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Citation
van den Boomen, Maaike, Riemer H.J.A. Slart, Enzo V. Hulleman, Rudi A.J.O. Dierckx, Birgitta K. Velthuis, Pim van der Harst, David E. Sosnovik, Ronald J.H. Borra, and Niek H.J. Prakken. 2017. “Native T1 reference values for nonischemic cardiomyopathies and populations with increased cardiovascular risk: A systematic review and meta-analysis.” Journal of Magnetic Resonance Imaging 47 (4): 891-912. doi:10.1002/jmri.25885. http://dx.doi.org/10.1002/jmri.25885.

Published Version
doi:10.1002/jmri.25885

Accessed
July 23, 2018 10:01:50 PM EDT

Citable Link
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Native T₁ Reference Values for Nonischemic Cardiomyopathies and Populations With Increased Cardiovascular Risk: A Systematic Review and Meta-analysis

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Background: Although cardiac MR and T₁ mapping are increasingly used to diagnose diffuse fibrosis based cardiac diseases, studies reporting T₁ values in healthy and diseased myocardium, particular in nonischemic cardiomyopathies (NICM) and populations with increased cardiovascular risk, seem contradictory.

Purpose: To determine the range of native myocardial T₁ value ranges in patients with NICM and populations with increased cardiovascular risk.

Study Type: Systemic review and meta-analysis.

Population: Patients with NICM, including hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), and patients with myocarditis (MC), iron overload, amyloidosis, Fabry disease, and populations with hypertension (HT), diabetes mellitus (DM), and obesity.

Field Strength/Sequence: (Shortened) modified Look–Locker inversion-recovery MR sequence at 1.5 or 3T.

Assessment: PubMed and Embase were searched following the PRISMA guidelines.

Statistical Tests: The summary of standard mean difference (SMD) between the diseased and a healthy control populations was generated using a random-effects model in combination with meta-regression analysis.

Results: The SMD for HCM, DCM, and MC patients were significantly increased (1.41, 1.48, and 1.96, respectively, P < 0.01) compared with healthy controls. The SMD for HT patients with and without left-ventricle hypertrophy (LVH) together was significantly increased (0.19, P = 0.04), while for HT patients without LVH the SMD was zero (0.03,

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Nonischemic cardiomyopathy (NICM) is a prevalent disease characterized by different patterns of fibrosis in the myocardium that can eventually cause heart failure. According to the American Heart Association (AHA) and the National Institutes of Health (NIH), NICM comprises a heterogeneous group of cardiac diseases presenting as: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), or restrictive cardiomyopathy (RCM). HCM alone affects 1/500 adults and its prevalence increases with age. Other populations also have an increased risk of developing NICM according to the AHA. These include the one-third of the USA population that has high blood pressure, the approximately one-tenth that suffers from diabetes type 2 (DM), and the two-thirds that are either overweight (body mass index [BMI] ≥25) or obese (BMI ≥30). Early detection of NICM is of key importance in preventing major cardiac events. However, the subtle changes that are often seen in the early stages of NICM are difficult to detect and distinguish from normal variation. Cardiac MR is commonly used to diagnose NICM by imaging standard parameters such as ventricular function, wall-mass, and myocardial fibrosis using late gadolinium enhancement (LGE). In the more advanced stages of NICM, cardiac MR can reveal fibrosis combined with either an increase in wall-mass (HCM) or in dilatation of the ventricular cavity (DCM). However, in the earlier stages of NICM the increases in wall-mass and dilatation are less obvious, and the fibrosis patterns remain difficult to detect. This makes it difficult to recognize NICM at the onset of the disease. It is even more difficult to distinguish NICM from hypertension (HT), diabetes melitus type 2 (DM), or obesity, because of their similarities in cardiac characteristics, especially when left-ventricle hypertrophy (LVH) is present. Common characteristics include: increased left ventricular wall-thickness, diastolic dysfunction, increased left ventricle mass, and infiltration of myocardial fat. These similarities may lead to incorrect interpretation and possible mistreatment. Therefore, additional diagnostic techniques are needed to ensure accurate diagnosis of NICM.

T1 mapping has been proposed as a technique to aid earlier diagnosis of NICM patients. Previous research has shown that cardiac native T1-mapping can differentiate between healthy myocardial tissue and pathologies including HCM, myocarditis (MC), iron loading, amyloidosis, and Fabry disease. In addition, T1 values of myocardial tissue in HT patients without LVH do not seem to change, suggesting that it may be possible to differentiate HT from NICM tissue. Further research is needed to determine whether T1 mapping can enable earlier detection of these NICM.

Although there are concerns about the physical accuracy of T1 mapping, the overall precision and reproducibility are fairly high and of substantial clinical utility. There is, therefore, an increasing demand for normative reference T1 values. These reference values will be of particular importance for HT, DM, and obese patients because they share cardiac MR characteristics with NICM. Because methodological differences can eventually affect the myocardial T1 values, a meta-analysis is a suitable approach to determine the normal myocardial T1 reference values.

Materials and Methods

Search Strategy

In June 2017, two independent reviewers (M.v.d.B and E.V.H) systematically searched for eligible studies published since 2011 in PubMed/MEDLINE and EMBASE using cardiac T1 mapping in humans. The search was restricted to studies to NICM, cardiac inflammatory, or storage diseases and populations with increased cardiovascular risk. Keywords used were “cardiomyopathy,” “hypertension,” “obesity,” “diabetes mellitus,” “magnetic resonance imaging,” and “T1-mapping” (see online Appendix for full search term).

Studies were included if they 1) published results from randomized controlled trials or cohort studies; 2) investigated human adults; 3) included subjects with NICM, MC, iron overload, amyloidosis, HT, DM or obesity who underwent cardiac MR with T1 mapping; 4) contained native T1 values from a modified Look-Locker inversion-recovery (MOLLI) or shortened MOLLI (ShMOLLI) sequence; and 5) excluded subjects with a history of coronary artery disease or myocardial infarction. Studies had to be available in full text, published in peer-reviewed journals, and written in English. No additional hand-searched papers were found. The Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement and the Cochrane Handbook for Systematic Review were used to perform and report this systematic review and meta-analysis.

Study Selection

M.v.d.B and E.V.H. independently assessed the title and abstract of the studies that were proposed by the databases. Full-text reports...
of the eligible studies were obtained and again independently assessed by these same authors for inclusion in this review. Differences of opinion between the two authors were resolved, which led to consensus about included papers. Quality assessment was performed by using the Newcastle-Ottawa quality assessment scale (NOS), in which the quality of the study was appraised using three domains: selection of study groups (0–4 stars), comparability of groups (0–2 stars), and ascertainment of exposure/outcome (0–3 stars). The cohort or case control version of the NOS was used, depending on the study type.

