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# Native T<sub>1</sub> 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 T<sub>1</sub> mapping are increasingly used to diagnose diffuse fibrosis based cardiac diseases, studies reporting T<sub>1</sub> 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 T<sub>1</sub> 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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$P = 0.52$ ). The number of studies on amyloidosis, iron overload, Fabry disease, and HT patients with LVH did not meet the requirement to perform a meta-analysis. However, most studies reported a significantly increased  $T_1$  for amyloidosis and HT patients with LVH and a significant decreased  $T_1$  for iron overload and Fabry disease patients.

**Data Conclusions:** Native  $T_1$  mapping by using an (Sh)MOLLI sequence can potentially assess myocardial changes in HCM, DCM, MC, iron overload, amyloidosis, and Fabry disease compared to controls. In addition, it can help to diagnose left-ventricular remodeling in HT patients.

**Level of Evidence:** 2

**Technical Efficacy:** Stage 3

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**N**onischemic 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).<sup>1</sup> HCM alone affects 1/500 adults<sup>2</sup> 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,<sup>3</sup> the approximately one-tenth that suffers from diabetes<sup>4</sup>; and the two-thirds that are either overweight (body mass index [BMI]  $\geq 25$ ) or obese (BMI  $\geq 30$ ).<sup>5,6</sup>

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).<sup>7–9</sup> 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).<sup>10</sup> However, in the earlier stages of NICM the increases in wall-mass and dilation are less obvious, and the fibrosis patterns remain difficult to detect. This makes it difficult to recognize NICM at the onset of the disease.<sup>11</sup> It is even more difficult to distinguish NICM from hypertension (HT), diabetes mellitus type 2 (DM), or obesity, because of their similarities in cardiac characteristics,<sup>12</sup> especially when left-ventricle hypertrophy (LVH) is present. Common characteristics include: increased left ventricular wall-thickness,<sup>13</sup> diastolic dysfunction,<sup>14</sup> increased left ventricle mass,<sup>15</sup> and infiltration of myocardial fat.<sup>15</sup> These similarities may lead to incorrect interpretation and possible mistreatment. Therefore, additional diagnostic techniques are needed to ensure accurate diagnosis of NICM.

$T_1$  mapping has been proposed as a technique to aid earlier diagnosis of NICM patients.<sup>11</sup> Previous research has shown that cardiac native  $T_1$ -mapping can differentiate between healthy myocardial tissue and pathologies including HCM, myocarditis (MC), iron loading, amyloidosis, and

Fabry disease.<sup>16</sup> In addition,  $T_1$  values of myocardial tissue in HT patients without LVH do not seem to change,<sup>13,17</sup> suggesting that it may be possible to differentiate HT from NICM tissue. Further research is needed to determine whether  $T_1$  mapping can enable earlier detection of these NICM.

Although there are concerns about the physical accuracy of  $T_1$  mapping, the overall precision and reproducibility are fairly high and of substantial clinical utility.<sup>18</sup> There is, therefore, an increasing demand for normative reference  $T_1$  values.<sup>19–21</sup> These reference values will be of particular importance for HT, DM, and obese patients because they share cardiac MR characteristics with NICM.<sup>13–15</sup> Because methodological differences can eventually affect the myocardial  $T_1$  values,<sup>18,21</sup> a meta-analysis is a suitable approach to determine the normal myocardial  $T_1$  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  $T_1$  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 “ $T_1$ -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  $T_1$  mapping; 4) contained native  $T_1$  values from a modified Look-Locker inversion-recovery (MOLLI)<sup>22–24</sup> or shortened MOLLI (ShMOLLI)<sup>25</sup> 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<sup>26</sup> and the Cochrane Handbook for Systematic Review<sup>27</sup> 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 T<sub>1</sub> 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.<sup>28</sup> 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 T<sub>1</sub> 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). I<sup>2</sup> was used as a measure of heterogeneity with I<sup>2</sup> ≥ 50% and P < 0.05 on the χ<sup>2</sup> 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.<sup>27</sup> A mixed-effect model approach was used for the meta-regression and performed with available covariates to determine association with the myocardial T<sub>1</sub> 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 T<sub>1</sub> values under 1200 msec the MOLLI and (Sh)MOLLI have good overall agreement.<sup>25</sup> 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. 3.22 (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

