ORIGINAL ARTICLE

Reference Values of T1 Mapping in Healthy Individuals in 3.0 Tesla Cardiovascular Magnetic Resonance. Age and Sex Dependence and Comparison with Different Populations

Valores de referencia de T1mapping en individuos sanos en Resonancia Magnética Cardíaca 3.0 Tesla. Relación con edad y sexo. Comparación con diferentes poblaciones

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ABSTRACT

Background: T1mapping is a technique that improves tissue characterization by cardiovascular magnetic resonance (CMR), and there is growing evidence favoring its use as a tool for early diagnosis and stratification. We present the results of native myocardial T1 quantification in a 3.0 T field in healthy individuals, in order to provide local reference values.
Methods: A total of 124 consecutive adults with normal studies, referred to our center for CMR, were included in the study. T1 relaxation time was measured in a midventricular short axis slice, analyzing age and sex dependance. For comparison, 27 patients with hypertrophic cardiomyopathy, 11 with dilated cardiomyopathy and 8 with cardiac amyloidosis were also included.
Results: Mean global T1mapping of the 124 studies analyzed was 1220.7 ±21.2 msec, and rounding to unity, 1178-1263 msec (p5-p95) was considered as "normal range". A slightly longer T1 time was observed in women and no differences were found with respect to age. Excellent reproducibility was obtained, evaluated by intraclass correlation coefficient (0.97) and Bland-Altman plot. T1 mapping values were significantly higher in both groups of individuals with cardiomyopathy.
Conclusions: We report normal values of native T1 mapping in a local healthy adult population. Times were slightly higher in women, a difference that was not considered clinically relevant. When comparing with individuals with hypertrophic or dilated cardiomyopathy, a very good discrimination was obtained between the 3 populations. The interobserver variability was very low.

Keywords: Magnetic Resonance Imaging – Cardiomyopathy, Hypertrophic – Cardiomyopathy, Dilated – Amyloidosis – Cardiac Imaging Techniques.

RESUMEN

Introducción: El *T1 mapping* es una técnica que permite mejorar la caracterización tisular por resonancia magnética cardíaca (RMC), y posee creciente evidencia a su favor como herramienta de diagnóstico precoz y estratificación. Presentamos los resultados de la cuantificación del T1 nativo miocárdico en individuos sanos, estudiados en un campo de 3.0 T, a fin de proveer valores de referencia para el medio local.
Material y métodos: Se incluyeron 124 individuos consecutivos derivados a nuestro centro para realización de RMC, cuyos estudios resultaron normales. Se midió el *T1 mapping* en un eje corto medioventricular. Se analizaron los resultados según edad y sexo. Se incluyeron también 27 pacientes con diagnóstico de miocardiopatía hipertrófica, 11 con diagnóstico de miocardiopatía dilatada y 8 con amiloidosis cardíaca.
Resultados: Se analizaron 124 estudios. La media global de T1 mapping fue de 1220,7 ± 21,2 mseg. Redondeando a valores enteros, se consideró 1178-1263 mseg como "rango de normalidad" (p5-p95). Se observó un tiempo T1 ligeramente superior en mujeres. No hubo diferencias con respecto a la edad. Se observó una excelente reproducibilidad, evaluada por el coeficiente de correlación intraclase (0,97) y el método de Bland-Altman. Los valores de *T1 mapping* fueron significativamente superiores en los grupos de individuos portadores de miocardiopatía.
Conclusiones: Reportamos valores normales de *T1 mapping* nativo en una población adulta local. Los mismos son levemente mayores en mujeres, diferencia que no impresiona relevante desde el punto de vista clínico. Al comparar con individuos portadores de miocardiopatía hipertrófica, dilatada o con amiloidosis cardíaca, se obtuvo una muy buena discriminación. La variabilidad interobservador fue muy baja.