Data Collection

Data were extracted by the same authors noting: study population, age, gender, BMI, native T1 value, magnetic field strength (Tesla), vendor, imaging analysis method, and MR sequence. No authors were contacted for additional information. The data were collected as reported (mean ± standard deviation). The mean and standard deviation were calculated using the approach of Hozo et al. for studies that only reported the median with interquartile (IQR) or full range. For studies with multiple groups, only the data from the relevant population were extracted. The data of healthy control groups (controls) were also extracted.

Data Analysis

The T1 outcome values of the individual studies were combined in a random-effects model, leading to computations of standard mean difference (SMD) and 95% confidence intervals (CI). I² was used as a measure of heterogeneity with I² ≥ 50% and P < 0.05 on the χ² test defined as a significant degree of heterogeneity. This was further explored by meta-regression, bias, and sensitivity analyses for groups with sufficient (>10) included studies. A mixed-effect model approach was used for the meta-regression and performed with available covariates to determine association with the myocardial T1 value. A backwards elimination approach with a removal criteria of P > 0.05 was used for this. Included covariates were at least: gender, age, field strength, MRI vendor information, and the used sequence, even though it is shown that for T1 values under 1200 msec the MOLLI and (Sh)MOLLI have good overall agreement. Funnel plots with missing studies analysis and Egger test were performed to determine publication bias. Sensitivity analysis was conducted by omitting each study sequentially and recalculating the model. These statistical analyses were performed using Review Manager (RevMan) v. 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and the package “metafor” in R v 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Furthermore, the weighted mean and weighted standard deviation were determined separately for all studied populations and field strengths using the number of subjects as weight-factor. These results are also presented to give a complete overview of the analysis.

Results

Results of the Literature Search

The search strategy identified 660 relevant abstracts in PubMed and EMBASE. In addition, eight handpicked papers were included. After removing the duplicates, a total of 557 abstracts were evaluated. In total, 49 articles remained for the meta-analysis; 305 studies were excluded based on title and abstract, 173 were excluded based on full text screening, and 30 were excluded based on the published data. More specific reasons for exclusion are listed in Fig. 1. A total of ten studies were included for the HCM group, nine for DCM, nine for MC, five in iron overload, six in amyloidosis, two in Fabry disease, ten in HT, twelve in DM, and one in obesity (Table 1). The field strength is known to influence the T1 values significantly; therefore, results from studies performed on a 1.5T or 3T are shown separately, but used as covariant in the meta-regression analysis.

Study Quality

One study received the maximum score in the NOS in all areas and only two studies received the full score in the category of study group selection. Not every study included a control group, which led to a minimum score at the comparability area and a lower score in ascertainment for these studies. The studies that did include control subjects, but had a poor description of patient and control subject selection, received a lower score in the selection category. A total of 24 studies reported the use of blinded analysis and evaluation by at least two analysts, which increased their score on ascertainment (see Table 1 for NOS scores).

Hypertrophic and Dilated Cardiomyopathy

The weighted mean (Sh)MOLLI T1 values in HCM patients and controls, respectively, measured at 1.5T were...
| First author, year | Disease (n)/ Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|-------------------|-------------------------|------------------|------------------|---------|---------------|--------------|------------------------|---------|------------|
| Fontana 2014 (29) | 46/52                   | 1026 ± 64        | 967 ± 34         |         | Average basal SAX or 4-chamber | Prospective, single center | ShMOLLI (25) | 3,0,2    | fulfilling diagnostic criteria, 72% asymmetrical septal HCM, 60% LV outflow obstruction, 76% LGE. Controls were pre-screened. |
| Goebel 2016 (30)  | 12/54                   | 980 ± 43.6       | 955 ± 33.5       | <0.05   | Average mid-SAX | Retrospective single center | MOLLI 5(3)3 FA=35 T1= 120-4103 | 3,0,1    | Unselected subjects referred for CMR, diagnosis after image analysis |
| Kuruvilla 2015 (17)| 20/22                   | 996 ± 32.5       | 967.4 ± 35       | <0.01   | Average basal and mid-SAX | Prospective, single center | MOLLI (22) FA=35 | 3,0,1    | HCM based on ventricular mass >81g/m² for man and >61g/m² for woman, with HT BPM >140/90 mmHg |
| Malek 2015 (31)   | 25/20                   | 987 ± 52*        | 939.7 ± 47.9*    | <0.01   | Segment basal or mid septal/ lateral | Prospective, single center | ShMOLLI (25) | 2,0,1    | Clinically diagnosed HCM referred for CMR, confirmed with LV muscle hypertrophy ≥15mm |
| White 2013 (32)   | 25/50                   | 1058 **          | 968 **           |         | 4-chamber septum basal-mid LGE ROI | Prospective, single center | ShMOLLI (25) | 3,0,2    | Diagnostic criteria, 80% asymmetrical septal HCM, mean max wall thickness 20 ± 4mm, 21 with LGE. |
| Dass 2012 (33)    | 28/12                   | 1209 ± 28        | 1178 ± 13        | <0.05   | Average 3 SAX | Prospective, single center | ShMOLLI (25) | 2,0,1    | Genetic determination of pathogenic mutation or LV hypertrophy ≥15 or ≥ 12mm familial disease |
| Hinojar 2015 (34) | 95/23                   | 1102 ± 58        | 1023 ± 44        |         | Average mid-SAX | Prospective, multicenter | MOLLI (23) 3(3)3(3)5 | 4,2,2    | LV hypertrophy > 15mm, nondilated LV and absence LV wall stress, expressed asymmetrical septal HCM |
| First author, year | Disease (n)/Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|-------------------|------------------------|------------------|------------------|---------|---------------|--------------|------------------------|---------|------------|
| Puntmann 2013 (35) | 25/20                  | 1254 ± 43        | 1070 ± 55        | <0.01   | Rectangular ROI septal mid-SAX | Prospective, single center | MOLLI (22, 23, 25) 3(3)5 FA=50 | 3,0,2   | LV hypertrophy, absence of increase LV wall stress or other systemic diseases. All asymmetric septal HCM |
| Wu 2016 (36)      | 28/14                  | 1241 ± 78.5      | 1114.6 ± 36.5    | <0.05   | Average basal and mid-SAX | Prospective, single center | MOLLI (23) | 2,0,1 | LV wall thickness ≥ 15mm by CMR, LGE + and LGE-divided (only LGE-included) |
| Wu 2016 (37)      | 11                     | 1216 ± 26.5      |                  |         | Basal and mid SAX       | Prospective, single center | MOLLI (23) | 3,0,1 | LV wall thickness ≥ 15mm by CMR, LGE + and LGE-divided (only LGE-included) |
| Dilated Cardiomyopathy |                      |                  |                  |         |               |              |                        |         |            |
| 1.5T               |                        |                  |                  |         |               |              |                        |         |            |
| aus dem Siepen 2015 (38) |            | 29/56            | 1056 ± 62        | <0.01   | Mean of mid-SAX ROI in 17 AHA segments | Prospective and retrospective single center | MOLLI (23) T1=100-4400 FA=35 | 3,0,1   | Retrospectively DCM patients with HF symptoms suspected of DCM diagnosis, increased LVEDV and LVEDD and reduced LVEF (≤45%) |
| Chen 2016 (39)    | 21                     | 1075 ± 83        |                  |         | ROI septal 1 mid SAX       | Prospective, single center | MOLLI 3(3)5 FA=50 | 2,0,2   | Referred for cardiac resynchronization therapy, pre-implant MRI |
| Goebel 2016 (30)  | 17/54                  | 992 ± 37.3       | 955 ± 33.5       | <0.01   | Average mid-SAX            | Retrospective single center | MOLLI 5(3)3 FA=35 T1=120-4103 | 3,0,1   | Unselected subjects referred for CMR, diagnosis after image analysis |
| Puntmann 2016 (11) | 357                    | SAX: 945 ± 141*  | Septal: 1004 ± 73* |        | Septal and full mid-SAX    | Prospective, Multicenter | MOLLI (31) 3(3)(3)5 FA=50 | 3,0,2   | Cohort of adult patients with non-ischemic DCM. Diagnosis was confirmed by CMR on basis of increased LVEDV indexed to body surface area and reduced EF |
**TABLE 1: Continued**