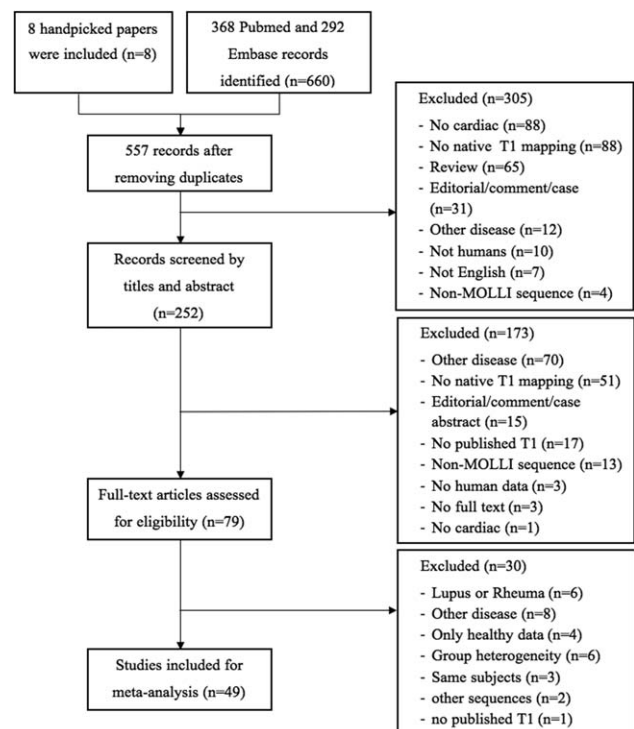


FIGURE 1: Overview of study review process according to the PRISMA flow diagram.<sup>26</sup>

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,<sup>17,29–37</sup> nine for DCM,<sup>11,30,33,35,38–42</sup> twelve in MC,<sup>30,43–53</sup> five in iron overload,<sup>54–58</sup> six in amyloidosis,<sup>32,59–63</sup> two in Fabry disease,<sup>64,65</sup> ten in HT,<sup>13,17,34,37,66–71</sup> four in DM,<sup>72–75</sup> and one in obesity<sup>74</sup> (Table 1). The field strength is known to influence the T<sub>1</sub> values significantly<sup>65</sup>; 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<sup>34</sup> received the maximum score in the NOS in all areas and only two studies<sup>46,57</sup> 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 T<sub>1</sub> values in HCM patients and controls, respectively, measured at 1.5T were

TABLE 1. NOS Scores

First author, year	Disease (n)/ Control (n)	T1 (msec) Disease	T1 (msec) Control	P value	ROI placement	Study design	Sequence and specifics	Quality	Population
Hypertrophic Cardiomyopathy									
1.5T									
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 TI=120-4103	3,0,1	Unselected subjects referred for CMR, diagnosis after image analysis
Kuruwilla 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/m <sup>2</sup> for man and >61g/m <sup>2</sup> for woman, with HT BPM >140/90 mmHg
Malek 2015 (31)	25/20	987 ± 52*	939.7 ± 47.9*	<0.01 <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.
3T									
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

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
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 <0.01	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	1020 ± 40	<0.01	Mean of mid-SAX ROI in 17 AHA segments	Prospective and retrospective single center	MOLLI (23) TI=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 septum 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 TI=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(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
3T									
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 ROI: 1145 ± 37	SAX: 1035 ± 47 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 TI=188-3382	2,0,2	Recent-onset HF, LVEF < 45%, no coronary artery disease, Endomyocardial biopsy and CMR confirmed

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
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 ≥ 40mm <sup>2</sup> > 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)5	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



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
Radunski 2014 (50)	104/21	1098 ± 62*	1041 ± 42*	<0.01	End diastolic 3 SAX global	Prospective, single center	MOLLI FA=35 TI=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 TI=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)
3T									
Hinojar 2015 (46)	A:61, C:67 / 40	A: 1189 ± 52 C: 1099 ± 22	1045 ± 23	<0.05 <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 C: 1185 ± 78			VLA, HLA, SA whole myocardium ROI	Prospective, single center	MOLLI 3(3)5 FA=35 TI=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

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
Toussaint 2015 (53)	6	LGE ROI 1179.2 ± 48.3			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

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
Amyloidosis									
1.5T									
aus dem Siepen 2015 (59)	9	1009 ± 48*			Mean SAX	Prospective single center	MOLLI FA=35 TI=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 inferoseptum (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	958 ± 20	<0.01 <0.01 <0.01	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.

