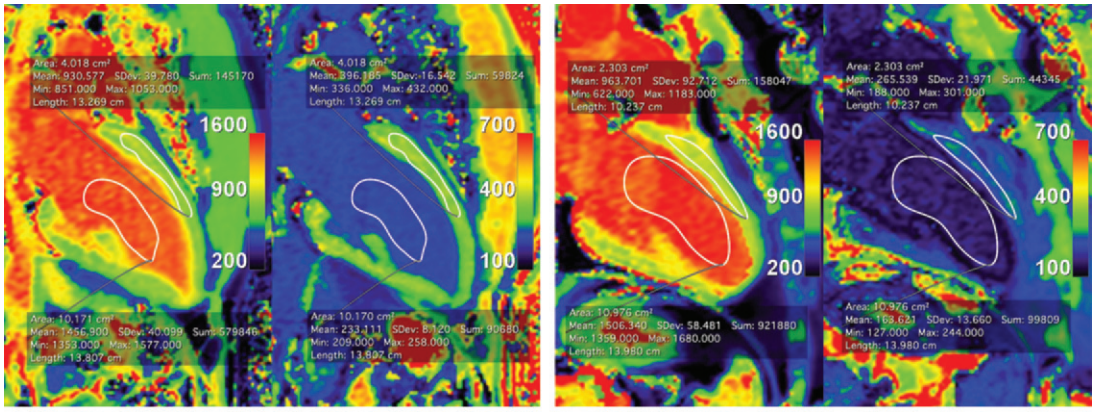
Selected Applications of T1 and T2 Mapping

Characteristic patterns of myocardial fibrosis on LGE MR images have been described for various types of ischemic and nonischemic cardiomyopathy (4). The presence of fibrosis or scarring (indicative of myocardial remodeling) has been shown to be an independent risk factor for overall mortality (related to ventricular arrhythmia and decompensated heart failure) and the possible need for cardiac transplantation (53,54). Quantifying the degree of fibrosis may guide treatment with regard to revascularization, device implantation, and medical therapy. Although endomyocardial biopsy is the most sensitive technique for assessing myocardial scarring or fibrosis, a recent study by Sibley et al (23) demonstrated that contrast-enhanced T1 mapping represents a viable noninvasive alternative. Importantly, this study showed that even when visible LGE was absent on traditional cardiac MR images, shortened T1 relaxation times at contrast-enhanced myocardial mapping were associated with a greater degree of histologically confirmed interstitial fibrosis. A study by Appelbaum et al (55) shows that intermediate-intensity LGE is a better predictor of ventricular arrhythmia in hypertrophic cardiomyopathy than is high-intensity LGE, further supporting the use of mapping for quantitation of myocardial T1 values for risk stratification. Mapping can noninvasively represent a "sample" of tissue from the entire myocardium and can supplement or potentially replace invasive transvenous myocardial biopsy (which usually is limited to the right ventricular myocardium) (23). At a minimum, T1 mapping may help identify the most appropriate location for biopsy, if biopsy is deemed clinically necessary.

Teaching Point

Acute or Chronic Myocardial Infarction

Cellular degradation in acute myocardial infarction results in increased permeability and enlargement of the extravascular space and an increased volume of distribution for the extracellular contrast agent (gadolinium chelate). Additionally, gadolinium chelates wash out of infarcted tissue more slowly than out of healthy myocardium (3). Although delayed enhancement by itself is not specific, LGE (subendocardial or transmural) in a vascular distribution and in the appropriate clinical context corresponds to myocardial infarction



a. b.

Figure 4. T1 mapping with ECV calculations in patients with healthy and diseased myocardium. (Scale is in milliseconds.) **(a)** T1 maps show a normal ECV (23.3%) in a healthy 55-year-old man without known cardiac disease (hematocrit, 0.42). **(b)** T1 maps show an abnormal ECV (30.1%) in a 40-year-old woman with long-standing type 2 diabetes (hematocrit, 0.40). The patient was admitted for heart failure, and her coronary arteries were normal at cardiac catheterization. No evidence of fibrosis was seen at LGE MR imaging, but the increased ECV may have important long-term prognostic implications.

(3–5,22,56). Given the increased mortality rate for patients with undiagnosed old or chronic myocardial infarction (which may not show Q waves at electrocardiography), cardiac MR imaging can also be useful for confirmation of myocardial infarction in the nonacute setting.

Nonenhanced T1 mapping, combined with traditional T1-weighted LGE MR images and traditional T2-weighted sequences, is a viable method for assessing the acuity, severity, and extent of myocardial injury, including the full extent of a myocardial infarct as well as the area at risk (22,47,57) (Figs 5, 6). Ischemic myocardium shows signal hyperintensity due to edema on T2-weighted images. However, qualitative analysis of T2-weighted images can be compromised by factors such as signal loss in tachycardia, through-plane motion, and signal intensity overestimation in areas of slow-flowing blood (15,58). T2 mapping allows quantification of T2 relaxation times and is unaffected by these factors (12,15,33,58). Additionally, T2 prolongation in infarcted segments is seen in the first 48 hours after myocardial infarction and can persist for up to 6 months (59), providing a possible longitudinal clinical marker.

Hypertrophic Cardiomyopathy

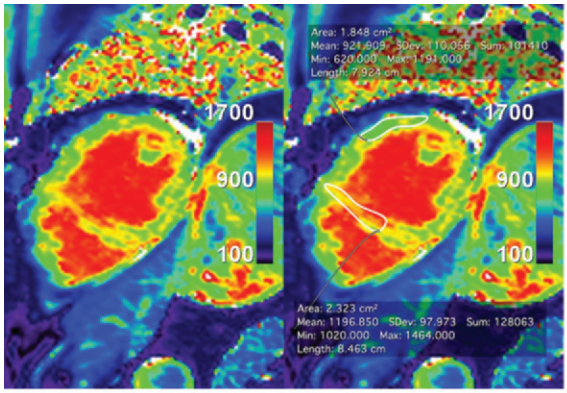
Hypertrophic cardiomyopathy is characterized by abnormal thickening of the left ventricular wall in the absence of dilatation (60). The distribution of myocardial thickening varies, ranging from involvement of the basal anterior septum (most common) to apical involvement or total concentric hypertrophy. Outflow tract obstruction leads to systolic anterior motion of the mitral valve. Impaired regional contractility, decreased coronary reserve, and ventricular arrhythmias can also be seen (61,62).

