Journal Pre-proof

Current evidence on the diagnostic and prognostic role of Native T1 mapping in heart diseases

Elisabetta Tonet MD , Andrea Baggiano MD , Rita Pavasini MD , Marco Guglielmo MD , Stefano Censi MD , Alberto Cossu MD , Claudio Rapezzi MD , Giuseppe Muscogiuri MD , Angelo Squeri MD , Gianluca Campo MD , Gianluca Pontone MD

Please cite this article as: Elisabetta Tonet MD , Andrea Baggiano MD , Rita Pavasini MD , Marco Guglielmo MD , Stefano Censi MD , Alberto Cossu MD , Claudio Rapezzi MD , Giuseppe Muscogiuri MD , Angelo Squeri MD , Gianluca Campo MD , Gianluca Pontone MD , Current evidence on the diagnostic and prognostic role of Native T1 mapping in heart diseases, *Trends in Cardiovascular Medicine* (2020), doi: https://doi.org/10.1016/j.tcm.2020.08.001

Current evidence on the diagnostic and prognostic role of Native T1 mapping in heart diseases

Elisabetta Tonet[1], MD, Andrea Baggiano[2], MD, Rita Pavasini[1], MD, Marco Guglielmo[2], MD,

Stefano Censi[3], MD, Alberto Cossu[4], MD, Claudio Rapezzi[3], MD, Giuseppe Muscogiuri[2], MD,

Angelo Squeri[3], MD, Gianluca Campo[1,3], MD, Gianluca Pontone[2], MD

1: Cardiology Unit, Azienda Ospedaliero-Universitaria of Ferrara, Cona, FE, Italy

2: Department of Cardiovascular Imaging, Centro Cardiologico Monzino, IRCCS, Milan, Italy

3: Maria Cecilia Hospital, GVM Care & Research, Cotignola, RA, Italy

4: Department of Morphology, Surgery and Experimental Medicine, Section of Radiology,

University of Ferrara, FE, Italy

Brief Title: native T1 mapping in heart disease

Word count: 4880

No conflict of interests

Address for correspondence:

Elisabetta Tonet, MD

Cardiology Unit, Azienda Ospedaliero-Universitaria of Ferrara, Cona, FE, Italy

Via Aldo Moro 8, Cona, FE, Italy

Phone: 00390532237227

Email: tonet.elisabetta@gmail.com

ABSTRACT

Tissue characterization represents a prerogative of cardiac magnetic resonance. Beside late gadolinium enhancement, native T1 mapping (nT1m) reveals tissue composition. It could represent a useful tool for example when contrast medium can't be administrated. The present review summarises current evidence about nT1m in main heart diseases.

INTRODUCTION

Tissue characterization represents one of the most important features of cardiac magnetic resonance (CMR). The non-contrast T1 mapping technique focuses on the myocardial composition, whose abnormalities determine different T1 maps values without contrast medium administration [1]. It consists in the acquisition of images with different inversion time, after radiofrequency pulse which contribute to the signal genesis. Based on these images, a T1 recovery curve is derived and consequently a map describing the relaxation value on a voxel-by-voxel basis [2]. T1 value changes depending on myocardial extracellular water (edema), focal or diffuse fibrosis, fat, iron, and amyloid protein content. Despite late gadolinium enhancement (LGE) representing the gold standard technique in CMR, its diagnostic value can be amplified by information obtained with native T1 mapping (nT1m) Indeed, nT1m could supplement LGE information delivering a point-by-point quantification of T1 time, being accurate in detecting tissue abnormalities both in focal and diffuse myocardial diseases (Table 1). Moreover, conditions like severe renal dysfunction contraindicate gadolinium administration. In such situations, nT1m could play a crucial diagnostic role thanks to its high sensitivity for myocardial abnormalities with a favorable cost-effectiveness [2].

The present review summarises evidence, prognostic role and emerging concepts about nT1m in main heart diseases, listed in alphabetical order.

Brief methodological considerations

A Medline search of full-text articles published in English until February 2020 was performed. Overall, 420 records were identified. The search terms were: (native T1 mapping) OR (non contrast) AND ((CMR) OR (cardiac magnetic resonance)). Only papers published in English and in peer reviewed journals were selected. The main heart diseases in which nT1m was explored include amyloidosis, aortic stenosis, Fabry disease, hypertrophic cardiomyopathy (HCM), idiopathic dilated cardiomyopathy (IDCM), iron overload cardiomyopathy, ischemic heart disease (IHD), myocarditis and sarcoidosis. After evaluation of title and abstract a total of 52 studies were analysed as full text. The quality of selected papers was tested using MINORS criteria [3]. Unblinded reviewers performed the analysis of the full texts for quality assessment. Discrepancies between reviewers have been solved by consensus. The maximum score obtained was 14 and the minimum 8. We included in the present review only studies obtaining a score of 10. A total of 36 papers were then considered for this overview.