| First author, year | Disease (n)/ Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|---------------------|--------------------------|-------------------|-------------------|---------|---------------|--------------|-----------------------|---------|------------|
| Van Oorschot 2016 (40) | 20/8 | 1166 ± 66 | 1026 ± 21 | <0.01 | ROI histology based in 3 mid-SAX | prospective, single center | MOLLI (22, 23) FA=35 | 0.0,1 | Idiopathic DCM in addition to MRI on explanted hearts of DCM |
| Dass 2012 (33) | 18/12 | 1225 ± 42 | 1178 ± 13 | <0.01 | Average 3 SAX | Prospective, single center | ShMOLLI (25) | 2.0,1 | echocardiography LVEF < 45% and coronary angiography (exclude coronary artery disease) |
| Hong 2015 (41) | 41/10 | 1247.5 ± 66.8 | 1205.4 ± 37.4 | Not sig | Average segments ROI in 3 SAX | Prospective, single center | MOLLI 3(3)3(3)5 FA = 35 | 3.0,2 | LV dilatation, LVEDD ≥ 6cm, systolic dysfunction and LVEF≤40% (excluding ischemic and restrictive CM) |
| Puntmann 2013 (35) | 25/30 | 1254 ± 43 | 1070 ± 55 | 0.05 | Rectangular ROI septal mid-SAX | Prospective, single center | MOLLI (22, 23, 25) 3(3)5 FA = 50 | 3.0,2 | Non-ischemic DCM, based on increased LV volume and reduced systolic function (no LGE enhancement) |
| Puntmann 2014 (42) | 82/47 | SAX: 1102 ± 72 SAX: 1035 ± 47 | ROI: 1145 ± 37 ROI: 1055 ± 22 | <0.01 | Rectangular ROI septal + full mid-SAX | Prospective, single center | MOLLI (35) 3(3)5 FA = 50 | 3.0,1 | Increased LVEDV indexed to body surface area, reduced LVEF, no LGE enhancement, absence other causes. |
| Puntmann 2016 (11) | 280 | SAX: 1048 ± 127* Septal: 1111 ± 69* | Septal and full mid-SAX | | Prospective, Multicenter | MOLLI (35) 3(3)3(3)5 FA = 50 | 3.0,2 | Cohort of adult patients with non-ischemic DCM. Diagnosis was confirmed by CMR on basis of increased LVEDV indexed to body surface area and reduced EF. |