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
Fabry Disease									
1.5T									
Pica 2014 (65)	LVH- 25 and LVH+ 38 /63 ± 50	904 ± 46 /853	968 ± 32		Average septal 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
Chronic Hypertension									
1.5T									
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 ± 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
Kuruwilla 2015 (17)	LVH-23 and LVH+ 20 /22 ± 33	974 ± 34 /996	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

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
Rodrigues 2016 (69)	L VH-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)	L VH-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)	L VH- 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)	L VH- 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									
Hinojar 2015 (34)	L VH- 69 /23	1033 ± 68	1023 ± 41		Whole 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)	L VH+ 20	1197 ± 10.5			Basal and mid SAX	Prospective, single center	MOLLI (23)	3,0,1	

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
Diabetes Mellitus									
1.5T									
Jellis 2014 (72)	49	850 ± 293 881 ± 227			T1 maps in 16 segments in 3 SAX	Prospective, single center	MOLLI FIESTA readout (73)	2,0,1	Screening Healthy subjects with type 2 DM with echocardiography for myocardial dysfunction (included)
Jellis 2011 (73)	13 and 54	Reg E: 786 ± 43 Irreg E: 841 ± 185			Mean T1 from 16 segmented 3 SAX	Prospective single center	MOLLI FIESTA readout (73)	1,0,1	Type 2 DM without vascular complications, valvular or ischemic heart disease or other comorbidities
Khan 2014 (74)	11/6	944.0 ± 93	985.5 ± 86.6	0.457	Whole mid ventricular 1 SAX	Prospective, single center	MOLLI (23)	2,2,1	Type 2 DM without history of cardiovascular diseases from primary and secondary care services.
3T									
Levelt 2016 (75)	46/20	1194 ± 32	1182 ± 28	0.23	Myocardial 1 mid SAX	Prospective, single center	ShMOLLI (25)	2,2,1	Only stable type 2 DM, no known complications. No history of cardiovascular disease, chest pain, smoking, HT, ischemic changes on electrocardiography.
Obesity									
1.5T									
Khan 2014 (75)	9/6	962.3 ± 116.1	985.5 ± 86.6		Whole mid ventricular 1 SAX	Prospective, single center	MOLLI (23)	2,2,1	Obese, non-diabetic controls, excluding body mass >150kg.

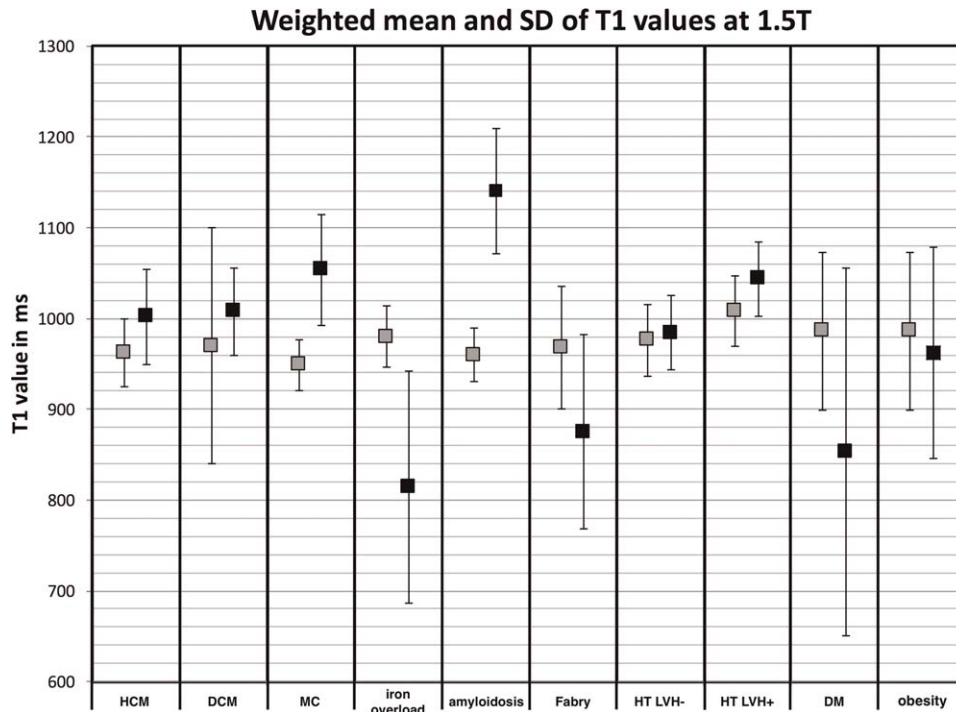


FIGURE 2: Weighted mean T<sub>1</sub> values with weighted mean and standard deviation of all included studies per HCM, DCM, MC, iron overload, amyloidosis, HT with (LVH+) and without (LVH-) left ventricular hypertrophy, DM, and OB population (black) and healthy controls (gray) in 1.5T studies.