Traditional cardiac MR imaging plays a valuable role in the analysis of ventricular function and mitral regurgitation, with contrast-enhanced studies revealing patchy delayed enhancement in areas of hypertrophy, which are believed to be related to microvascular abnormalities leading to subclinical myocardial ischemia, which in turn leads to microscopic foci of myocardial necrosis and subsequent fibrosis (20,63,64). In addition to its use in primary diagnosis, myocardial mapping may serve at least two other purposes in this population: *(a)* longitudinal quantitative follow-up of the degree of fibrosis (which may portend prognosis and stratification of risk for adverse events) and *(b)* quantitative analysis of scarring after transcatheter septal ablation (to indicate successful destruction of myocardial tissue) (65). A study by Rogers et al (7) showed a similar application of T1 mapping in patients with left ventricular hypertrophy, compared with subjects with a low pretest likelihood of cardiomyopathy, measuring native T1 values as a reproducible, standardized technique to distinguish healthy from diseased myocardium. Contrast-enhanced T1 mapping studies in patients with hypertrophic cardiomyopathy have also been validated (26). Examples of T1 mapping in patients with septal and apical hypertrophic cardiomyopathy variants are provided in Figures 7 and 8.

Myocarditis

Myocardial injury in acute myocarditis (often caused by infectious agents, frequently viruses) leads to interstitial edema, lymphocytic infiltration, myocyte breakdown, and subsequent necrosis

Figures 5, 6. **(5)** T1 mapping in a 34-year-old man who presented with acute ST-elevation myocardial infarction, with a 100% left anterior descending occlusion seen at cardiac catheterization. (Scale is in milliseconds.) **(a–d)** MOLLI native T1 mapping short-axis **(a)** and vertical long-axis **(c)** images at 1.5 T show an abnormally increased T1 signal in the areas of infarction involving the anteroseptal and anterior wall of the left ventricle and extending to the apex. The T1 mapping abnormalities correlate with areas of LGE on phase-sensitive inversion-recovery (PSIR) LGE MR images obtained at corresponding levels **(b, d)**. **(e)** T2 map shows increased signal intensity due to increased edema, in a similar distribution to the abnormalities seen in **a–d**. **(6)** Lateral wall infarction in a 37-year-old woman. Short-axis MOLLI (1.5 T) T1 mapping images acquired 26 minutes after gadolinium-based contrast agent administration show a focal area of decreased T1 values in the lateral wall of the left ventricle. The absolute T1 value at contrast-enhanced mapping is less important than the regional differences between normal and abnormal myocardium because the LGE T1 value depends on the amount of contrast agent injected, the time after contrast agent administration when the image is acquired, renal function, and the hematocrit. (Scale is in milliseconds.)



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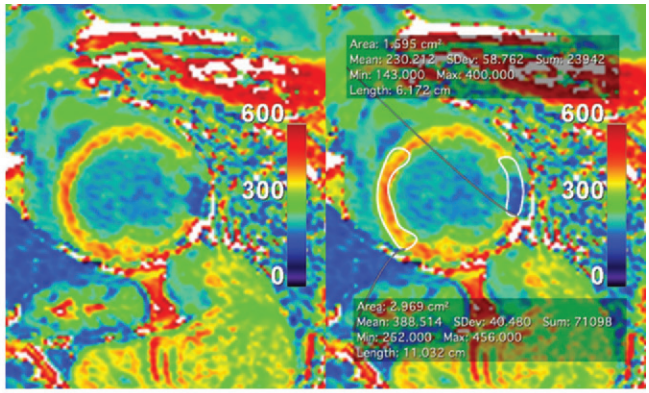

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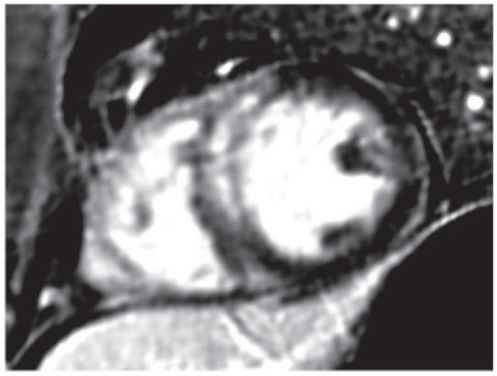

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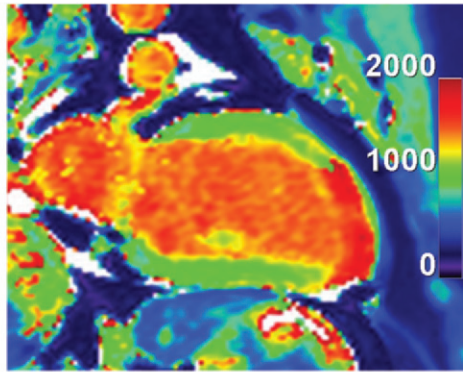

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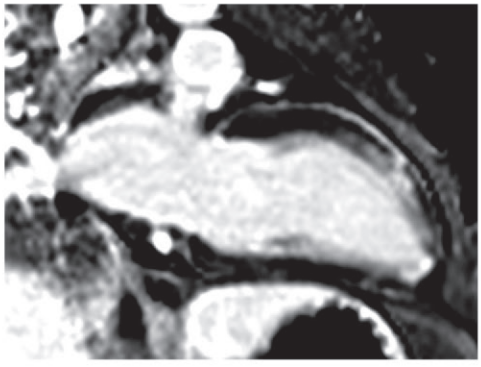

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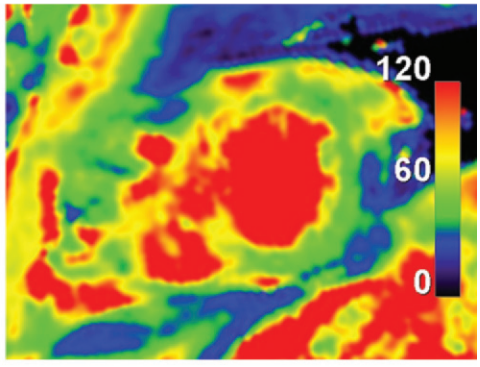


5e.