**Myocarditis**

**1.5T**

| Bohnen 2015 (43) | 16 of 31 | 1125 ± 93.5* | <0.05 | Mean 3 SAX | Prospective, Single center | MOLLI (22, 23) FA = 35 T1= 188-3382 | 2.0,2 | Recent-onset HF, LVEF<45%, no coronary artery disease, Endomyocardial biopsy and CMR confirmed |
| First author, year | Disease (n)/Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|-------------------|------------------------|-------------------|------------------|---------|---------------|-------------|------------------------|---------|------------|
| Ferreira 2014 (44) | 60/50 1011 ± 64 | 946 ± 23 | <0.01 | Mean of basal-, apical-SAX | Prospective, multicenter | ShMOLLI (25) | 2,2,1 | Suspected acute myocarditis |
| Ferreira 2013 (45) | 50/45 1010 ± 65 | 941 ± 18 | <0.01 | ROI myocardium ≥ 40mm² > threshold | Prospective, multicenter | ShMOLLI (25) | 2,2,1 | Suspected myocarditis, acute chest pain, elevation in troponin I level, recent viral disease, no ischemic |
| Goebel 2016 (30) | A:19, C:26 / 54 | A: 974 ± 35.9 C: 965 ± 39.5 | 955 ± 33.5 | <0.05 0.240 | Average single mid-SAX | Retrospective, single center | MOLLI 5(3)3 FA=35 TI=120-4103 | 3,0,1 | Established diagnostic criteria |
| Hinojar 2015 (46) | A:61, C:67 / 40 | A: 1064 ± 37 C: 995 ± 19 | 940 ± 20 | <0.05 <0.05 | Single mid-SAX | Prospective, international multicenter | MOLLI (23) 3(3)3(3)3 | 3,0,1 | Clinical diagnosis of viral myocarditis (list), active: within week after symptoms and serological marker convalescent; no symptoms and no serological marker |
| Luetkens 2016 (47) | 34/50 MOLLI: 1048.6 ± 51.9 ShMOLLI: 887 ± 37.2 | MOLLI: 966.9 ± 27.8 ShMOLLI: 831.4 ± 26.9 | <0.01 <0.01 | 3 SAX (basal, mid, apex), segmental approach | Prospective, single center | MOLLI (23) 3(3)3(3)5 / ShMOLLI (25) | 2,0,2 | Suspected acute MC based on clinical observation (clinical and laboratory). Controls were referred for nonspecific thoracic pain with no CMR results of abnormalities. |
| Luetkens 2016 (48) | 24/45 1047.7 ± 44.0 | 965.1 ± 28.1 | <0.01 | End diastolic SAX (basal, mid, apex) segmental approach | Prospective, single center | MOLLI (23) 3(3)3(3)5 FA=35 | 3,0,2 | Clinically defined acute myocarditis (acute chest pain, myocardial injury, viral infection, serum marker) |
| Lurz 2016 (49) | A:43, C:48 A: 1113 ± 67 C: 1096 ± 64 | <0.05 | VLA, HLA, SA whole myocardium manual ROI | Prospective, single center | MOLLI (84, 85) | 1,0,1 | Suspected MC (onset symptoms, myocardial damage, viral disease, no CAD) acute ≤ 14 days /chronic > 14 days – excluding MC without biopsy evidence |
| First author, year | Disease (n)/Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|-------------------|--------------------------|-------------------|-------------------|---------|---------------|--------------|-----------------------|---------|------------|
| Radunski 2014 (50) | 104/21 1098 ± 62*       | 1041 ± 42*        | <0.01             | End diastolic SAX global | Prospective, single center | MOLLI FA=35 T1=150-3871 | 2,0,2    | Recent infection, elevated troponin, acute chest pain (n=38) or new onset heart failure (n=66) |
| Radunski 2016 (51) | 20/20 1225 ± 109*       | 1045 ± 34*        | <0.01             | 3 SAX with ROI based on LGE manual/auto | Prospective, single center | MOLLI 3(3)5 FA=35 T1=88-3382 | 1,0,1    | Recent infection, elevated troponin, acute chest pain and Lake Louise Criteria, including CMR reference method for myocardial injury (some of the data was previously published(46) |
| Hinojar 2015 (46)  | A:61, C:67 /40          | A: 1189 ± 52      | 1045 ± 23         | <0.05   | Single mid-SAX | Prospective, international multicenter | MOLLI (23) 3(3)3(3)5 | 3,0,1 | Clinical diagnosis of viral myocarditis, active: within week after symptoms and serological marker convalescent: no symptoms and no serological marker |
| Luetkens 2014 (52) | 24/42 1185.3 ± 49.3     | 1089.1 ± 44.9     | <0.01             | End systolic 3 SAX segmental approach | Prospective, single center | MOLLI (23) | 2,0,1 | Acute MC, viral infection, elevated serum marker, myocardial injury, no history heart disease, no CAD. Controls: healthy and referred for non-specific thoracic pain (normal CMR) |
| Lurz 2016 (49)     | A:43, C:48              | A: 1203 ± 71      | VLA, HLA, SA whole myocardium ROI | Prospective, single center | MOLLI 3(3)5 FA=35 T1=108-2965 | 1,0,1 | Suspected MC (onset symptoms, myocardial damage, viral disease, no CAD) acute ≤ 14 days/chronic > 14 days – excluding MC without biopsy evidence |
| First author, year | Disease (n) / Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|---------------------|---------------------------|-------------------|-------------------|---------|---------------|--------------|----------------------|---------|-------------|
| Toussaint 2015 (53) | 6 LGE ROI 1179.2 ± 48.3 | 1179.2 | 648.3 | Manually defined ROIs LGE based | Prospective, single center | MOLLI (23) | 1.0,1 | Clinical MC: chest pain, fever, ECG changes, elevation of cardiac enzyme levels |
| Iron Overload 1.5T | | | | | | | | |
| Alam 2015 (54) | 53/20 939 ± 113* 1005 ± 40* | 0.21 | T2* threshold mid-SAX septum ROI | Prospective, single center | MOLLI (23) FA= 35 TI= 120-280 | 2.2,2 | Referral for cardiac siderosis screening or follow-up. Wide dynamic range of iron overload population |
| Feng 2013 (55) | 52 653 ± 133 | | ROI left ventricular septum, mid-SAX | Prospective, single center | MOLLI (23) TI= 100-260 | 1.0,0 | Regularly transfused patients with thalassemia major receiving iron chelation therapy, 52 had T2* < 20ms |
| Hanneman 2015 (56) | 19/10 850.3 ± 115.1 1006.3 ± 35.4 | <0.01 | Basal, apical, mid-SAX | Prospective, single center | MOLLI 5(3)3 FA= 35 TI= 120-4000 | 2.0,2 | Thalassemia major patients who received regular blood transfusion (iron chelation therapy) with T2* < 20ms |
| Sado 2015 (57) | 88/67 827 ± 135 968 ± 32 | <0.01 | T2* threshold ROIs | Prospective, single center | ShMOLLI (25) | 4.0,2 | 88 patients with 53 beta-thalassemia major and the others had several different other underlying diagnosis |
| 3T | | | | | | | | |
| Alam 2015 (54) | 53/20 1038 ± 167* 1155 ± 52* | <0.01 | T2* threshold mid-SAX septum ROI | Prospective, single center | MOLLI (23) FA= 35 TI= 100-260 | 2.2,2 | Referral for cardiac siderosis screening or follow-up. Wide dynamic range of iron overload population |
| Camargo 2016 (58) | 5/17 868.9 ± 120.2 1171.2 ± 25.5 | <0.05 | ROI ventricular mid-septum | Prospective, single center | MOLLI (22) FA= 35 | 3.0,2 | Referred patients for iron quantification, all patients has T2* < 20ms |
| First author, year | Disease (n)/Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|---------------------|-------------------------|-------------------|-------------------|---------|---------------|--------------|-----------------------|---------|------------|
| aus dem Siepen 2015 (59) | 9 | 1009 ± 48* | Mean SAX | Prospective single center | MOLLI FA=35 T1=100-4400 | 2,2,2 | Histologically proven TTR amyloid by endomyocardial biopsy and exclusion of any TTR gene variant by molecular genetic testing |
| Banypersad 2015 (60) | 100/54 | 1080 ± 87 | 954 ± 34 | <0.01 | ROI in 4-chamber in basal septum | Prospective, single center | ShMOLLI (25) | 3,0,2 | Included 60 patients from baseline study (61). Histological proof systemic AL amyloidosis and assessed at AM Center |
| Fontana 2015 (61) | 250 (30 and 83) / all:1082 ± 75 AL:1150 ± 68 ATTR: 1113 ± 47 | ROI in 4-chamber basal-mid interosep-tum (2 segments) | Prospective, single center | ShMOLLI (25) | 2,0,1 | Biopsy proven systemic AL, 91% histological proof ATTR, 9 TTR mutations people with no evidence |