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<sub>1</sub> 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

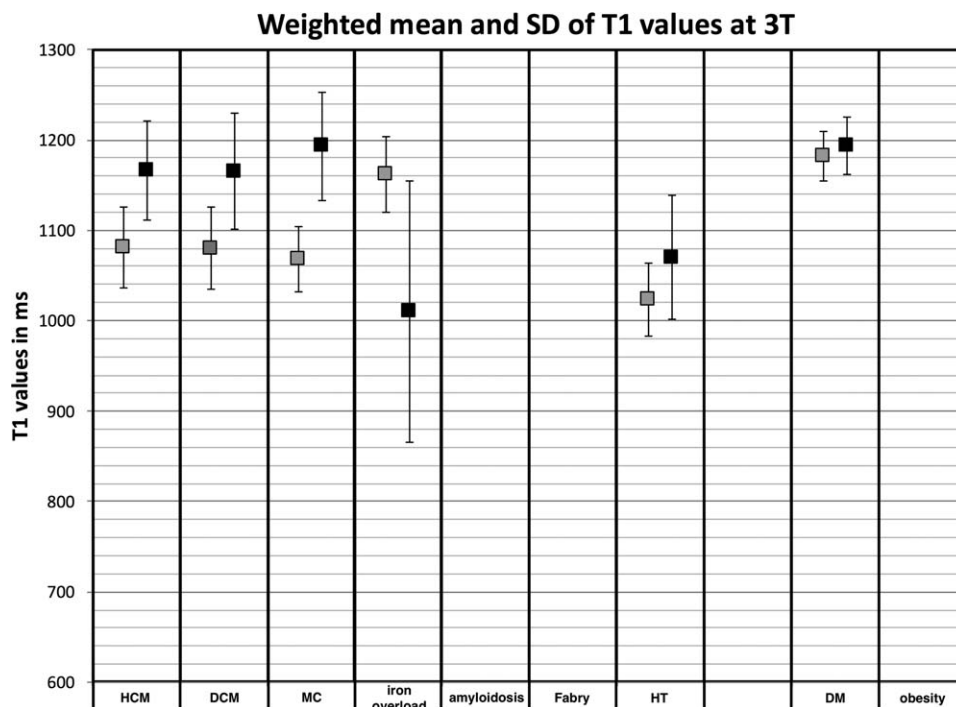
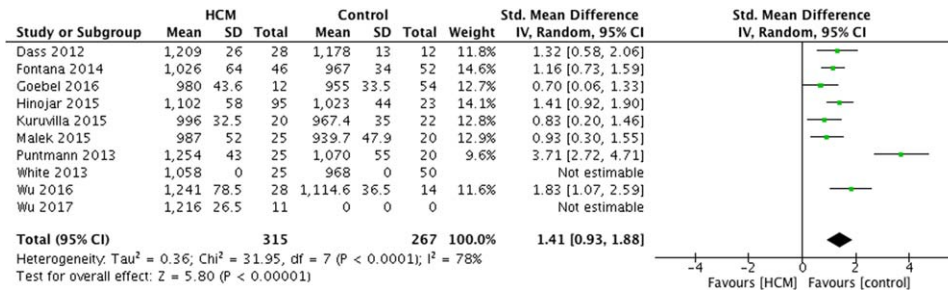


FIGURE 3: Weighted mean T<sub>1</sub> values with weighted mean and standard deviation of all included studies per HCM, DCM, MC, iron overload, amyloidosis, HT with (LVH+) and without (LVH-) left ventricular hypertrophy, DM, and obesity population (black) and healthy controls (gray) in 3T studies.



**FIGURE 4: Standardized mean difference between native myocardial T<sub>1</sub> of HCM patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.**

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<sup>35</sup> 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 ( $44 \pm 11$  years) compared to the other studies.

The weighted mean (Sh)MOLLI T<sub>1</sub> 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<sub>1</sub> values in the myocardium for DCM patients (SMD = 1.48, 95% CI 0.86–2.10,  $P < 0.01$ , I<sup>2</sup> = 85%, 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.

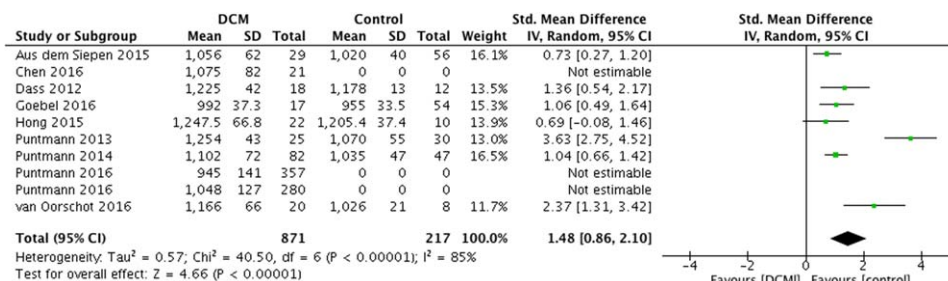
**Myocarditis, Iron Loading, Amyloidosis, and Fabry Disease**