(66). The insidious nature and variety of clinical manifestations in acute myocarditis can complicate diagnosis. Patients may present with vague symptoms such as fatigue, palpitations, or weakness after an acute bout of fever and angina. Acute myocarditis also can manifest as florid heart failure and may progress to chronic myocarditis and dilated cardiomyopathy (67). Thus, early testing and accurate diagnosis can positively affect patient outcome.

Cardiac MR imaging is the imaging tool of choice in diagnosing acute myocarditis (68);

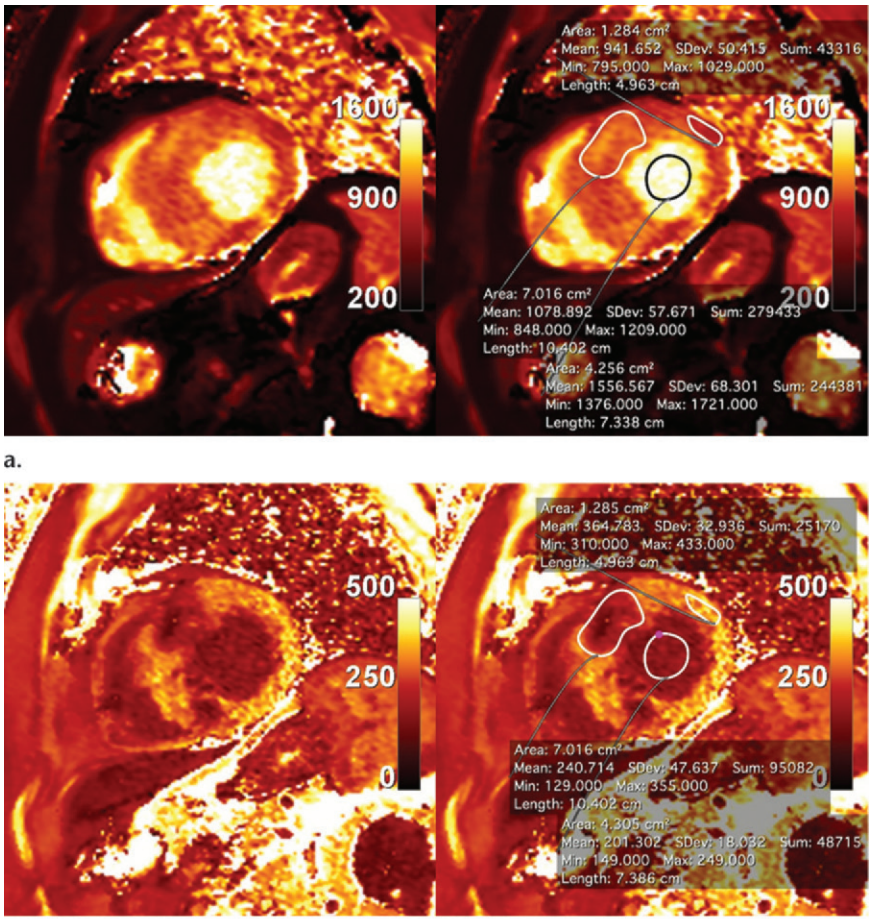


Figure 7. T1 mapping in a 55-year-old man with septal hypertrophic cardiomyopathy. **(a)** Short-axis nonenhanced MOLLI (1.5 T) T1 map demonstrates prolonged T1 values in the area of myocardial hypertrophy, with relatively normal values in the lateral wall. **(b)** T1 map obtained at LGE MR imaging shows abnormal shortening of the T1 values in the hypertrophied segments. The extracellular volume for the hypertrophied segments was abnormally elevated (41.7% vs 21.7% for the lateral wall) (hematocrit, 0.44). (Scale in **a** and **b** is in milliseconds.) **(c)** PSIR LGE MR image through the same plane shows patchy midwall enhancement, a finding characteristic of hypertrophic cardiomyopathy.

clinical examination, electrocardiography, and laboratory data are often of limited value (69). Subepicardial patchy or nodular LGE in conjunction with an underlying wall-motion abnormality is a classic finding in the initial phase (<7 days); however, the enhancement pattern usually becomes diffuse within 7 days after infection (69). Also, in the early phase, correlation with T2-weighted images (for edema) and nonenhanced and contrast-enhanced images (for hyperemia) helps to establish the diagnosis.

Recently, Ferreira et al (41) showed that T1 mapping for detection of acute myocarditis showed superior diagnostic performance compared with T2 mapping and higher sensitivity compared with T2-weighted and LGE MR imaging techniques. In this study, a cutoff T1 value of 990 msec or higher (with a ShMOLLI sequence at 1.5 T) was used for detection of acute edema and demonstrated a positive predictive value and a negative predictive value of about 90% across the board. LGE (specificity, 97%; positive predictive value, 97%) demonstrated lower sensitivity (74%) when compared with nonenhanced T1 mapping. Of note, T1 mapping with LGE improved specificity only slightly (97% compared with 91%), at the expense of lower sensitivity (70% compared with 90%), which was not better than with LGE sequences alone. The improved diagnostic ability of T1 mapping was attributed to shorter breath holds limiting motion artifact, heart rate independence (better for imaging of acutely ill patients), and lack of need for a contrast agent or reference normal myocardium (better for imaging of patients with global edema) (41). T2 mapping has also been shown to depict myocardial involvement in myocarditis and shows