| Gallego-Delgado 2016 (62) | 31 (5 and 26) / all:1197 ± 54 not cardiac: 1265 ± 31 cardiac: 1184 ± 47 | ROI mid basal and mid SAX and 4-chamber | Prospective, multicenter | MOLLI | 1,0,1 | Genetically proven TTR, cardiac/non cardiac was defined on CMR findings. Cardiomyopathy AM was defined as presence uptake 99mTC-DPD tracer |
| Karamitsos 2013 (63) | 14, 11 and 28 /36 | No: 1009 ± 31 Possible: 1048 ± 48 Definite: 1140 ± 61 | Average T1 of mid SAX and 4-chamber | ShMOLLI (25) | 3,0,1 | Histological confirmation of systemic AL AM and echocardiography for no, possible and definite cardiac AM |
| White 2013 (32) | 20/50 | 1137** | 968** | ROI basal-mid in 4-chamber, LGE based | ShMOLLI (25) | 3,0,2 | Cardiac AL AM, proven by noncardiac biopsy and echocardiography with Mayo clinic classification 2 or 3 |
| Study | Disease | ROIs | ROIs placement | Study design | Sequence and specifics | Quality | Population |
|-------|---------|------|----------------|--------------|------------------------|---------|------------|
| Pica 2014 (65) | LVH- 25 and LVH+ 38 /63 | 904 ± 46 /853 ± 50 | 968 ± 32 | Average septum mid to basal SAX | Prospective single center | ShMOLLI | 3,2,2 | Genetically confirmed diagnosis of Fabry disease from department of inherited cardiovascular diseases |
| Sado 2013 (64) | 44/67 | 882 ± 47 | 968 ± 32 | Average of ROI in basal and mid SAX | Prospectively Single center | ShMOLLI (25) | 3,0,1 | Genetically proven Fabry disease Patients from inherited cardiac disease unit |
| Edwards 2015 (66) | LVH- 43 /43 | 956 ±31 | 955 ±30 | Not sig | Average ROI septum basal/mid SAX | Prospective single center | MOLLI 3(3)5 | 1,2,1 | As control group for renal patients: treated HT patients referred to a dedicated hypertension clinic with no LVH |
| Ferreira 2016 (67) | LVH- 14 /31 | 958 ±23 | 954 ±16 958 ± 19 | Not sig | 6 segments per slice | Prospective, single center | ShMOLLI (25) | 2,2,1 | Essential HT, no other significant comorbidities, antihypertensive treatment >3 months, no severe LV hypertrophy |
| Kuruvilla 2015 (17) | LVH-23 and LVH+ 20 /22 | 974 ± 34 /996 ± 33 | 967.4 ±35 | Not sig/ < 0.05 | Basal and mid- SAX | Prospective, single center | MOLLI (22) FA= 35 TI= 30-10000 | 3,0,1 | HT with and without LV hypertrophy: HT sbp > 140mmHg or dbp>90mmHg or taking medication |
| Rodrigues 2016 (68) | LVH-80 and LVH+20 /25 | 1035 ± 37 / 1070 ± 46 | 1026 ±41 | Not sig/ <0.05 | Mean pixels in ROI mid-septum SAX | Prospective, single center | MOLLI (85) FA= 35 | 3,0,2 | HT clinic, on SBP and DBP, no cardiomyopathy, no decreased filtration rate, no severe valvular heart disease. With and without LVH |
| First author, year | Disease (n)/Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|-------------------|-------------------------|------------------|------------------|---------|---------------|-------------|-----------------------|---------|------------|
| Rodrigues 2016 (69) | LVH-41 + 15 and LVH+ 24 + 8 /29 | 1031 ± 35 1029 ± 45/1054 ± 41 1062 ± 41 | 1024 ± 41 | Not sig/<0.05 | ROI in mid-septum SAX | Observational, single center | MOLLI (85) FA=35 | 3.0,2 | Tertiary HT clinic referred for CMR, no decreased filtration rate, no severe valvular heart disease. With and without LVH in 2 different groups |
| Roux 2016 (70) | LVH-10 /10 | 952 ± 51 929 ± 80 | Not sig | Manual ROI mean T1 in 6 segments | Prospective Single center | MOLLI 3(3)3(3)5 FA=35 | 1.0,2 | As control group for Cushing’s disease: asymptomatic HT volunteers with no other cardiovascular risks and no LVH |
| Treibel 2015 (13) | LVH- 40 /50 | 948 ± 31 965 ± 38 | Not sig | Septum basal-SAX | Prospective, single center | ShMOLLI (87) | 3.1,1 | HT patients were included without LV hypertrophy but 35% still showed LVH on MRI with BPM ≥140/90mmHg |
| Venkatesh 2014 (71) | LVH- M: 208/415 F: 196/377 | M: 970 ± 38 F: 984 ±48 | M: 966 ± 37 F: 986 ± 45 | Not sig | Single mid- SAX, manual ROI around core myocardium | Observational cohort study, multicenter | MOLLI (24) | 1.0,2 | MESA, population based observational cohort study of 6814 men and woman in 4 ethnic groups. HT based on Joint National Committee VI criteria |
| 3T | LVH- 69 /23 | 1033 ± 68 1023 ± 41 | Whol mid SAX and septal ROI | Prospective, single center | MOLLI (23) 3(3)3(3)5 | 4.2,2 | Treated HT SBP>140mmHg DBP>95mmHg and concentric LVH >12mm in basal and without dilated LV |
| Wu 2016 (2 (37) | LVH+ 20 | 1197 ±10.5 | Basal and mid SAX | Prospective, single center | MOLLI (23) | 3.0,1 | |
| First author, year | Disease (n)/Control (n) | T1 (msec) Disease | T1 (msec) Control | P value | ROI placement | Study design | Sequence and specifics | Quality | Population |
|-------------------|------------------------|------------------|-----------------|---------|---------------|-------------|-----------------------|---------|------------|
| Diabetes Mellitus | 1.5T                   |                  |                 |         |               |             |                       |         |            |
| Jellis 2014       | 49                     | 850 ± 293        | 881 ± 227       |         | T1 maps in 16 segments in 3 SAX | Prospective, single center | MOLLI FIESTA 2,0,1 readout (73) | Screening Healthy subjects with type 2 DM with echocardiography for myocardial dysfunction (included) |
|                    | 13 and 54              | Reg E: 786 ± 43  | Irreg E: 841 ± 185 |         | Mean T1 from 16 segmented 3 SAX | Prospective single center | MOLLI FIESTA 1,0,1 readout (73) | Type 2 DM without vascular complications, valvular or ischemic heart disease or other comorbidities |
| Khan 2014          | 11/6                   | 944.0 ± 93       | 985.5 ± 86.6    | 0.457   | Whole midventricular 1 SAX | Prospective, single center | MOLLI (23) 2,2,1 | Type 2 DM without history of cardiovascular diseases from primary and secondary care services. |
| Obesity            | 1.5T                   |                  |                 |         |               |             |                       |         |            |
| Khan 2014          | 9/6                    | 962.3 ± 116.1    | 985.5 ± 86.6    |         | Whole midventricular 1 SAX | Prospective, single center | MOLLI (23) 2,2,1 | Obese, non-diabetic controls, excluding body mass >150kg. |
1002 ± 52 msec and 962 ± 37 msec (Table 1, Fig. 2). At 3T these weighted means were 1166 ± 55 msec and 1081 ± 45 msec, respectively (Table 1, Fig. 3). The meta-analysis showed a significant increase of the myocardial \( T_1 \) values for HCM patients (SMD = 1.41, 95% CI 0.93–1.88, \( P < 0.01 \), \( I^2 = 78\% \), Fig. 4). The meta-regression determined the machine vendor and the age of HCM patients as significant covariates, which accounted for the heterogeneity in the meta-regression model, with no other remaining significant residual factors (\( I^2 = 0\% \)). This indicates that the
SMD between HCM patients and controls is independent of field strength and MOLLI sequence. Only younger HCM patients and the use of a Siemens MRI (Avanto or Trio) scanner were shown to decrease the SMD. No significant funnel asymmetry was found for the random or mixed effect models ($P < 0.24$ and $P < 0.37$, respectively). The sensitivity analysis demonstrated that one study influenced the model, but this was not significant ($P > 0.09$). This specific study used a different scanner and a relatively young HCM patient population (44 ± 11 years) compared to the other studies.