The weighted mean (Sh)MOLLI T<sub>1</sub> 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<sub>1</sub> value for MC patients. The meta-analysis confirmed this significant increase (SMD = 1.96; 95% CI 1.42–2.51; I<sup>2</sup> = 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<sup>2</sup> = 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<sup>46</sup> 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<sub>1</sub> value, in iron overload patients and controls, respectively, measured at 1.5T were  $814 \pm 128$  msec and  $980 \pm 34$  msec (Table 1, Fig. 2). At 3T these were  $1010 \pm 144$  msec and  $1162 \pm 42$  msec, respectively (Table 1, Fig. 3). Only three studies restricted the inclusion to one specific iron overload patient population,<sup>54–56</sup> the other two studies used a mixed population of patients.<sup>57,58</sup> 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.<sup>76</sup> The weighted mean (Sh)MOLLI T<sub>1</sub> values were only measured at 1.5T and were  $1140 \pm 69$  ms for patients and  $960 \pm 29$  for controls (Table 1, Fig. 2). Three



**FIGURE 5: Standardized mean difference between native myocardial T<sub>1</sub> of DCM patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.**



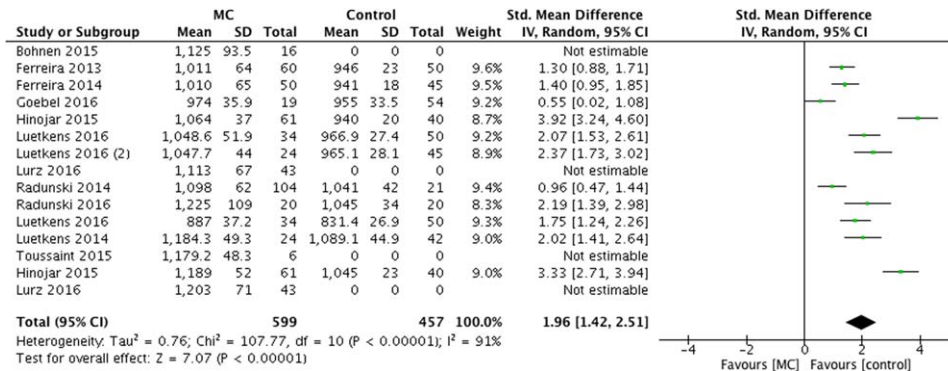


FIGURE 6: Standardized mean difference between native myocardial T<sub>1</sub> of MC patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

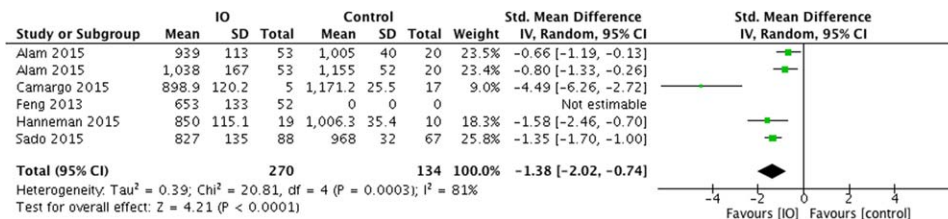


FIGURE 7: Standardized mean difference between native myocardial T<sub>1</sub> of iron overload (IO) patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

studies<sup>32,60,63</sup> compared amyloidosis patients with controls, and all concluded that there was a significant increase of the T<sub>1</sub> for amyloidosis patients. Some studies divided the amyloidosis patient populations in immunoglobulin light chain (AL) or transthyretin (ATTR),<sup>29</sup> or cardiac or no cardiac involvement amyloidosis.<sup>62,63</sup> Karamitsos et al.<sup>63</sup> showed that all their subpopulations, including no cardiac involvement amyloidosis patients, had a significantly increased T<sub>1</sub> 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 T<sub>1</sub> values at 1.5T were 875 ± 48 msec for patients and both studies used the same pool of controls that had T<sub>1</sub> values of 968 ± 23 msec (Table 1, Fig. 2). No further meta-analysis or regression could be performed on these data (Fig. 9)

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

The weighted mean (Sh)MOLLI T<sub>1</sub> 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<sup>13,17,68,69</sup> compared HT patients with LVH to controls and HT patients without LVH. They all reported a significant increase of T<sub>1</sub> of the LVH populations compared with controls (P < 0.05) and three<sup>13,68,69</sup> also reported a significant increase compared with HT patients without LVH, while this last group had no significant change in T<sub>1</sub> values. Two studies<sup>34,37</sup> compared HT patients to HCM patients. The comparison with HT without LVH showed a significant higher T<sub>1</sub> value for HCM patients (P < 0.01),<sup>34</sup> while the comparison with HT with LVH showed no significant difference between the two.<sup>37</sup> The meta-analysis of all HT patients (with and