Palabras clave: Imágenes de Resonancia Magnética – Cardiomiocardiopatía Hipertrófica – Cardiomiopatía Dilatada – Amiloidosis – Técnicas de Imagen cardíaca

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INTRODUCTION

Cardiovascular magnetic resonance (CMR), in addition to being the gold standard to estimate cardiac chamber volumes, provides different techniques of tissue characterization, which confer it great applicability for the diagnosis and follow-up of multiple cardiovascular diseases. (1) Specifically, T1 relaxation time quantification at a "pixel level" (T1 mapping) has developed a growing body of evidence favoring its clinical use and reproducibility. Native T1 mapping has been postulated for the identification of diffuse myocardial fibrosis (as a complement for the detection of focal fibrosis through late gadolinium enhancement imaging), edema, amyloid deposit, iron overload and lipid accumulation (e.g. Anderson-Fabry disease). (2) To maximize diagnostic precision, it is highly relevant to establish a technical standard and analyze the relationship of these variables with age and sex, among others. Since the imaging acquisition method varies for each scanner manufacturer and model, there are no universal cut-off points. Moreover, most published studies have used 1.5 Tesla (T) magnetic strength scanners. Use of high field strength (3.0T) machines with greater signal gain would increase temporal and spatial resolution. (3)

We present native myocardial T1 quantification results in apparently healthy individuals, studied with 3.0T field scanners, to provide local reference values. In addition, patients with hypertrophic cardiomyopathy (HCM), non-ischemic dilated cardiomyopathy (DCM) and cardiac amyloidosis (CA) diagnosis were studied to assess native T1 relaxation time in these cases.

METHODS

This was a single-center, cross-sectional study.

Study population

A total of 124 individuals, referred to our center for CMR imaging, whose result was considered normal by two independent investigators, were included in the study. Subjects had to fulfill the following criteria to be considered "normal": a) no personal or family history of cardiovascular disease (CD); b) no chronic medication; c) being asymptomatic; d) presenting with preserved chamber volumes and biventricular regional motility in the CMR; e) not presenting pathological late gadolinium enhancement (4 patients with focal, slightly extended enhancement, at the junction zone were included). Twenty-seven patients with HCM, 11 with DCM and 8 with CA were simultaneously included.

CMR study

In all cases, a 3.0T high-field Philips Ingenia® V5 scanner (Philips Healthcare, Best, The Netherlands) equipped with an advanced cardiac package including magnetic field radiofrequency shimming techniques (MultiTransmit) was used to perform CMR. Carbon, non-ferromagnetic electrodes were placed to obtain electrocardiographic-gated images. A surface multiple-detector antenna was placed on the thorax. Axial anatomical images were acquired with black blood sequence [T1 single shot turbo spin echo (TSE)]. Turbo spin-echo sequences were used for T1 and T2 short-T1 inversion recovery (STIR) images. Cine-images were performed with balanced-fast field echo (FFE) sequences. Post-contrast images were obtained after 0.3 mmol/Kg gadolinium infusion and T1 adjustment, with phase-sensitive inversion-recovery (PSIR) turbo field echo (TFE) sequences. A modified Look-Locker (MOLLI) sequence, a balanced steady state precession, requiring brief apnea of approximately 12 seconds, was used to obtain T1 mapping images from a single short-axis midventricular slice, before contrast administration. This was programmed with the following parameters: time to echo (TE)/repetition time (RT)/flip-angle (FA): 1.02 ns/2.2 ns, voxel size 2 × 2 × 10 mm, n = 166 phase-encoding steps, 11 three-inversion images (3 + 3 + 5) with pauses after three heart beats before the second and the third inversion and an adiabatic pre-pulse.

Image analysis

A commercially available software (ViewForum®, Extended Workspace, Philips Healthcare, The Netherlands) was used to perform routine CMR analysis by two independent investigators (LD and PS), a physician and a radiology technician, both with over 5 years of experience in the acquisition of CMR studies. Myocardial native T1 values were quantified placing a conservative "region of interest" (ROI) at the septal level, taking care of not contaminating the measurement with a ventricular chamber signal. In the case of individuals suffering from cardiomyopathy, the ROI was intentionally placed in segments with no late gadolinium enhancement.

Statistical analysis

Stata 14.0 (StataCorp LLC, College Station, Texas, USA) software package was used for statistical analysis. Normal distribution was evaluated through histogram inspection and normal probability graph, and also using the Kolmogorov-Smirnov test. Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation or median and interquartile range, as appropriate. Student's t test or one-way analysis of variance (ANOVA with Bonferroni post-hoc test) were used to compare two or three variables, respectively. Simple linear or multivariate regression analysis was employed to explore variable association. Interobserver variability was analyzed using the Bland-Altman method and the intraclass correlation coefficient.