The weighted mean (Sh)MOLLI $T_1$ values in DCM patients and controls, respectively, measured at 1.5T were $1008 \pm 48$ msec and $970 \pm 130$ msec (Table 1, Fig. 2). At 3T these were $1165 \pm 64$ msec and $1080 \pm 46$ msec, respectively (Table 1, Fig. 3). The meta-analysis confirmed this increase in $T_1$ values for the myocardium for DCM patients (SMD = 1.48; 95% CI 0.86–2.10, $P < 0.01$, Fig. 5). The heterogeneity and study bias could not be investigated further, because there were fewer than 10 studies included that compared DCM patients with controls. However, an exploratory meta-regression analysis indicated that the percentage men in the DCM population and the age of the subjects in the control population might be the source of heterogeneity.

Myocarditis, Iron Loading, Amyloidosis, and Fabry Disease

The weighted mean (Sh)MOLLI $T_1$ value in active/acute MC patients and controls, respectively, measured at 1.5T were $1054 \pm 61$ msec and $949 \pm 28$ msec (Table 1, Fig. 2). At 3T these were $1193 \pm 60$ msec and $1068 \pm 36$ msec, respectively (Table 1, Fig. 3). Studies that compared the active/acute MC patients with controls showed a significant increase of the $T_1$ value for MC patients. The meta-analysis confirmed this significant increase (SMD = 1.96; 95% CI 1.42–2.51; $I^2 = 91\%$, $P < 0.01$, Fig. 6). Significant covariates were vendor and left ventricular ejection fraction (LVEF) of the MC patients, which accounted for the heterogeneity in the meta-regression model with no other remaining significant residual factors ($I^2 = 0\%$, $P = 0.77$). A significant funnel asymmetry was found for the random effect model with one possible missing study ($P = 0.03$), but not for the mixed effect model including the two moderators ($P = 0.45$). The sensitivity analysis demonstrated that one study introduced some heterogeneity into the model, but only the 1.5T data of this study had significant influence on the model fit ($P < 0.05$).

The weighted mean (Sh)MOLLI $T_1$ value, in iron overload patients and controls, respectively, measured at 1.5T were $1010 \pm 144$ msec and $1162 \pm 42$ msec, respectively (Table 1, Fig. 2). At 3T these were $1100 \pm 148$ msec and $1238 \pm 42$ msec, respectively (Table 1, Fig. 3). Only three studies restricted the inclusion to one specific iron overload patient population, but the other two studies used a mixed population of patients. The number of included studies was not sufficient to conduct a meta-analysis, but the direction of the overall effect was similar for all studies (Fig. 7).

Amyloidosis is the most typical type of restrictive cardiomyopathy. The weighted mean (Sh)MOLLI $T_1$ values were only measured at 1.5T and were $1140 \pm 69$ ms for patients and $960 \pm 29$ ms for controls (Table 1, Fig. 2). Three

![FIGURE 4: Standardized mean difference between native myocardial $T_1$ of HCM patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.](image)

![FIGURE 5: Standardized mean difference between native myocardial $T_1$ of DCM patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.](image)
studies compared amyloidosis patients with controls, and all concluded that there was a significant increase of the T₁ for amyloidosis patients. Some studies divided the amyloidosis patient populations in immunoglobulin light chain (AL) or transthyretin (ATTR), or cardiac or no cardiac involvement amyloidosis. Karamitsos et al. showed that all their subpopulations, including no cardiac involvement amyloidosis patients, had a significantly increased T₁ value compared to healthy controls. No meta-analysis was performed because of the small number of included studies. However, the direction of the overall effect was similar for all studies (Fig. 8).

Fabry disease is a less common restrictive cardiomyopathy and only two studies were included. Nevertheless, the weighted mean (Sh)MOLLI T₁ value measured by 1.5T was 1044 ± 41 for HT patients with LVH, 984 ± 41 msec for HT patients without LVH, and 975 ± 40 msec for controls (Table 1, Fig. 2). At 3T these were 1070 ± 68 msec for HT patients and 1023 ± 41 msec for controls (Table 1, Fig. 3). Four studies compared HT patients with LVH to controls and HT patients without LVH. They all reported a significant increase of T₁ of the LVH populations compared with controls (P < 0.05) and three also reported a significant increase compared with HT patients without LVH, while this last group had no significant change in T₁ values. Two studies compared HT patients to HCM patients. The comparison with HT without LVH showed a significant higher T₁ value for HCM patients (P < 0.01), while the comparison with HT with LVH showed no significant difference between the two. The meta-analysis of all HT patients (with and

### Chronic Hypertension, Overweight/Obesity, and Type 2 Diabetes Mellitus

The weighted mean (Sh)MOLLI T₁ value measured by 1.5T was 1044 ± 41 for HT patients with LVH, 984 ± 41 msec for HT patients without LVH, and 975 ± 40 msec for controls (Table 1, Fig. 2). At 3T these were 1070 ± 68 msec for HT patients and 1023 ± 41 msec for controls (Table 1, Fig. 3). Four studies compared HT patients with LVH to controls and HT patients without LVH. They all reported a significant increase of T₁ of the LVH populations compared with controls (P < 0.05) and three also reported a significant increase compared with HT patients without LVH, while this last group had no significant change in T₁ values. Two studies compared HT patients to HCM patients. The comparison with HT without LVH showed a significant higher T₁ value for HCM patients (P < 0.01), while the comparison with HT with LVH showed no significant difference between the two. The meta-analysis of all HT patients (with and