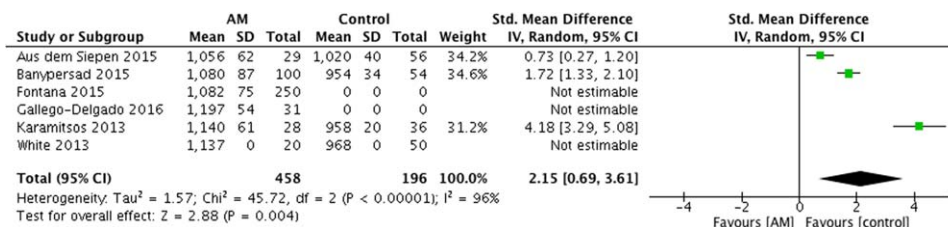


FIGURE 8: Standardized mean difference between native myocardial T<sub>1</sub> of amyloidosis (AM) patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

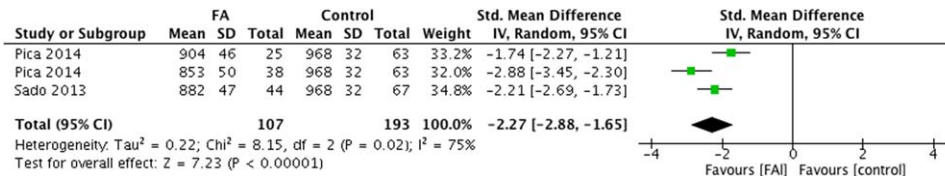


FIGURE 9: Standardized mean difference between native myocardial T<sub>1</sub> of Fabry (FA) disease patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

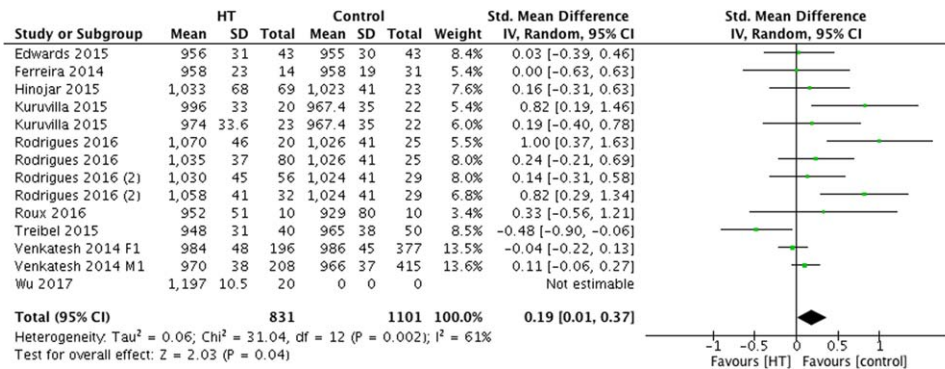


FIGURE 10: Standardized mean difference between native myocardial T<sub>1</sub> of all HT patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance, F1 = female subgroup, M1 = male subgroup.

without LVH) together showed a significant difference between T<sub>1</sub> values of healthy controls and HT patients (SMD: 0.19; 95% CI 0.01–0.37; I<sup>2</sup> = 61%; P = 0.04, Fig. 10). The meta-regression analysis showed that in HT patients LVH was the only significant covariate which changed the I<sup>2</sup> 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 T<sub>1</sub> values of healthy controls and HT patients (SMD: 0.03; 95% CI –0.07–0.13; I<sup>2</sup> = 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 T<sub>1</sub>-mapping compared with the above-

mentioned diseases. The weighted mean MOLLI T<sub>1</sub> value measured on 1.5T was 853 ± 202 msec for DM patients,<sup>72–74</sup> 963 ± 116 msec for obesity subjects and 986 ± 87 msec for controls<sup>74</sup> (Table 1, Fig. 2). At 3T the only measured T<sub>1</sub> values were 1194 ± 32 msec for DM patients and 1182 ± 28 msec for controls<sup>75</sup> (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 T<sub>1</sub> values changes significantly in patients with HCM, DCM, MC, amyloidosis, and iron overload. This supports previously published research on the diagnostic value of native T<sub>1</sub> mapping to detect diffuse myocardial fibrosis, inflammation, iron accumulation, and protein deposition.<sup>16,77</sup> HT patients without any LVH