Brief technical considerations

T1 mapping consists of quantifying the T1 relaxation time of a tissue by using analytical expressions of image-based signal intensities. The signal intensity of pixels is based on the relaxation of protons in a static magnetic field (Figure 1) [2]. T1 value represents each voxel intensity value, influenced by several substances such as fibrosis or fat with different T1 relaxation times. NT1m increases in case of edema (acute myocardial infarction, inflammation) and fibrosis (scar, cardiomyopathy). On the contrary, nT1m is reduced in case of Anderson-Fabry disease, iron accumulation (Figure 2). The most widely used techniques for T1 maps are the modified Look-Loker inversion-recovery (MOLLI) sequence (Figure 1), the shortened MOLLI (ShMOLLI) sequence and the saturation recovery single-shot acquisition (SASHA). Table 2 describes the pros and cons of these techniques.

NATIVE T1 MAPPING APPLIED TO CARDIAC DISEASE

Amyloidosis

Cardiac involvement in amyloidosis is the most important determinant of prognosis. LGE-CMR represents the current gold standard for the assessment of cardiac involvement. However, about one third of patients with amyloidosis present severe renal disfunction (eGFR of <30 mL/min) [4-5]. Moreover, there are some atypical LGE patterns (i.e. localized enhancement) that make the diagnosis a challenge [4]. Extensive infiltration of the myocardium by amyloid fibrils leads to a diffuse increase of T1 time, which could precede LGE evidence [4]. Baggiano et al. conducted a prospective study investigating the diagnostic accuracy of nT1m in a large cohort of patients with suspected amyloidosis developing a diagnostic algorithm to rule in or out the presence of cardiac involvement in most patients without the need of contrast administration [6]. In 53 patients with AL amyloidosis, Karamistos et al. demonstrated that mean nT1m values were significantly raised (1140 ms) compared with the healthy counterpart (958 ms) with a cut-off value of 1020 ms having a diagnostic accuracy of 92% [7]. Interestingly, it was shown how nT1m values could be higher in AL amyloid than in the ATTR type, despite the greater thickness of the left ventricular (LV) wall in ATTR amyloid. This could be due to a lower amyloid burden, less hydration, less collagen and different effects on the intracellular signal. Furthermore, it is plausible that AL amyloid could determine edema because of light chain toxicity [8]. In terms of prognosis, nT1m predicts mortality. A study by Banypersad et al showed that in 100 cardiac AL patients followed for 23 months, a nT1m value of >1044 ms carried a hazard ratio (HR) for death of 5.39 [9]. Martinez-Naharro et al. showed how in 215 patients with ATTR amyloidosis nT1 values predicted death (HR 1.225 for each 59-ms increase) [10]. Finally, emerging data showed that nT1m could evaluate the response to treatment with tafamidis. A case report by Shintani Y et al. highlighted no significant worsening of T1 values after 12 months of tafamidis administration in a 73-year-old man with TTR amyloid

cardiomyopathy and Val30Met mutation, suggesting that the treatment may have suppressed the progression of the disease [11].

Aortic stenosis

The value of LGE-CMR in patients with aortic stenosis was previously demonstrated. The evidence of myocardial fibrosis is related to poor prognosis in these patients [12]. However, as for amyloidosis, about 50% of patients with aortic stenosis suffer from renal failure [12]. Taking this background into consideration, the role of nT1m was investigated. Park et al. assessed the correlation between nT1m and subclinical myocardial dysfunction in asymptomatic patients with aortic stenosis, showing that nT1m values reflect the degree of diffuse fibrosis when compared with histologic examination. The nT1m correlates with both the LV remodelling and the degree of aortic stenosis in asymptomatic patients [13]. Moreover, Lee et al. demonstrated that nT1m correlated well with aortic stenosis progression and that high T1 values identified patients at higher risk of poor prognosis both before and after aortic valve replacement [14]. Notably, since the mechanism of diffuse myocardial fibrosis occurs early, evaluating it using nT1m could enable us to detect patients at higher risk sooner [15]. Hwang IC et al. found that in 43 patients one year after aortic valve replacement, nT1m significantly decreased and it was associated with LV mass regression and systolic function improvement. Additionally, patients with a reduction of nT1m values after aortic valve replacement showed a better outcome when compared with patients without nT1m changes [16].