Ethical considerations

This study was carried out according to current international ethical guidelines to perform studies in human beings, as stated in the Declaration of Helsinki (World Medical Association, 1964, last updated 2013 version).

All study data were treated with maximum confidentiality, in anonymous and codified manner, with access restricted only to authorized personnel for study purposes, according to current legal regulations established by the National Personal Data Protection Law No. 25 326 (Habeas Data Law). An informed consent was waived since it was a non-interventional study, with retrospective data emerging from usual medical practice.

RESULTS

Study population

A total of 124 consecutive patients with a CMR study considered as normal were included in the study between January 2018 and June 2020. Additionally, in the same period, 30 patients with HCM and 14 pa-

tients with DCM were identified, but as 3 studies per group were excluded due to poor image quality, 27 and 11 patients, respectively, were finally included. Also, 8 patients with CA were incorporated in the study.

Baseline population characteristics are detailed in Table 1a. There was adequate age (52 between 18-39 years, 74 between 40-59 years, 36 ≥ 60 years) and sex (49% women) representation among apparently healthy individuals.

The most common reason for CMR indication was the presence of frequent ventricular extrasystoles (36%), followed by HCM/DCM/right ventricular arrhythmogenic dysplasia (35%). (See Table 1b for more details).

Cardiovascular magnetic resonance results in healthy individuals are described in Table 1c.

Normal T1 mapping values. Relationship with age and sex. Interobserver variability.

Mean global T1 mapping was 1220.7±21.17 msec. Taking this value as reference and rounding to unity, a global "normal range" of 1178-1263 msec (p5-p95) could be established. The maximum and minimum values observed were 1169 and 1270 msec, respectively.

A slight but significantly higher native T1 was observed in women: 1228.1±18.9 vs. 1213.6±20.9 msec, p=0.0001.

Considering p5-p95 as "normal range", differential ranges: 1172-1255 msec for men and 1190-1266 msec for women could be established.

Interobserver variability, evaluated with the Bland-Altman plot (Figure 1) evidenced good reproducibility. The intraclass correlation test also showed excellent correlation (0.97).

Comparison of T1 mapping values with cardiomyopathy patients

Table 2 shows T1 mapping estimated results in the different groups. Native values were significantly higher in the three groups of cardiomyopathy patients. Moreover, the difference between HCM individuals with respect to DCM or CA patients was also statistically significant (difference of means: -31.6; 95 CI -60.4 to -2.8; p=0.03, and -99.5; 95 CI -138.3 to -60.7; p<0.00001, respectively). Figure 2 shows boxplot results.

Table 1. Population baseline characteristics

1a.	**n=124**
Age, years	43 (IQR 36-56)
Female sex	61 (49%)
Weight, kg	75 ±15
Height, cm	168.5 ±9.8
BSA (m^2)	1.86 ±0.22
1b. Reason	**n (%)**
Frequent ventricular arrhythmia	45 (36.3%)
Suspected HCM	29 (23.4%)
Suspected NCCM/RVAD	14 (11.3%)
Volume assessment/EF	4 (3.23%)
Other (heart valve diseases/suspected intracardiac shunt myocarditis/eval. Aorta/changes in ergometry/other)	32 (25.8%)
1c. Cardiovascular magnetic Resonance	
Left ventricle	
EDV (ml)	145±28
ESV (ml)	52±14
SV (ml/beat)	94±17
EF (%)	64.7±4.89
Ventricular mass (g)	91±29.5
Indexed EDV (ml/m^2)	78±12.6
Indexed ESV (ml/m^2)	28±6.8
Indexed ventricular mass (g/m^2)	48±13.5
Right ventricle	
EDV (ml)	159±35
ESV (ml)	66±19
SV (ml/lat)	93±18
EF (%)	59±4.9
Indexed EDV (ml/m^2)	85±15.3
Indexed ESV (ml/m^2)	35.1±8.7

BSA: Body surface area; HCM: Hypertrophic cardiomyopathy; NCCM: Non-compacted cardiomyopathy; RVAD: Right ventricular arrhythmogenic dysplasia; EF: Ejection fraction; EDV: End-diastolic volume; ESV: End-systolic volume; SV: Stroke volume.