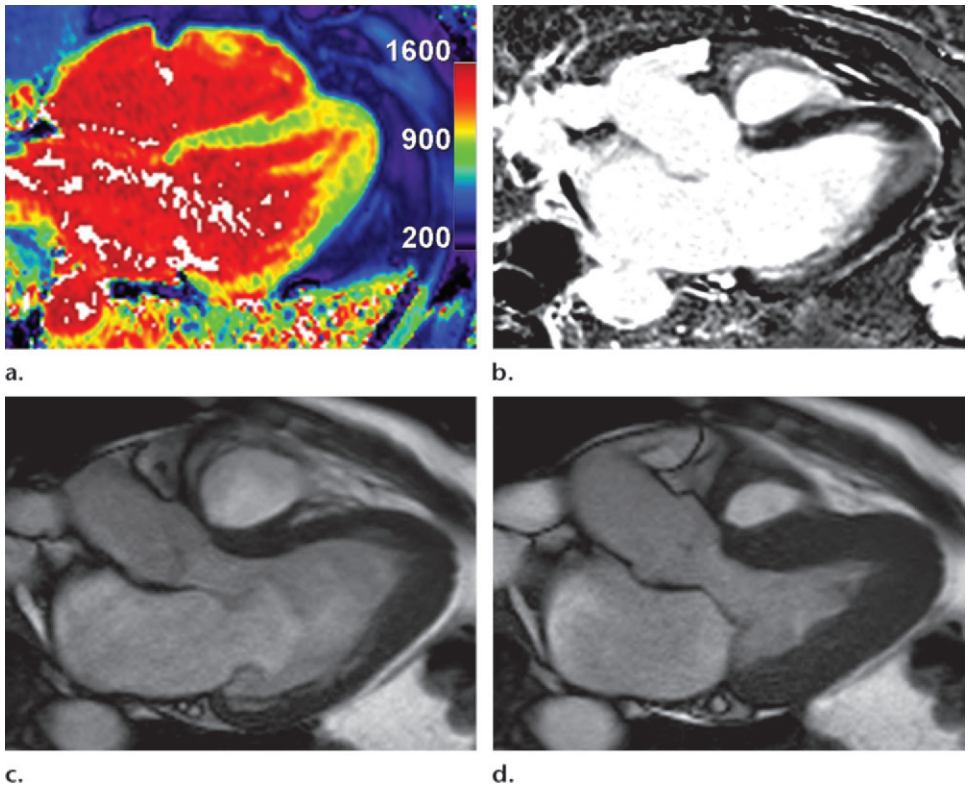


Figure 8. T1 mapping in a 65-year-old man with apical variant hypertrophic cardiomyopathy that was initially detected at electrocardiography. **(a)** Nonenhanced three-chamber MOLLI native T1 map at 1.5 T shows abnormally increased T1 values in the apical segments of the left ventricle. (Scale is in milliseconds.) **(b)** Corresponding LGE MR image in the same plane shows enhancement in the same area. **(c, d)** SSFP MR images obtained in end diastole **(c)** and end systole **(d)** show the characteristic "spade" shape of the left ventricular cavity (maximum thickness, 16 mm), with obliteration of the apical lumen.

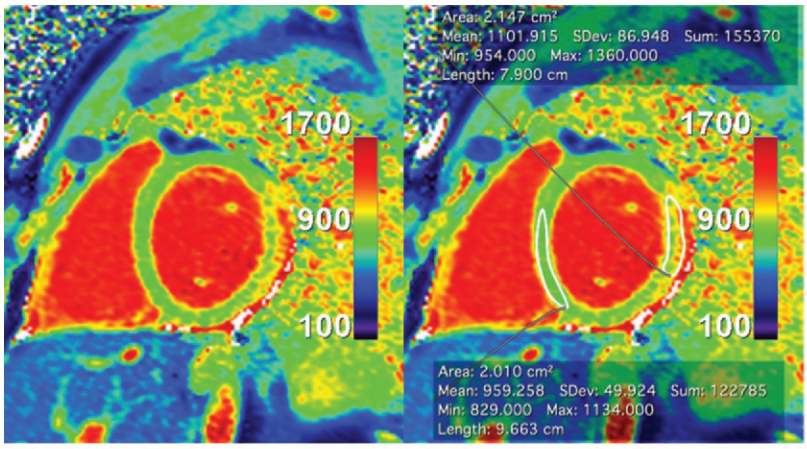
a greater extent of disease involvement when compared with qualitative T2-weighted and LGE MR imaging sequences (34) (Fig 9).

Given that edema detected at T2-weighted imaging is susceptible to artifact and myocarditis may be a diffuse process, the strength of T2 mapping lies in its ability to depict prolonged T2 relaxation times in the absence of normal myocardium for comparison. An additional example of global edema and the potential of T2 mapping is allograft rejection in cardiac transplant, where identification of rejection in the first 12 months after transplant has a major effect on patient survival. Whereas endomyocardial biopsy and traditional cardiac MR imaging have been used to detect myocardial inflammation and edema, T2 mapping may provide a noninvasive and quantitative alternative. The results of a pilot study by Usman et al (36) suggest that T2 mapping of myocardial edema may be useful for monitoring of transplant patients, although further study is needed.

Amyloidosis

Primary or secondary amyloidosis is a cause of restrictive cardiomyopathy secondary to myocardial infiltration with fibrillar proteins and leads to loss of ventricular compliance, diastolic dysfunction, and reduced systolic function (3). Cardiac dysfunction in these patients can cause cardiac death shortly after the onset of heart failure, thus necessitating early diagnosis of myocardial involvement.

Cardiac MR imaging patterns of enhancement in amyloid deposition vary by subtype and can be diffuse, heterogeneous, and nonspecific in the lack of clinical context; however, the classic pattern on LGE T1-weighted MR images is diffuse left ventricular subendocardial enhancement (4). In cases of diffuse myocardial involvement, the lack of a normal region of myocardium for comparison can make traditional cardiac MR images difficult to interpret. Given that amyloid protein itself causes prolonged T1 relaxation (70), Karamitsos et al (42) evaluated the utility of nonenhanced T1 mapping (ShMOLLI at 1.5 T) in patients with primary amyloid light-chain (AL) amyloidosis compared with normal controls and patients with aortic stenosis. Their study showed that among patients with amyloidosis with overt cardiac involvement, the T1