Fabry disease

Heart involvement in Fabry disease is characterized by LV hypertrophy and valvular abnormalities causing myocardial fibrosis and, eventually, cardiac decompensation. CMR shows a mid-wall basal inferolateral LGE as a distinctive hallmark of cardiac involvement. Due to characteristic intracellular accumulation of sphingolipids that shortens myocardial T1 relaxation time,

pathognomonic low nT1 values, coupled with morphological features, enable the correct diagnosis [17]. Furthermore, nT1m values were proved to be an early disease marker, being significantly low in patients with Fabry disease but without overt LV hypertrophy. However, nT1m values should be interpreted with caution with the progression of the disease. Initially there is an increased sphingolipid deposition inducing diffuse low T1 values, then, inflammation and fibrosis could follow, with focal relative increase of T1 relaxation time (T1 pseudo-normalization) in areas with sphingolipid deposition, inflammation and fibrosis. In the final stages of Fabry disease, the high prevalence of fibrosis is related to increased nT1m values [17]. Diagnosis of Fabry disease with nT1m could be difficult due to different stages, especially in the T1 pseudo-normalization phase. The additive value of T2 mapping could be useful: it is another non-contrast technique that quantifies the prolongation of T2 relaxation time due to increased water content, as it happens in inflammation. Inflammation and edema frequently appear in Fabry disease in basal inferolateral position, as LGE, and they increase T2 values. Therefore, in the diagnostic process of Fabry disease, nT1m and T2 are two fundamental instruments to suspect and diagnose the cardiac involvement [18-19].

Hypertrophic cardiomyopathy

CMR has a diagnostic and prognostic role in HCM detecting fibrosis thus proving prognostic information in terms of heart failure and arrhythmias [20]. Previous studies reported that in HCM T1 values were significantly longer in segments with LGE. Malek et al. found that nT1m showed a good correlation with LGE in 25 patients with HCM. They proposed a threshold of 1060 ms as the cut-off value to detect fibrosis in HCM patients [20]. Interestingly, nT1m was demonstrated to detect early myocardial changes in subjects with sarcomere-gene mutations but negative phenotype, suggesting that abnormal T1 values could act as an early disease marker, anticipating hypertrophy [21]. Moreover, T1 values were shown to be higher in HCM patients without LGE compared to healthy subjects, underlining how HCM patients could have interstitial fibrosis within the

hypertrophied segments despite the absence of LGE [21]. These findings support the concept that LGE imaging can easily identify dense focal scar, but is also less accurate in depicting more subtle diffuse extracellular matrix expansion due to fibrosis, inflammation, edema and infiltration, abnormalities conversely admirably spotted by nT1m. This could be explained by the earliest mechanism underlying HCM. As reported by previous studies, there is an early upregulation of genes involved in the synthesis of extracellular matrix and this pathway is activated before the development of LV hypertrophy or focal fibrosis [21]. CMR in HCM is also important for the assessment of the risk of arrhythmias and sudden cardiac death (SCD). Presence of LGE has been considered an additional risk factor in the risk stratification for SCD [22]. While a robust comparison between prognostic role of LGE and nT1m is missing, Xu et al found that nT1m values were associated with SCD in 258 subjects with HCM but without LGE [22].

Idiopathic dilated cardiomyopathy

In idiopathic dilated cardiomyopathy (IDCM), LGE is present in 40% of patients with a distinct mid-myocardial pattern and it is associated with increased risk of ventricular arrhythmias and adverse outcome. However, arrhythmias could also occur in patients without any evidence of scar. There is little knowledge about the mechanism behind these arrhythmic events, but it was highlighted that interstitial fibrosis and myocyte disarray create the responsible substrate [23]. All these myocardial abnormalities could be detected by T1 maps, as demonstrated by a prospective study by Shah et al, in which patients with IDCM showed diffuse higher nT1m values if compared to healthy subjects [23]. Moreover, Puntmann et al found that increased nT1m predicted heart failure events and all-cause mortality in IDCM independently from both LV function and LGE presence [24]. The association between nT1m and SCD in IDCM has not been deeply analysed yet. One study assessed the link between nT1m and ventricular arrhythmias in patients with ICD: in 59 non-ischemic patients, nT1m was the only independent predictor of appropriate ICD therapies [25]. Additionally, a study by Nakamori et al demonstrated that nT1m was independently associated with

ventricular arrhythmic events beyond LV function and LGE [26]. A recent analysis from the

DANISH trial highlighted that in patients with non-ischemic systolic heart failure including IDCM,

LGE predicted all-cause mortality [27].

Iron overload

CMR represents the best imaging technique for the identification of myocardial iron deposition.