Table 3 details ROC analysis results, as well as the diagnostic yield of the initially postulated native T1 cut-off point (1263 msec). Considering all the diagnostic alternatives as a whole, the chosen cut-off point exhibited 71.74% sensitivity and 97.6% specificity (90.6% correctly classified), and an area under the ROC curve (AUC) of 0.91 (Table 3). Logically, higher cut-off values provide greater specificity (>99% for 1270 msec), while lower ones improve sensitivity (>80% for 1255 msec).

DISCUSSION

This study reports normal native T1 values (pre-contrast T1 mapping) in a local adult population, using a 3.0T scanner. In addition, the possible association with age and sex was explored and it was compared with three small samples of patients with HCM and DCM or CA.

Native T1 essentially depends on three factors (2): tissue composition (extracellular volume/intracellular volume ratio), the magnet used (1.5 vs. 3.0 T are practically the only ones used in CMR) and its isolation, and the sequence used (depending on the scanner brand/model and sequence setup). The assessment of this time is recognized as a very useful tool in the identification of normal myocardium, (4) and is also used to diagnose, stratify and monitor the treatment of different cardiac diseases (amyloidosis, myocarditis and Anderson-Fabry disease, among others). (5) As most T1 mapping reference values stem from studies performed with 1.5T scanners, we consider it is relevant to provide data of our experience with a 3.0T magnet. Normal values may vary widely depending on the scanner and adjust sequence, which highlights even more the importance of acquiring local normal values and review them periodically.

In agreement with previously published studies, (4) native T1 at 3.0T is slightly but significantly higher in women than in men. No relationship between age categories and T1 values was found.

Compared with other published studies using 3.0T scanners, only Roy et al. (6) used the same machine employed in our work (Philips Ingenia® V5), reporting a mean value of 1162±81 msec. In a sample of 30 individuals, using a different model (Philips Achieva® TX), Putmann et al. found T1 values closer to those obtained with a 1.5T scanner (1070±50 msec). (7)

Similar differences were observed between studies published with Siemens scanners: Liu et al., with an S. Avanto® and a sample of 80 individuals, reported a mean of 1230±50 msec (8), while von Knobelsdorff-Brenkenhoff et al. (9), in a S. Magnetom Verio® found mean values of 1159±41 msec.

This variability can be explained by the technique used: sequence setup, slice obtained (midventricular short axis vs. long or combined axes) and ROI placement (septal vs. average of all the segments).

Regarding a dissimilar mean value according to biological sex, this finding has not been consistent in different studies. Some groups have reported disparities (6) whereas others have not found significant differences. (8) Something similar occurs in studies with 1.5T scanners; MESA study (10) or Pienchik et al. (11) observed a slightly higher T1 value in women, while Dabir et al (12) found no differences.