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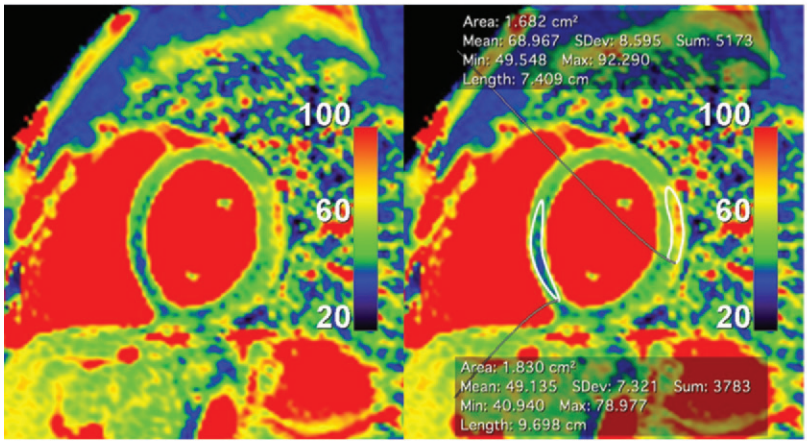

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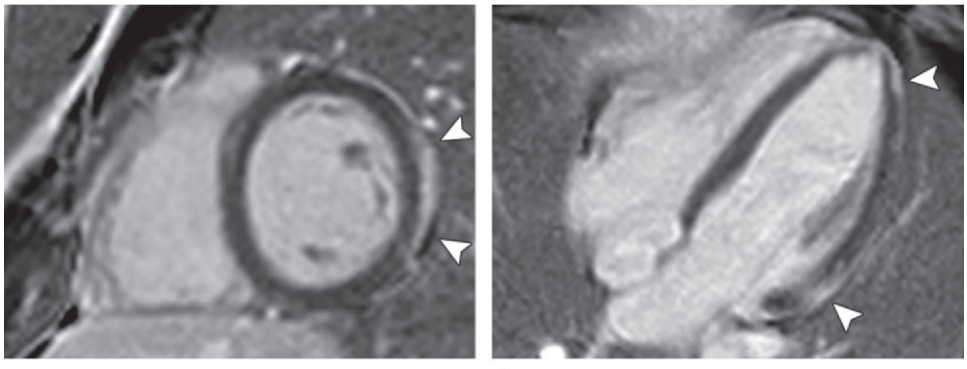


c. d.

Figure 9. T1 and T2 mapping in an 18-year-old man with myopericarditis. **(a, b)** Short-axis nonenhanced MOLLI T1 **(a)** and SSFP T2 **(b)** maps obtained at 1.5 T through the base of the left ventricle show prolonged T1 and T2 relaxation times in the lateral wall, corresponding to areas of myocardial injury from myocarditis. The patient had a reduced ejection fraction with hypokinesis in the lateral and apical walls (not shown). (Scale is in milliseconds.) **(c, d)** Short-axis **(c)** and four-chamber PSIR **(d)** LGE MR images show typical epipericardial enhancement characteristic of myopericarditis that involves the basal lateral and apical regions (arrowheads). Note that the T1 map in **a** shows more extensive signal abnormality (corresponding to the extent of myocardial injury) than the delayed contrast-enhanced images.

increases are more pronounced than in patients with aortic stenosis, with a similar degree of ventricular wall thickening (possibly due to a greater proportion of amyloid protein itself or greater T1 prolongation by amyloid compared with fibrosis). Specifically, they found that a T1 nonenhanced threshold of 1020 msec resulted in 92% accuracy for diagnosis of cardiac amyloid. Furthermore, nonenhanced T1 relaxation times correlated well with markers for systolic and