### FIGURE 7: Standardized mean difference between native myocardial T₁ of iron overload (IO) patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

### FIGURE 8: Standardized mean difference between native myocardial T₁ of amyloidosis (AM) patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.
without LVH) together showed a significant difference between T1 values of healthy controls and HT patients (SMD: 0.19; 95% CI 0.01–0.37; I² = 61%; P = 0.04, Fig. 10). The meta-regression analysis showed that in HT patients LVH was the only significant covariate which changed the I² to 4%. A second meta-regression was performed excluding those patients with LVH. The analysis of the HT patients without LVH showed no significant difference between the T1 values of healthy controls and HT patients (SMD: 0.03; 95% CI −0.07–0.13; I² = 2%; P = 0.52, Fig. 11). Analysis on funnel symmetry, missing studies or influencing studies, of this restricted inclusion all turned out to be not significant for both analyses (HT without LVH: P < 0.83, P = 0.5, and P > 0.05, respectively, and all HT: P = 0.09, P = 0.5, P > 0.05, respectively).

DM and obese patient populations are studied less extensively with T1-mapping compared with the above-mentioned diseases. The weighted mean MOLLI T1 value measured on 1.5T was 853 ± 202 msec for DM patients,72–74 963 ± 116 msec for obesity subjects and 986 ± 87 msec for controls74 (Table 1, Fig. 2). At 3T the only measured T1 values were 1194 ± 32 msec for DM patients and 1182 ± 28 msec for controls75 (Table 1, Fig. 3). No meta-analysis was performed, because of the small number of included studies (Figs. 12 and 13).

Discussion

The findings of this systematic review and meta-analysis show that native myocardial T1 values changes significantly in patients with HCM, DCM, MC, amyloidosis, and iron overload. This supports previously published research on the diagnostic value of native T1 mapping to detect diffuse myocardial fibrosis, inflammation, iron accumulation, and protein deposition.16,77 HT patients without any LVH

| Study or Subgroup | HT Mean SD | Control Mean SD | Total Mean SD | Total Weight | Std. Mean Difference IV, Random, 95% CI |
|-------------------|-----------|-----------------|--------------|-------------|----------------------------------------|
| Edwards 2015      | 956 31    | 43 955 30 41    | 8.4%         | 0.03 [-0.19, 0.46] |                                        |
| Ferrari 2014      | 958 21    | 34 958 19 31    | 5.4%         | 0.01 [-0.63, 0.61] |                                        |
| Hincear 2015      | 1,033 69  | 69 1,023 41 23 | 7.6%         | 0.16 [-0.31, 0.36] |                                        |
| Kurukulas 2015    | 996 33    | 20 967 4 35    | 25%          | 0.82 [0.19, 1.46]  |                                        |
| Kurukulas 2015    | 974 31.6   | 23 967 4 35    | 22%          | 0.03 [-0.40, 0.78] |                                        |
| Rodrigues 2016    | 1,070 46  | 20 1,026 41 25 | 9.9%         | 0.14 [-0.31, 0.58] |                                        |
| Rodrigues 2016    | 1,058 41  | 41 1,024 41 29 | 6.9%         | 0.02 [0.29, 1.34]  |                                        |
| Roux 2016         | 952 51    | 10 929 90 10   | 3.4%         | 0.33 [-0.56, 1.21] |                                        |
| Trebel 2015       | 948 31    | 40 965 38 50   | 8.5%         | -0.48 [-0.80, -0.06] |                                        |
| Venkatesh 2014 F1 | 904 40    | 80 986 35 27   | 12.5%        | -0.04 [-0.22, 0.12] |                                        |
| Venkatesh 2014 M1 | 970 38    | 208 966 37 415 | 10.6%        | 0.11 [-0.06, 0.27]  |                                        |
| Wu 2017           | 1,197 10.5 | 20 0 0 0      |              | Not estimable          |                                        |

FIGURE 11: Standardized mean difference between native myocardial T1 of HT patients without LVH with associated random effects weight factors, CI = confidence interval, IV = inverse variance, F1 = female subgroup, M1 = male subgroup.
showed no significant change in the $T_1$ value, which indicates the absence of the tissue modifications, while HT patients with LVH had a significantly increased $T_1$ value. Insufficient numbers of publications have been conducted in Fabry disease and populations with increased cardiovascular risk (DM and obesity) to draw any conclusions about changes in those myocardial $T_1$ values.

The current meta-analysis confirms the clinical potential of $T_1$ mapping, but also shows a lack of standardization considering the different reported $T_1$ values for controls. Although $T_1$ values at 1.5T seemed to vary, none of the $T_1$ values of the controls were significantly different from the expected MOLLI $T_1$ value of 950±21 msec. In studies performed at 3T, none of the $T_1$ values for controls were significantly different from the expected MOLLI $T_1$ value of 1053±23 msec. Moon et al. stressed the need to improve standardization of $T_1$ mapping by describing protocol recommendations. However, they also state that there is no current standard for $T_1$ mapping sequences, nor for analysis and mapping methods. It is recognized that the $T_1$ value is influenced by these factors, which probably led to the inconsistencies in the reported $T_1$ values.

In addition, the postprocessing of the $T_1$ map can also introduce bias, errors, and loss of precision, particularly in protocols using regional regions of interest (ROIs), image segmentation, variable slice orientations. Almost half of the included studies used ROIs to determine the $T_1$. Conversely, Moon et al. recommended global myocardial $T_1$ measurements. Puntmann et al. clearly showed the importance of this in their studies on DCM patients. They used rectangular ROIs in the septum, the average of the whole short axis slice (SAX). The $T_1$ value for the whole SAX showed no significant difference between DCM patients and controls ($P = 0.05$), while the $T_1$ values in the septal ROI were significantly increased for DCM patients ($P < 0.05$).

In addition to this, the $T_1$ values of studies that used the segmental approach also suffered from averaging. Furthermore, some studies used the 4-chamber plane for $T_1$ mapping, which can lead to errors due to through-plane respiratory motion. All these factors, together with the lack of standard protocols, make it difficult to determine a normative $T_1$ value range for healthy myocardium, and therefore also for diseased myocardium.

Fortunately, SMD between controls and the studied cardiac diseases are shown to be less variable across studies and sites. The SMDs were shown to be independent of the applied field strength and MR sequence, and only for the HCM and MC population the SMD did depend on the system type (vendor). Moon et al. recommend correcting for variation in the scanner’s characteristics and this meta-analysis demonstrates that this correction should probably mainly be based on vendor. Apart from the variation and lack of standardization, the SMD shows that native $T_1$ has diagnostic value for most of the included cardiac diseases.