Although non-contrast T2* represents the gold standard, it appears to be limited in the identification

of mild iron deposition. NT1m could overcome these limitations: a low concentration of iron is

typically inversely related to T1 time [28]. Thus, nT1m can be used to improve the detection of iron

deposition over T2* method. Torlasco et al reported that in established cardiac iron overload nT1m

resulted to detect iron in the 20-30 ms T2* range, supporting the idea that T1 recognizes missed

iron in 1 out of 3 subjects with normal T2* [29]. In a cohort of 200 patients with thalassemia,

Krittayaphong R et al demonstrated that nT1m can differentiate between severe, mild-to-moderate

and no cardiac iron overload with the best cut-off value of 887 ms with a sensitivity of 100% and a

specificity of 98,4% [30]. Consistent data on prognostic role of nT1m in iron overload are missing.

Ischaemic heart disease

LGE technique represents the best CMR method to evaluate myocardial infarction scars.

Messroghli et al found that nT1m was also able to detect segmental defects caused by acute

myocardial infarction (AMI) with high diagnostic performance (96% sensitivity and 91%

specificity) [31]. Nonetheless, more evidence and multivendor studies are needed in order to

develop a standardized protocol with reproducible nT1 threshold values.

The role of nT1m was also studied in stress CMR. Liu et al validated stress nT1m comparing this

technique to invasive coronary measures for detecting coronary disease and microvascular

dysfunction. According to their study, stress nT1m significantly outperformed gadolinium first pass

perfusion [32]. The underlying mechanism seems to correlate with the increased water content:

coronary vasodilatation increases myocardial blood volume and consequently prolongs T1 [32]. In asymptomatic subjects with type 2 diabetes mellitus, Levelt et al demonstrated that stress and rest nT1m recognized microvascular abnormalities useful to provide early therapeutic strategy [33]. Therefore, current evidence shows promising results, but concerns regarding real-world applicability of this technique were raised, due to the small T1 time variations between rest and stress conditions of ischaemic and remote myocardium.

Myocarditis

Non-ischaemic LGE pattern (mid-wall and subepicardial distribution), associated with edema detected by T2-weighted sequences, represents the typical CMR pattern in acute myocarditis. However, LGE and traditional T2-weighted sequences could underestimate both the presence and the extent of myocardial inflammation. The higher sensitivity (up to 90%) of T1 maps can overcome above-mentioned limitations. Ferreira et al demonstrated how nT1m can diagnose acute myocarditis with great diagnostic performance [34]. Moreover, NT1m was shown to have a better sensitivity also than the currently recommended Lake Louise Criteria [35]. The role of CMR in this setting is not just limited to the diagnostic phase. Bohnen et al demonstrated in 48 patients with acute myocarditis how nT1m could be safely used for monitoring the myocardium in the healing phase [36]. Furthermore, Hinojar et al showed how a combined approach with nT1m and T2 mapping could be useful also in lupus myocarditis, enabling the cardiac involvement identification and tracking the response to anti-inflammatory treatment [37].

Sarcoidosis

In sarcoidosis T1 and T2 mapping are reported to be useful for early detection of cardiac involvement. Greulich et al. showed that T1 mapping provided an incremental value in detecting subclinical myocardial involvement in systemic sarcoidosis when there were no abnormalities of LGE and LV function. Additionally, it was shown that the native T1 is increased not only by

acutely injured myocardium but also by the incidence of fibrosis in chronic myocardial changes [38]. Puntmann et al. demonstrated that patients with systemic sarcoidosis had reported to have higher myocardial nT1m and T2 mapping and lower ejection fraction. Furthermore, nT1m was a marker of the onset of the disease. There was also a significant reduction of nT1m in the patients undergoing treatment [39].

Current theoretical and practical limitations and future directions for the clinical application

The large majority of evidence about nT1m comes from single-center experience. The cases series are limited and study populations included few hundreds of patients. In addition, no randomized clinical trials investigated the additional diagnostic and/or prognostic value of nT1m vs. LGE or other non-invasive imaging techniques. The next steps should include multicenter and multivendor studies, with the aim of overcoming current limitations, such as the absence of standardized normal values and threshold values widely applicable for the diagnosis of each specific cardiac disease. Currently, nT1m technique is not used in all imaging laboratories due to the lack of hardware and software, but its diffusion is growing; indeed it is now part of current guidelines and it has demonstrated a favorable cost-effectiveness [40]. Future studies should analyse more deeply the prognostic value of nT1m in conditions such as HCM and IDCM where CMR data could implement available prognostic scores. Similarly, non-contrast analysis of myocardial perfusion should be further investigated, representing an intriguing non-invasive evaluation of myocardial ischemia based on vasodilatation influence on T1 without the need of contrast administration.

Conclusions

The native T1 mapping represents a novel technique that could be routinely implemented. NT1m has all the strengths to be considered as a solid supplement for LGE imaging, but some crucial

aspects need to be investigated. According to what has already been achieved in terms of scientific evidence, it will not be long before further robust results can be obtained.