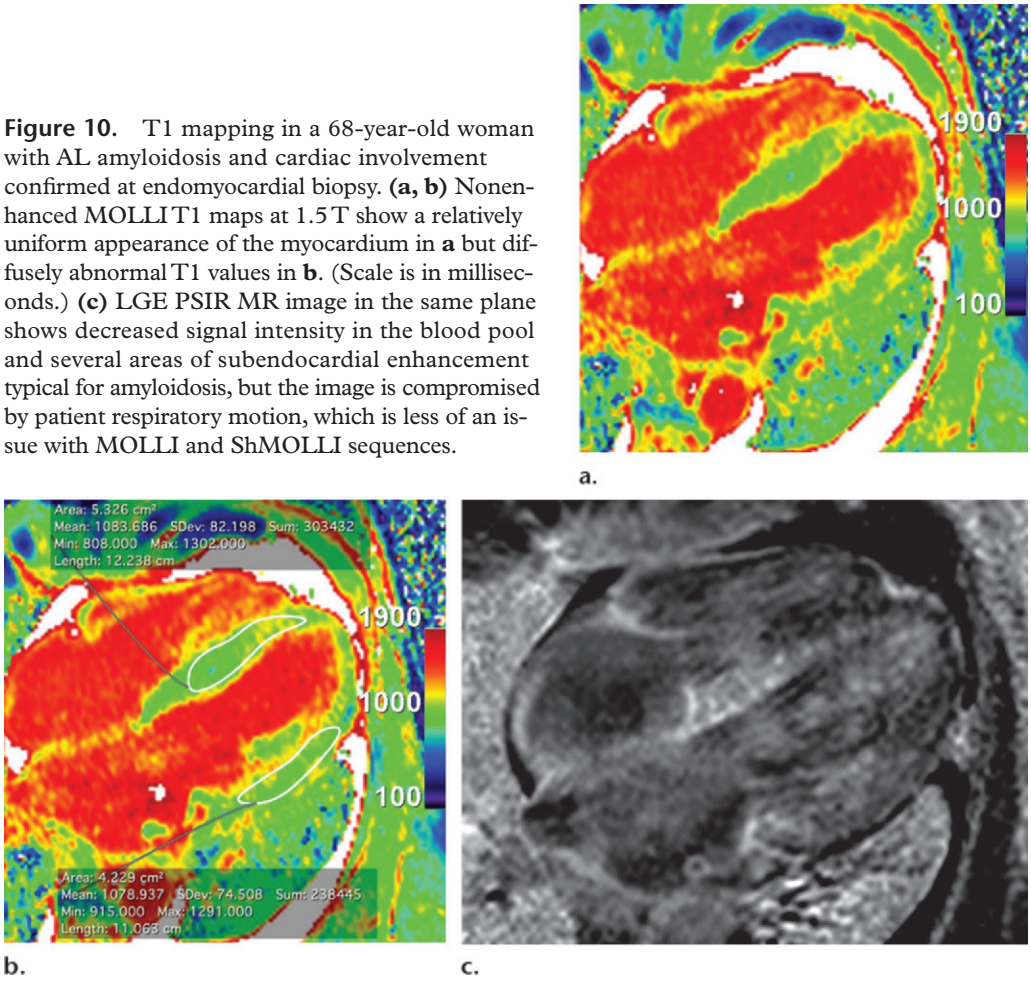


Figure 10. T1 mapping in a 68-year-old woman with AL amyloidosis and cardiac involvement confirmed at endomyocardial biopsy. **(a, b)** Nonenhanced MOLLI T1 maps at 1.5 T show a relatively uniform appearance of the myocardium in **a** but diffusely abnormal T1 values in **b**. (Scale is in milliseconds.) **(c)** LGE PSIR MR image in the same plane shows decreased signal intensity in the blood pool and several areas of subendocardial enhancement typical for amyloidosis, but the image is compromised by patient respiratory motion, which is less of an issue with MOLLI and ShMOLLI sequences.

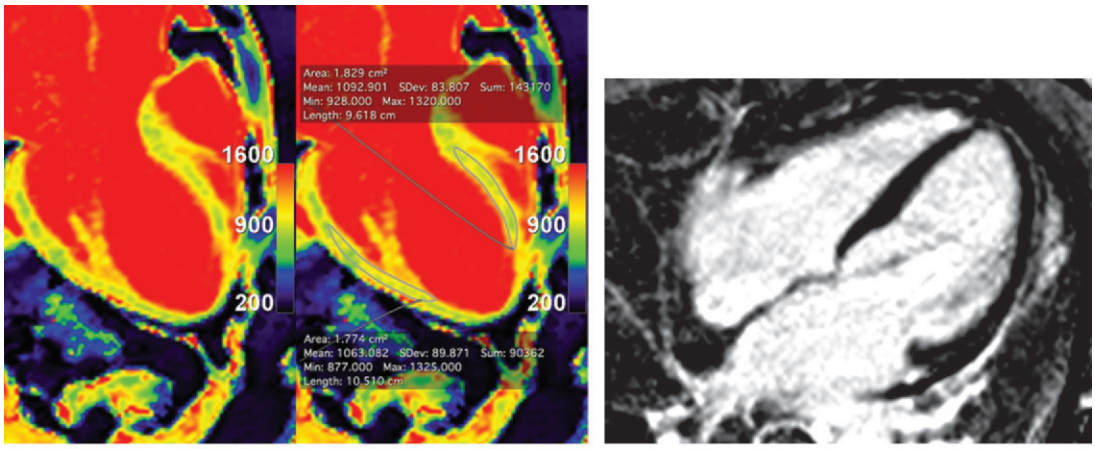
diastolic dysfunction, indicating that an elevated myocardial T1 value likely reflects the severity of cardiac involvement (42) (Fig 10).

More recent analysis by Fontana et al (71) demonstrated that native myocardial T1 mapping is also effective in the detection of transthyretin amyloidosis and that T1 times, although still elevated relative to normal myocardium, may not be as high as in the AL subtype. Their study of 85 patients with transthyretin amyloidosis showed an average T1 value of 1097 msec ± 43 (ShMOLLI at 1.5 T), compared with an average T1 value of 1130 msec ± 68 in patients with AL amyloidosis. This differentiation is clinically relevant because treatment and prognosis vary by subtype (72).

Dilated Cardiomyopathy

When the underlying cause of cardiomyopathy is unknown, patients at most centers undergo coronary angiography, and those without significant coronary disease are diagnosed with nonischemic cardiomyopathy (63). Dilated cardiomyopathy is the most common form of nonischemic cardiomyopathy, and although up to 50% of cases are idiopathic, many of the rest can be traced to previous infection, alcohol or drug abuse, or drug toxicity (4). Determining the underlying cause of dilated cardiomyopathy is important, as the exact cause may alter therapeutic options and patient prognosis.

Cardiac MR imaging has been well documented as a useful tool for monitoring morphologic and functional parameters in patients with cardiomyopathy (1). Cardiac LGE MR imaging has value for distinguishing ischemic cardiomyopathy from nonischemic cardiomyopathy (63). Patchy or diffuse midwall LGE in patients with dilated cardiomyopathy is thought to represent fibrosis in the setting of chronic myocardial remodeling; however, additional value is added by demonstration of a lack of subendocardial enhancement, which can exclude underlying infarction as a cause. It also has been shown that the degree of myocardial enhancement correlates with the severity of underlying functional abnormality (73). Cardiac mapping can quantify the degree of myocardial T1 abnormality and thus the degree of underlying fibrosis, which may have diagnostic and prognostic value. A recent study evaluated the use



a. b.

Figure 11. T1 mapping in a 60-year-old woman with nonischemic dilated cardiomyopathy. The patient presented with new-onset heart failure and had normal coronary arteries at angiography. Three-chamber nonenhanced MOLLI T1 maps obtained at 1.5 T **(a)** show mildly elevated diffuse T1 times, despite normal findings seen on a four-chamber PSIR LGE MR image **(b)**. (Scale in **a** is in milliseconds.)

of T1 mapping for differentiation of normal from diseased myocardium in patients with hypertrophic cardiomyopathy and dilated cardiomyopathy (7) (Fig 11).

Sarcoidosis

The formation of noncaseating granulomas in the myocardium in sarcoidosis may be clinically apparent in only a small percentage of patients; however, autopsy series show that 20%–50% of patients have myocardial involvement (74). Cardiac sarcoidosis often results in potentially malignant arrhythmias, left ventricular dysfunction, and development of restrictive cardiomyopathy, which make early detection paramount. Typically, when cardiac involvement is found, patients undergo steroid therapy or other forms of immunosuppressive treatment (1).