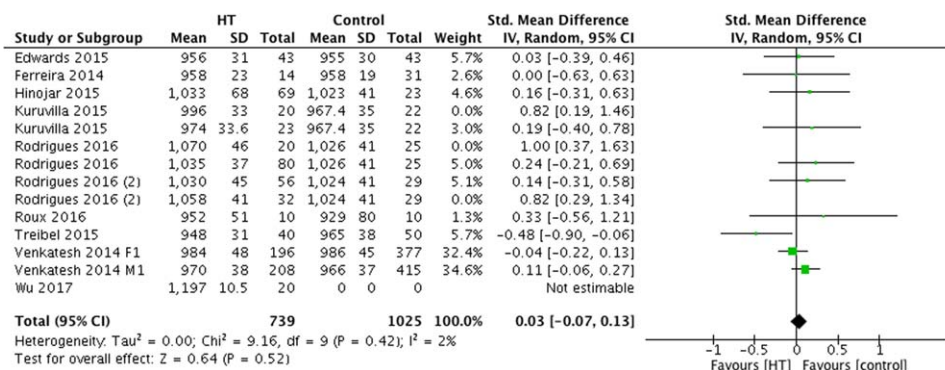


FIGURE 11: Standardized mean difference between native myocardial T<sub>1</sub> of HT patients without LVH with associated random effects weight factors, CI = confidence interval, IV = inverse variance, F1 = female subgroup, M1 = male subgroup.

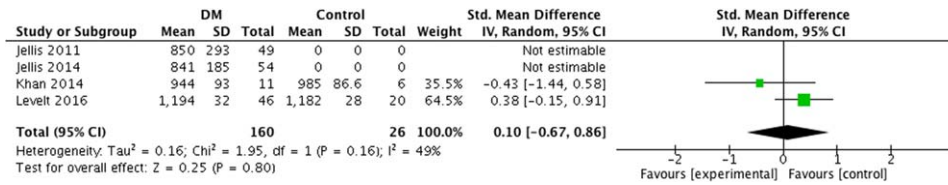


FIGURE 12: Standardized mean difference between native myocardial T<sub>1</sub> of DM patients and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

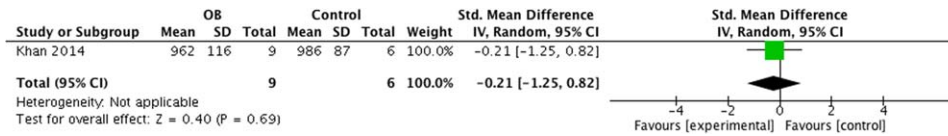


FIGURE 13: Standardized mean difference between native myocardial T<sub>1</sub> of obese (OB) populations and healthy controls with associated random effects weight factors, CI = confidence interval, IV = inverse variance.

showed no significant change in the T<sub>1</sub> value, which indicates the absence of the tissue modifications, while HT patients with LVH had a significantly increased T<sub>1</sub> 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<sub>1</sub> values.

The current meta-analysis confirms the clinical potential of T<sub>1</sub> mapping,<sup>78,79</sup> but also shows a lack of standardization considering the different reported T<sub>1</sub> values for controls. Although T<sub>1</sub> values at 1.5T seemed to vary, none of the T<sub>1</sub> values of the controls were significantly different from the expected MOLLI T<sub>1</sub> value of 950 ± 21 msec.<sup>80</sup> In studies performed at 3T, none of the T<sub>1</sub> values for controls were significantly different from the expected MOLLI T<sub>1</sub> value of 1053 ± 23 msec.<sup>80</sup> Moon et al.<sup>21</sup> stressed the need to improve standardization of T<sub>1</sub> mapping by describing protocol recommendations. However, they also state that there is no current standard for T<sub>1</sub> mapping sequences, nor for analysis and mapping methods. It is recognized that the T<sub>1</sub> value is influenced by these factors, which probably led to the inconsistencies in the reported T<sub>1</sub> values.<sup>18</sup>

In addition, the postprocessing of the T<sub>1</sub> map can also introduce bias, errors, and loss of precision, particularly in protocols using regional regions of interest (ROIs), image segmentation, variable slice orientations.<sup>21</sup> Almost half of the included studies used ROIs to determine the T<sub>1</sub>.<sup>32,35,38–42,45,49,51,53–55,57–62,66,68–71</sup> Conversely, Moon et al.<sup>21</sup> recommended global myocardial T<sub>1</sub> measurements. Puntmann et al. clearly showed the importance of this in their studies on DCM patients.<sup>11,35,42</sup> They used rectangular ROIs in the septum, the average of the whole short axis slice (SAX). The T<sub>1</sub> value for the whole SAX showed no significant difference between DCM patients and controls (P = 0.05), while the T<sub>1</sub> values in the septal ROI were significantly increased for DCM patients (P < 0.05).