REFERENCES

1. Reiter U, Reiter C, Krauter C, Fuchsjager M, Reiter G, Cardiac magnetic resonance T1 mapping: Part 2: Diagnostic potential and applications, Eur J Radiol 2018;109:235-247

2. Reiter G, Reiter C, Krauter C, Fuchsager M, Reiter U, Cardiac magnetic resonance T1 mapping. Part 1: Aspects of acquisition and evaluation, Eur J Radiol 2018;109:223-234

3. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003 Sep;73(9):712-6

4. Perugini E, Rapezzi C, Piva T, Leone O, Bacchi-Reggiani L, Riva L et al, Non-invasive evaluation of the myocardial substrate of cardiac amyloidosis by gadolinium cardiac magnetic resonance, Heart 2006;92(3):343-9

5. Lobato L, Rocha A, Transthyretin amyloidosis and the kidney, Clin J Am Soc Nephrol 2012;7:1337-46

6. Baggiano A, Boldrini M, Martinez-Naharro A, Kotecha T, Petrie A, Rezk T et al, Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis, JACC Cardiovasc Imaging 2020;13(1 Pt 1):69-80

7. Karamitsos TD, Piechnik SK, Banypersad SM, Fontana M, Ntusi NB, Ferreira VM et al, Noncontrats T1 mapping for the Diagnosis of Cardiac Amyloidosis, JACC Cardiovasc Imaging 2013;16(4):488-97

8. Shi J, Guan J, Jiang B, Brenner DA, Del Monte F, Ward JE et al, Amyloidogenic light chains induces cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway, Proc Natl Acad Sci USA 2010;107(9):4188-93

9. Banypersad SM, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A et al, T1 Mapping and survival in systemic light-chain amyloidosis, Eur Heart J 2015;36(4):244-51

10. Martinez-Naharro A, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C et al, Native T1 and Extracellular Volume in Transthyretin Amyloidosis, JACC 2019;12:810-19.

11. Shintani Y, Okada A, Morita Y, Hamatani Y, Amano M, Takahama H et al, Monitoring treatment response to tafamidis by serial native T1 and extracellular volume in transthyretin amyloid cardiomyopathy, ESC Heart Fail 2019;6(1):232-236

12. Lee H, Park JB, Yoon YE, Park EA, Kim HK, Lee W et al, Noncontrast Myocardial T1 Mapping by Cardiac Magnetic Resonance Predicts Outcome in Patients With Aortic Stenosis, JACC Cardiovasc Imaging 2018;11(7):974-983

13. Park SJ, Cho SW, Kim SM, Ahn J, Carriere K, Jeong DS et al, Assessment of Myocardial Fibrosis using Multimodality Imaging in Severe Aortic Stenosis: Comparison With Histologic Fibrosis, JACC Cardiovasc Imaging 2019;12(1):109-119

14. Lee SP, Lee W, Lee JM, Park EA, Kim HK, Kim YJ et al, Assessment of Diffuse Myocardial Fibrosis by Using MR Imaging in Asymptomatic Patients with Aortic Stenosis, Radiology 2015;274(2):359-69

15. Fehrmann A, Treutlein M, Rudolph T, Weiss K, Giese D, Bunck AC et al, Myocardial T1 and T2 mapping in severe aortic stenosis: potential novel insights into the pathophysiology of myocardial remodeling, Eur J Radiol 2018;107:76-83

16. Hwang IC, Kim HK, Park JB, Park EA, Lee W, Lee SP et al Aortic valve replacement-induced changes in native T1 are related to prognosis in severe aortic stenosis: T1 mapping cardiac magnetic resonance imaging study, Eur Heart J Cardiovasc Imaging 2019

17. Perry R, Shah R, Saiedi M, Patil S, Ganesen A, Linhart A et al, The Role of Cardiac Imaging in the Diagnosis and Management of Anderson-Fabry Disease, JACC Cardiovasc Imaging 2019;12(7 Pt 1):1230-1242

18. Augusto JB, Nordin S, Vijapurapu R, Baig A, Bulluck H, Castelletti S et al, Myocardial Edema, Myocyte Injury, and Disease Severity in Fabry Disease, Circ Cardiovasc imaging 2020;13:e010171.