Concerning age, our and other groups observed

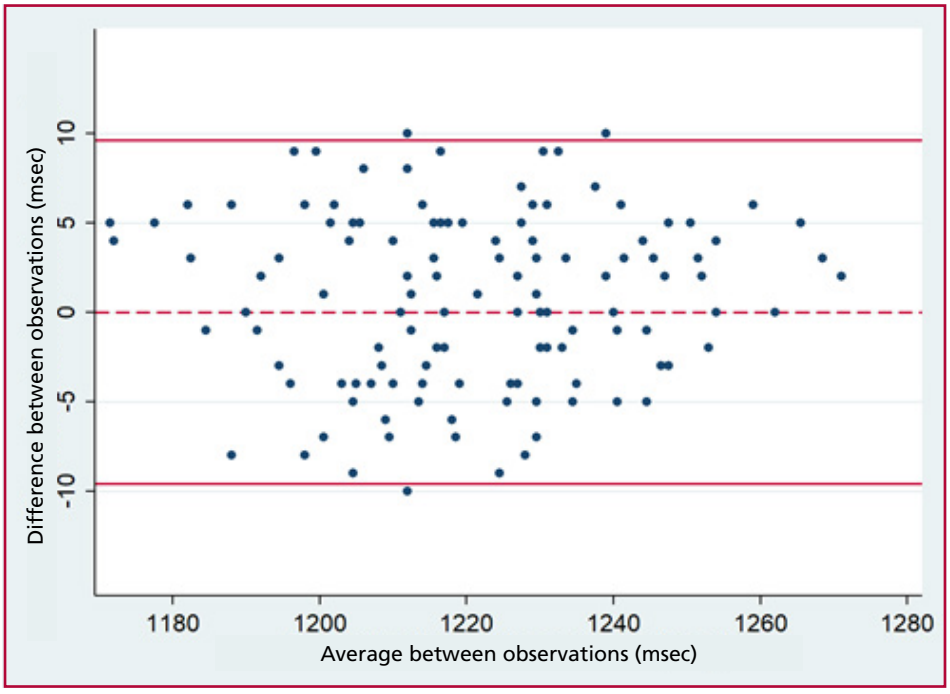

Fig. 1. Bland-Altman plot.

Table 2. Comparison between results obtained in the apparently healthy population and the different groups of patients with heart disease

	Healthy (n=124)	HCM (n=27)	DCM (n=11)	CA (n=8)	p
Native T1	1220.7±21.17	1268.9±41	1300.5±36.1	1367,8 ± 65,8	<0.00001

HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; CA: Cardiac amyloidosis.

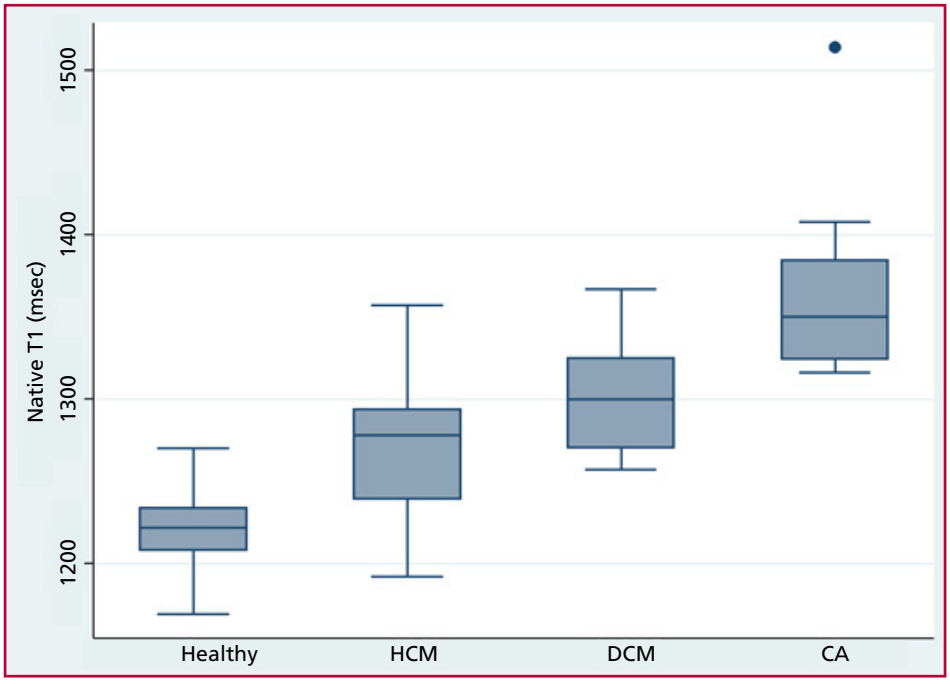

Fig. 2. Native T1 mapping boxplot in the different populations. HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; CA: Cardiac amyloidosis.

Table 3. Proposed upper cut-off point diagnostic yield (1263 msec) for the discrimination of populations with heart disease versus apparently healthy individuals. All patients with heart disease were considered as a single group to estimate the "Total".