In addition to this, the T<sub>1</sub> values of studies that used the segmental approach also suffered from averaging.<sup>31,38,47,48,52,59,61,67,70,72,73</sup> Furthermore, some studies used the 4-chamber plane for T<sub>1</sub> mapping,<sup>29,32,60–63</sup> 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<sub>1</sub> 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.<sup>21</sup> 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<sub>1</sub> has diagnostic value for most of the included cardiac diseases.

NICM can have subtle and diffuse fibrosis patterns that are difficult to determine<sup>11</sup> 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<sub>1</sub> values caused by the vendor, age or gender. These factors are well known to influence myocardial T<sub>1</sub> values and are important to correct for.<sup>21,81</sup> In addition, some studies<sup>32,33,36,41</sup> reported T<sub>1</sub> values of LGE-based ROIs, which is known to be highly nonspecific and misses the full representation of the disease.<sup>21,82</sup> 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<sub>1</sub>,

and although LGE is still the clinical standard to determine focal fibrosis, a change of native  $T_1$  is clearly also associated with an increase in fibrotic tissue.<sup>16</sup>

In addition to sensitivity for myocardial fibrosis,  $T_1$  values can also indicate edema formation (inflammation), and deposition of substances like protein and iron, which makes it a nonspecific parameter.<sup>16,78</sup>  $T_1$  values seem sensitive enough to differentiate between clinical disease stages of patients with myocarditis when a baseline scan and clinical records are provided.<sup>46,49,83</sup>  $T_1$  values may therefore help to follow disease progression and treatment<sup>83</sup>; however, this meta-analysis only confirms the significant changes in myocardial  $T_1$  values in the acute phase of MC.

Iron accumulation also changes myocardial  $T_1$  values by shortening the relaxation times significantly, which suggests  $T_1$  mapping is also of value in the assessment of myocardial iron loading.<sup>55,64</sup> One of the included studies<sup>57</sup> evaluated the  $T_2^*$  of an iron overload patient population and concluded that one-third had a normal  $T_2^*$  but a decreased  $T_1$  value. They state that  $T_1$  mapping might be more sensitive to iron accumulation than  $T_2^*$  imaging, but the amount of accumulated iron that correlates with these  $T_1$  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  $T_1$  values. Further research to the correlation between  $T_1$  values and the iron concentration in the myocardium is needed to determine whether  $T_1$  mapping could also be used for monitoring.

All amyloidosis studies reported a significant increase in myocardial  $T_1$  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,<sup>16</sup> which indicates that myocardial  $T_1$  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  $T_1$  mapping, which is commonly used to study amyloidosis patients.<sup>29,32,60</sup> Further research with cardiac axial slices is needed to determine the classification potential of the  $T_1$  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  $T_1$  values for HT patients without LVH. Only patients with HT in combination with LVH showed a significant change in  $T_1$  value.<sup>68,69</sup> However, all studies reported the mean  $T_1$  value, which ignores the fact that HT might be associated with inhomogeneous  $T_1$  distribution.<sup>84</sup> Further research is needed to determine the ability of  $T_1$  mapping to image this inhomogeneity and whether it is applicable to follow HT progression.

Two studies reported clearly decreased  $T_1$  values for DM,<sup>72,73</sup> 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  $T_1$  value.<sup>74</sup> However, the fat content of this myocardial steatosis is much smaller than in Fabry disease, and the number and size of  $T_1$  mapping studies was too small to determine the influencing factors in this population. Two other studies reported much higher  $T_1$  for DM patients and compared them with healthy controls, but both showed no significant change.<sup>74,75</sup> Levelt et al<sup>75</sup> used healthy control subjects with a BMI of  $28.6 \pm 5.7$ , 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  $31 \pm 5$ , which makes most of them obese. Only one study<sup>85</sup> 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  $T_1$  value, and whether it is possible to distinguish these populations from NICM patients.

$T_1$  mapping has numerous MRI-dependent and methodological factors that can influence the final  $T_1$  values.<sup>58</sup> 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  $T_1$  values at 3T are overall 100msec higher than at 1.5T. More research towards understanding the effect on accuracy, precision, and reproducibility of  $T_1$  mapping is needed.<sup>21,86</sup> Without this knowledge, it remains unknown whether the variance of the  $T_1$  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  $T_1$  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  $T_1$  mapping values.

The nonuniform reporting of data in the included studies: heterogeneity of included patient populations, methods for  $T_1$  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  $T_1$  values to enable determination of correlation. Finally, we had to compare the  $T_1$  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  $T_1$  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  $T_1$  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  $T_1$  values, although the change in  $T_1$  is opposite to that seen in noninfiltrative NICM. Further research into these risk populations is needed to determine the degree of overlap in myocardial  $T_1$  values in the healthy, cardiovascular risk, and NICM populations.

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