19. Chan VSH, Zhou W, Cheung SCW, Ng MY, Native T1 mapping for the diagnosis of Anderson-Fabry disease with myocardial hypertrophy, Hong Kong Med J 2019;25(3):252-3.e1-2

20. Dass S, Suttie JJ, Piechnik SK, Ferreira VM, Holloway CJ, Banerjee R et al, Myocardial tissue characterization using magnetic resonance noncontrast T1 mapping in hypertrophic and dilated cardiomyopathy, Circ Cardiovasc Imaging 2012;5(6):726-733

21. Malek LA, Werys K, Klopotowski M, Spiewak M, Milosz-Wieczorek B, Mazurkiewicz L et al, Native T1-mapping for non-contrast assessment of myocardial fibrosis in patients with hypertrophic cardiomyopathy – comparison with late gadolinium enhancement quantification, Magn Resonance Imaging 2015,33;718-724

22. Xu J, Zhuang B, Sirajuddin A, Shuang L, Huang J, Yin G et al, MRI T1 Mapping in Hypertrophic Cardiomyopathy: Evaluation in Patients Without Late Gadolinium Enhancement and Hemodynamic Obstruction, Radiology 2020;294(2):275-286

23. Shah RV, Kato S, Roujol S, Murthy V, Bellm S, Kashem A et al. Native Myocardial T1 as a Biomarker of Cardiac Structure in Non-Ischemic Cardiomyopathy. Am J Cardiol. 2016; 117(2):282–8

24. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S et al. T1-Mapping and Outcome in Nonischemic Cardiomyopathy. JACC Cardiovasc Imaging. 2016;9(1):40–50

25. Chen Z, Sohal M, Voigt T, Sammut E, Tobon-Gomez C, Child N et al. Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non-ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. Heart Rhythm 2015;12(4):792–801

26. Nakamori S, Bui AH, Jang J, El-Rewaidy HA, Kato S, Ngo LH et al, Increased myocardial native T1 relaxation time in patients with nonischemic dilated cardiomyopathy with complex ventricular arrhythmia, J Magn Reson Imaging 2018;47(3):779.786

27. Elming MB, Hammer-Hansen S, Voges I, Nyktari E, Raja AA, Svendsen JH et al, Myocardial fibrosis and the effect of primary prophylactic defibrillator implantation in patients with non-ischemic systolic heart failure – DANISH-MRI, Am Heart J 2020;221:165-176

28. Bjonerud A, Johansson LO, Briley-Saebo K, Ahlstrom HK, Assessment of T1 and T2* effects in vivo and ex vivo using iron oxide nanoparticles in steady state-dependence on blood volume and water exchange, Magn RTeson Med 2002;47(3):461-71

29. Torlasco C, Cassinerio E, Roghi A, Faini A, Capecchi M, Abdel-Gadir A et al, Role of T1 mapping as a complementary tool of T2* for non-invasive cardiac iron overload assessment, PLoS One 2018

30. Krittayaphong R, Zhang S, Saiviroonporn P, Viprakasit V, Tanapiburnpon P, Komoltri C et al, Detection of cardiac iron overload with native magnetic resonance T1 and T2 mapping in patients with thalassemia, Int J Cardiol 2017;248:421-426

31. Messroghli DR, Niendorf T, Schulz-Menger J, Dietz R, Friedrich MG, T1 mapping in patients with acute myocardial infarction, J Cardiovasc Magn Reson 2003;5(2):353-9

32. Liu A, Wijesurendra RS, Francis JM, Robson MD, Neubauer S, Piechnik SK et al, Adenosine Stress and Rest T1 Mapping Can Differentiate Between Ischemic, Infarcted, Remote, and Normal Myocardium Without the Need for Gadolinium Contrast Agents, JACC Cardiovasc Imaging 2016;9(1):27-36

33. Levelt E, Piechnik S, Liu A, Wijesurendra RS, Mahmod M, Ariga R et al, Adenosine stress CMR T1-mapping detects early microvascular dysfunction in patients with type 2 diabetes mellitus without obstructive coronary artery disease, J Cardiovasc Magn resonance 2017;19:81

34. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamistos TD, Francis JM, Ntusi N et al, Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents, J Cardiovasc Magn Res 2014;16:36

35. Pan JA, Lee YJ, Salerno M, Diagnostic Performance of Extracellular Volume, Native T1, and T2 mapping versus Lake Louise Criteria by CMR for Detection of Acute Myocarditis: A Meta-Analysis, Circ Cardiovsc Imaging 2018;11(7):e007598

36. Bohnen S, Radunski UK, Lund GK, Ojeda F, Looft Y, Senel M et al, Tissue characterization by T1 and T2 mapping cardiovascular magnetic resonance imaging to monitor myocardial inflammation in healing myocarditis, Eur Heart J Cardiovasc imaging 2017;18(7):744-751

37. Hinojar R, Foote L, Sangle S, Marber M, Mayr M, Carr-White G et al, Native T1 and T2 mapping by CMR in lupus myocarditis: Disease recognition and response to treatment, Intr J Cardiol 2016;222:717-726