	Mean (SD)	Sensitivity	Specificity	AUC ROC (95% CI)
HCM	1268.9 (41)	55.56%	97.58%	0.85 (0.75-0.956)
DCM	1300.5 (36.1)	90.91%	98.39%	0.995 (0.959-0.9998)
CA	1367.8 (65.8)	100%	97.58%	1
Total	-	71.74%	97.6%	0.911 (0.85-0.98)

AUC: Area under the ROC curve. HCM: Hypertrophic cardiomyopathy; DCM: Dilated cardiomyopathy; CA: Cardiac amyloidosis.

no differences, whereas some studies demonstrated an age related increased native T1, especially in men, both at 3.0T (6) as at 1.5T (13-15). Although two different cut-off points could be considered according to biological sex (1266 msec for women and 1255 msec for men), we acknowledge that these are preliminary data that would need prospective validation. A global cut-off point was used for this work (1263 msec) and the discrimination of healthy individuals vs. patients with heart disease was very good.

Considering that T1 mapping alone is not a specific diagnostic criterion for practically any condition, and that the difference observed between men and women does not impress as clinically relevant, the authors consider that it is preferable to prioritize the simplicity of using the same cut-off point for both sexes.

Reproducibility was good, since interobserver variability was marginal and similar to that published. (16)

Limitations

This study presents some limitations. Firstly, it is a single center study, using a single sequence in a moderate-sized Caucasian group of individuals. Secondly, although participants fulfilled "apparently healthy" criteria, as they were not volunteers, some selection bias could have occurred and/or inadvertently some individuals with non-evident heart disease could have been included (since it was a cross-sectional study, no follow-up data was available). Lastly, it was not pos-

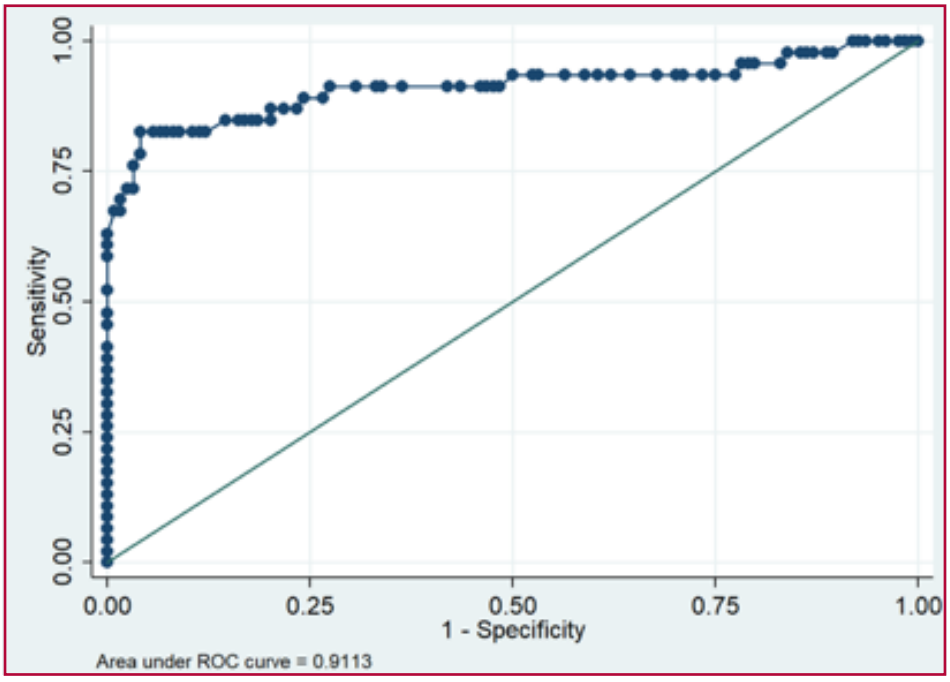

Fig. 3. ROC curve analyzing all cardiac disease diagnoses as a whole. The discrimination with the healthy population was excellent (AUC ROC=0.911).

sible to perform a hematocrit assessment at the time of the study, hampering the estimation of the extracellular volume fraction.

CONCLUSIONS

This study reports normal native T1 mapping values in a local adult population, which seem to be associated with sex (slightly higher in women) but not with age. This difference between sexes does not impress as relevant from a clinical viewpoint. The comparison with hypertrophic and dilated cardiomyopathy and amyloidosis patients revealed good discrimination between the populations. Finally, interobserver variability was very low, estimated by an experienced physician and radiology technician.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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