NICM can have subtle and diffuse fibrosis patterns that are difficult to determine and inclusion and study bias are a remaining concern in NICM studies. The funnel plots and Egger tests show that there is indeed some publication bias for the MC analysis, which should be kept in mind when evaluating the SMD. However, none of the other populations showed this bias, and only showed heterogeneity in $T_1$ values caused by the vendor, age or gender. These factors are well known to influence myocardial $T_1$ values and are important to correct for. In addition, some studies reported $T_1$ values of LGE-based ROIs, which is known to be highly nonspecific and misses the full representation of the disease. These LGE-based ROI data were excluded from the meta-analysis. After correcting the SMD for these heterogeneity factors, the meta-analysis still shows that there are significant changes in $T_1$. 

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**FIGURE 12:** Standardized mean difference between native myocardial $T_1$ of DM patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

**FIGURE 13:** Standardized mean difference between native myocardial $T_1$ of obese (OB) populations and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.
and although LGE is still the clinical standard to determine focal fibrosis, a change of native T1 is clearly also associated with an increase in fibrotic tissue.16

In addition to sensitivity for myocardial fibrosis, T1 values can also indicate edema formation (inflammation), and deposition of substances like protein and iron, which makes it a nonspecific parameter.16,78 T1 values seem sensitive enough to differentiate between clinical disease stages of patients with myocarditis when a baseline scan and clinical records are provided.46,49,83 T1 values may therefore help to follow disease progression and treatment83; however, this meta-analysis only confirms the significant changes in myocardial T1 values in the acute phase of MC.

Iron accumulation also changes myocardial T1 values by shortening the relaxation times significantly, which suggests T1 mapping is also of value in the assessment of myocardial iron loading.55,64 One of the included studies27 evaluated the T2* of an iron overload patient population and concluded that one-third had a normal T2* but a decreased T1 value. They state that T1 mapping might be more sensitive to iron accumulation than T2* imaging, but the amount of accumulated iron that correlates with these T1 values still needs to be confirmed by human histology. The differences in iron concentration of all included subjects in the different studies might have caused the broad range in T1 values. Further research to the correlation between T1 values and the iron concentration in the myocardium is needed to determine whether T1 mapping could also be used for monitoring.

All amyloidosis studies reported a significant increase in myocardial T1 values, even for amyloidosis patients who had no biopsy or decreased cardiac function that confirmed cardiac involvement. This meta-analysis shows that it is sensitive to increases of the interstitial space caused by myocardial protein depositions in amyloidosis,16 which indicates that myocardial T1 mapping might be better in early detection of amyloidosis deposition in the heart than regular cardiac MRI. The significant increase SMD is even found when there is a high variation caused by the studies that used the 4-chamber imaging plane for T1 mapping, which is commonly used to study amyloidosis patients.29,32,60 Further research with cardiac axial slices is needed to determine the classification potential of the T1 value in amyloidosis patients.

HT and NICM patients seem to have several standard cardiac MR parameters in common; nevertheless, none of the included studies in this meta-analysis reported a significant increase in T1 values for HT patients without LVH. Only patients with HT in combination with LVH showed a significant change in T1 value.68,69 However, all studies reported the mean T1 value, which ignores the fact that HT might be associated with inhomogeneous T1 distribution.84 Further research is needed to determine the ability of T1 mapping to image this inhomogeneity and whether it is applicable to follow HT progression.

Two studies reported clearly decreased T1 values for DM,72,73 but had no healthy control population to compare them with. A reason for this decrease might be that DM patients are known to develop myocardial steatosis due to their insulin resistance, and the associated myocardial fat lowers the native T1 value.74 However, the fat content of this myocardial steatosis is much smaller than in Fabry disease, and the number and size of T1 mapping studies was too small to determine the influencing factors in this population. Two other studies reported much higher T1 for DM patients and compared them with healthy controls, but both showed no significant change.74,75 Levelt et al75 used healthy control subjects with a BMI of 28.6 ± 5.7, which raises the question whether healthy controls should have a healthy weight (BMI <25). This concern is the same for the DM populations, because the DM patients in the included studies had a weighted mean BMI of 31 ± 5, which makes most of them obese. Only one study85 compared DM patients with a lean group of healthy controls and obese controls separately. However, the obesity subjects did not differ significantly from either of the two other populations in this study. Further research with lean controls and DM patients (BMI <25) is needed to confirm the reported changes in T1 value, and whether it is possible to distinguish these populations from NICM patients.

T1 mapping has numerous MRI-dependent and methodological factors that can influence the final T1 values.58 The field strength and sequence are two of these factors, but this meta-analysis shows that they do not influence the SMD, even though the T1 values at 3T are overall 100msec higher than at 1.5T. More research towards understanding the effect on accuracy, precision, and reproducibility of T1 mapping is needed.21,86 Without this knowledge, it remains unknown whether the variance of the T1 maps is mainly caused by variability in physiological effects, or the inaccuracy of the technique itself. The HCM, DCM, MC, and HT patient populations were studied in groups of sufficient size to suggest that the significant SMD of T1 values is probably caused by changes in tissue physiology. Further research should be conducted on DM and obese populations and on other possible factors associated with variance in T1 mapping values.

The nonuniform reporting of data in the included studies: heterogeneity of included patient populations, methods for T1 mapping, differences in ROI placement, and for amyloidosis, iron overload, DM, and obese, and the small number of studies formed the major limitations of this meta-analysis. Most studies did not publish their data per patient, especially the studies with great sample sizes, and therefore no conclusions could be drawn on a per-patient basis. Future prospective studies should provide complete patient-level insight, which may help mitigate selection bias for amyloidosis, iron overload, DM, and obese studies. In
addition, the patient characteristics should be published together with the T1 values to enable determination of correlation. Finally, we had to compare the T1 values of a smaller number of amyloidosis, iron overload, DM, and obese studies with more widely studied HCM, DCM, MC, and HT diseases. However, the direction of the overall effect was similar for the iron overload and amyloidosis studies and can be ascribed to the physiological changes associated with the diseases. For the DM and obese populations, this direction is less obvious.

In conclusion, this meta-analysis shows that native T1 mapping is a reliable way to distinguish HCM, DCM, MC, iron overload, amyloidosis, and HT patients with LVH from healthy controls and HT patients without LVH. This indicates that T1 mapping could help diagnose certain cardiomyopathies at an earlier stage than other cardiac MR techniques alone. In addition, DM and OB seem to affect myocardial T1 values, although the change in T1 is opposite and can be ascribed to the physiological changes associated from healthy controls and HT patients without LVH. This was similar for the iron overload and amyloidosis studies and can be ascribed to the physiological changes associated with the diseases. For the DM and obese populations, this direction is less obvious.

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