38. Greulich S, Kitterer D, Latus J, Aguor E, Steubing H, Kaesemann P et al, Comprehensive cardiovascular magnetic resonance assessment in patients with sarcoidosis and preserved left ventricular ejection fraction, Circ Cardiovasc Imaging 2016;9e005022

39. Puntmann VO, Isted A, Hinojar R, Foote L, Carr-White G, Nagel E, T1 and T2 mapping in recognition of early involvement in systemic sarcoidosis, Radiology 2017;285:63-72

40. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG et al, Standardized image interpretation and post-processing in cardiovascular magnetic resonance – 2020 update, J Cardiovasc Magn Reson 2020;22(1):19
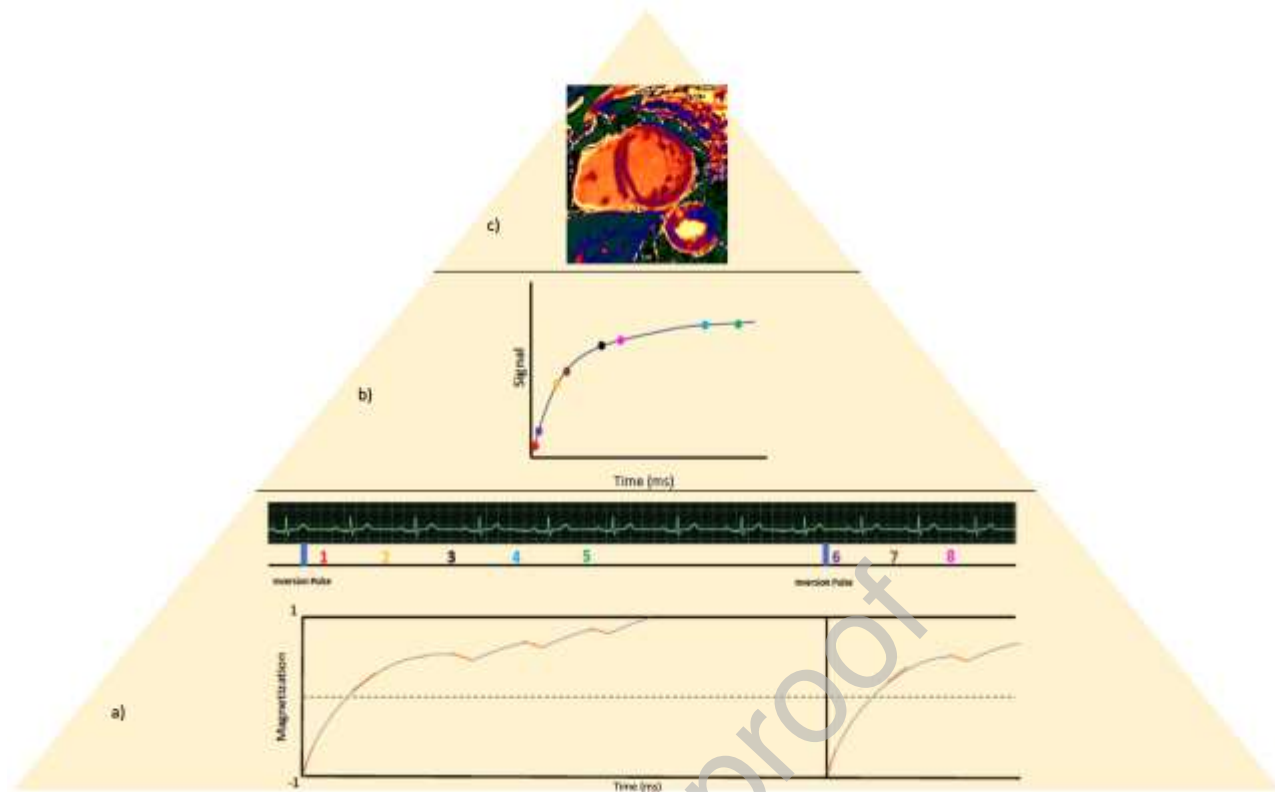
Figure 1. Acquisition strategy for the MOLLI sequences.

Proceeding from the bottom up:

a) acquisition of single-shot diastolic images over successive heartbeats (5 beats in this example) following an inversion radiofrequency pulse. Then, a rest period of 3 heartbeats is required, followed by another inversion pulse and the acquisition of other 3 images.

b) Multiple inversions with slightly different inversion times are used to more evenly sample the T1 recovery curve [2]. Images are sorted in order of increasing inversion time and the signal intensity of each pixel is fit to the curve (each coloured point in the curve corresponds to the multiple acquisitions).

c) Performing this technique for all pixels in the image yields a T1 map (at the top).

Figure 2. Trend of nT1m values in various heart diseases.

Myocardial infiltration of various molecules and consequent increase or lowering of nT1m values
(black arrows) depending on the T1 relaxation time of different substances.