The appearance of sarcoidosis at cardiac MR imaging largely depends on the timing of imaging. In the acute phase, myocardial inflammation or edema manifests as patchy increased signal intensity on T2-weighted images. LGE MR images in patients with sarcoidosis typically show a patchy midmyocardial, subepicardial, or epicardial pattern that is not in a vascular distribution (4,63). In chronic disease, nodular foci of LGE indicative of fibrosis and scar formation without corresponding T2-weighted signal intensity may be present. A literature search revealed no dedicated studies evaluating T1 mapping in sarcoidosis, but a recent publication by Crouser et al (35) suggests that detection of cardiac sarcoidosis may be improved with use of T2 mapping techniques. An example of T2 mapping in a patient with presumed cardiac sarcoidosis is shown in Figure 12.

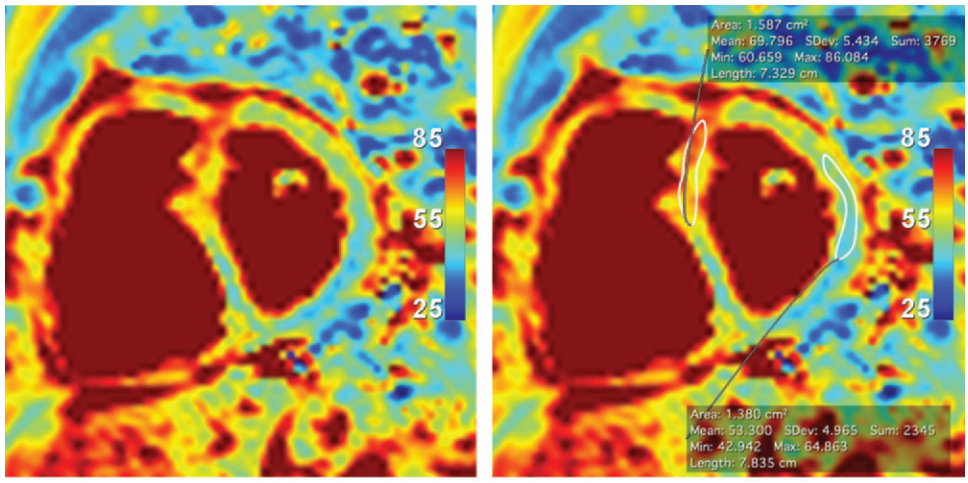
Stress (Takotsubo) Cardiomyopathy

Stress cardiomyopathy, also known as takotsubo cardiomyopathy or apical ballooning syndrome, is a rare form of myocardial stunning that occurs most often in postmenopausal women and mimics acute coronary syndrome. It is thought to be secondary to the transient release of catecholamines related to a significant stressor (physical or emotional) (2,75). Acute dyspnea, hypotension, and even cardiogenic shock with ischemic electrocardiographic changes and elevated cardiac enzymes may be the presenting symptoms of this condition (75), although no coronary blockage or flow-limiting stenosis is seen at angiography.

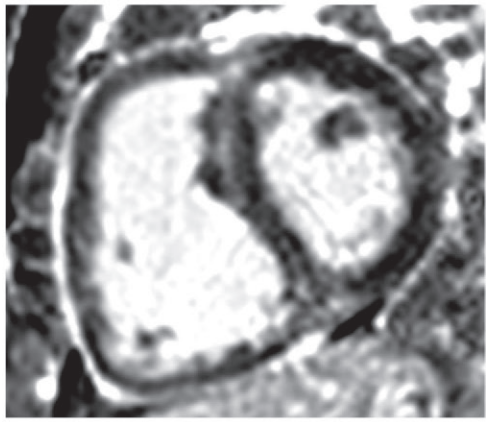
The role of cardiac MR imaging in takotsubo cardiomyopathy is to confirm the presence of typical wall-motion abnormalities, including midwall and apical left ventricle hypokinesis with normal basiventricular contraction (apical ballooning), in addition to depicting a lack of LGE that would be seen with infarction or other entities. T1 and T2 mapping can be used to confirm the presence of prolonged T1 and T2 relaxation times in the hypokinetic regions (34) (Fig 13).

Conclusions

T1 and T2 myocardial mapping offer quantitative techniques to detect changes in myocardial composition (as illustrated through the case examples provided). These techniques can be helpful in evaluating focal myocardial disease but are especially helpful in cases of diffuse myocardial fibrosis or edema, where no normal myocardium is present for a qualitative comparison. MOLLI and ShMOLLI sequences are useful for rapid, reproducible acquisition of T1 mapping values,



a. b.



c.

Figure 12. T2 mapping in a 68-year-old man with presumed cardiac sarcoidosis and pathologically proved pulmonary and mediastinal sarcoidosis who had normal coronary arteries at angiography. **(a, b)** Short-axis SSFP T2 maps obtained at 1.5 T show prolonged T2 times (indicative of myocardial edema) in the midanterior and anteroseptal left ventricle. The lateral and inferior walls show normal T2 values. (Scale is in milliseconds.) **(c)** PSIR LGE MR image shows patchy midwall enhancement and asymmetric thickening of the left ventricle, findings typical of cardiac sarcoidosis.

and SSFP sequences can be used for reproducible acquisitions of T2 mapping values.

Continued investigation is needed to establish "normal" reference ranges for native T1 and T2 relaxation values because variation exists among manufacturers, magnetic field strengths, and clinical parameters. These reference values are required to distinguish various disease conditions from normal myocardium, especially in cases of diffuse disease. Knowledge of the properties of specific MR imaging units is necessary for implementation of these techniques.

Quantitative myocardial analysis through T1 and T2 mapping is an exciting and active frontier in cardiac MR imaging. The full clinical utility of native T1 and T2 mapping is yet unknown because many diseases have not been adequately studied. Several questions remain: Can native T1 mapping potentially replace LGE MR imaging in the assessment of fibrosis (both focal and diffuse)? Is native T1 mapping more or less useful than T2 mapping in the evaluation of myocardial infarction, or are they complementary? How will ECV influence the clinical management of patients with heart disease? One of the current major obstacles is the variation in native T1 and T2 values related to imaging equipment and sequence, as was described earlier. Adoption of these sequences by the cardiac imaging community may hinge on a more confident understanding of what is considered "normal."