HCM = hypertrophic cardiomyopathy; IDCM = idiopathic dilated cardiomyopathy; IHD =
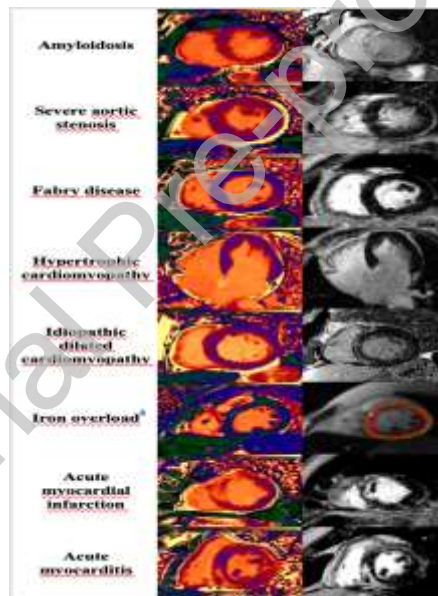ischaemic heart disease.

**Figure 3. Comparison between nT1m mapping and standard approaches in myocardial
diseases.**

Standard approach is represented by LGE imaging for all diseases except of iron overload [§], where
the standard approach is T2*.

Native T1 maps legend is showed by the color bars above each map.

It can be detected that LGE areas in myocardial diseases are well identified by native T1 maps,
demonstrating its accuracy.

nT1m = native T1 mapping.

TABLES

Table 1. Key concepts about nT1m.

WHAT is nT1m?	CMR technique for tissue characterization not needing gadolinium
WHY nT1m can be useful?	Sensitive technique, with detection of abnormal findings in early stages of several myocardial diseases
WHERE nT1m is applicable?	- Dilated cardiomyopathy - Hypertrophic phenotype - Iron overload - Ischaemic heart disease - Myocarditis
WHEN nT1m should be used?	- In patients with contraindications to contrast media - Detection of focal and diffuse fibrosis - Identification of myocardial abnormalities before evident structural changes
HOW nT1m can be performed?	- MOLLI - ShMOLLI - SASHA
WHAT is: - MOLLI? - ShMOLLI? - SASHA?	They are different strategies for nT1m: - MOLLI: Modified Look Locker inversion-recovery sequence. Acquisition of single-shot diastolic images over 17 successive heartbeats following inversion radiofrequency pulse - ShMOLLI: shortened MOLLI sequence. Acquisition of 5 images following the first inversion pulse and 4 further images during 9 heartbeats - SASHA: saturation recovery single-shot acquisition. Acquisition of 1 image without preparation and 10 images at different delays after saturation recovery preparation pulse which nulls the net magnetization vector instead of inverting it

Table 2. Pros and cons of the three main T1 mapping sequences.

SEQUENCES	PROS	CONS
MOLLI	√ High signal-to-noise ratio √ Precision	× 17 breath-hold heartbeats × Potential bias from T2 × Artefacts
shMOLLI	√ 9 breath-hold heartbeats √ Precision √ Few artefacts	× Potential bias from T2 × Signal-to-noise ratio × Accuracy
SASHA	√ 11 breath-hold heartbeats √ Accuracy	× Precision × 11 breath-hold heartbeats × Artefacts

Table 3. Summary of nT1m utilities in different heart diseases.

DISEASE	WHAT IS NT1M USEFUL FOR?	REFERENCES
Amyloidosis	Early detection of cardiac involvement	4-11
	Distinguish cardiac AL and ATTR	
	Prognostic role	
	Therapy effect monitoring	
Aortic stenosis	Diffuse fibrosis	12-16
	Association with subclinical myocardial dysfunction	
	Prognostic role	
	Monitoring after aortic valve replacement	
Fabry disease	Diagnosis accuracy	17-19
	Early diagnosis with abnormal values before hypertrophy	
	Detection of different stages of the disease	
HCM	Detection of the disease in negative phenotypes	20-22
	Ability to detect abnormal myocardium	
	Association with sudden cardiac death	
	Detection of diffuse fibrosis	
IDCM	Diagnostic accuracy	23-27
	Association with arrhythmias	
	Prognostic role	
Iron overload	Detection of mild deposition	28-30
IHD	Distinguish viable and non-viable segments	31-33
	Role in stress CMR	
	Detection of microvascular dysfunction	
Myocarditis	Diagnostic role	34-37

	Role in the monitoring of healing phase	
	Diagnosis and monitoring of lupus myocarditis	
Sarcoidosis	Early diagnosis	38-39
	Treatment monitoring	

HCM = hypertrophic cardiomyopathy; IDCM = idiopathic dilated cardiomyopathy; IHD = ischaemic heart disease.