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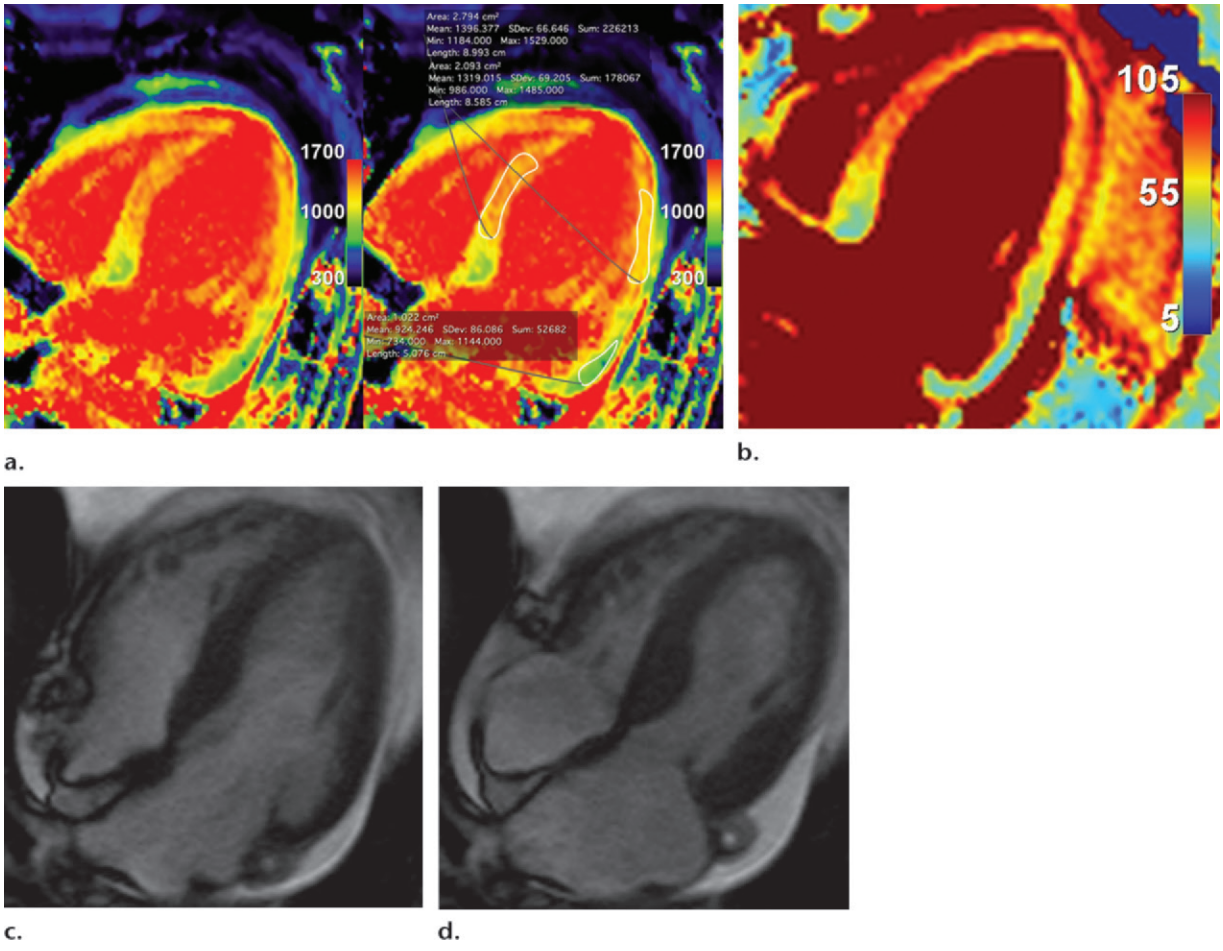
Figure 13. T1 and T2 mapping in an 85-year-old man with stress cardiomyopathy. **(a, b)** Four-chamber nonenhanced MOLLI T1 maps at 1.5 T **(a)** and SSFP T2 map at 1.5 T **(b)** demonstrate prolonged T1 and T2 times predominantly in the mid and apical segments of the left ventricle. (Scale is in milliseconds.) **(c, d)** SSFP MR images obtained in end diastole **(c)** and end systole **(d)** show the characteristic contraction pattern of stress cardiomyopathy, with relatively preserved function at the base of the left ventricle and hypokinetic mid and apical segments. There was no delayed enhancement on LGE MR images (not shown), and the patient's left ventricular function improved at follow-up echocardiography performed 1 month later.



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Mapping the Future of Cardiac MR Imaging: Case-based Review of T1 and T2 Mapping Techniques

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Traditional LGE MR images are most useful for evaluation of focal diseases, where normal myocardium can be used as a standard of reference and a pattern of enhancement can be detected. Diffuse fibrosis may go undetected on qualitative images if gadolinium uptake is uniform.

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Whereas qualitative sequences rely on the use of arbitrary signal intensity scales for T1 and T2 values that have interpatient and interimage variability, myocardial mapping offers the potential to produce images that have standardized, reproducible scales similar to the attenuation values used at computed tomography.

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The T1 map is a single image that represents a pixel map of the T1 values generated by curve fitting of all images in a sequence (ie, LL, MOLLI, or ShMOLLI). This image may be generated automatically at the imaging unit; however, open-source software is available for analysis and has been validated for clinical use.

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In conjunction with the hematocrit value, mapping enables quantification of the proportion of extracellular (interstitium and extracellular matrix) myocardial volume to cellular (myocyte) volume. An increased ECV is a marker of myocardial remodeling and is most often due to excessive collagen deposition (in the absence of amyloid or edema). Recent analyses have shown that the ECV may be as important as the left ventricular ejection fraction as a marker for cardiac disease severity, indicating vulnerable myocardium with decreased tolerance to ischemia.

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Mapping can noninvasively represent a "sample" of tissue from the entire myocardium and can supplement or potentially replace invasive transvenous myocardial biopsy (which usually is limited to the right ventricular myocardium). At a minimum, T1 mapping may help identify the most appropriate location for biopsy, if biopsy is deemed clinically necessary.