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ORIGINAL PAPER

Left ventricular myocardial T1 mapping and strain analysis evaluate cardiac abnormality in hypothyroidism

Min Liu[1] · Weifang Liu[1] · Peiyao Zhang[1] · Jing An[2] · Guang Wang[3]

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Abstract

Cardiovascular Magnetic Resonance (CMR)-based T1 mapping and Heart Deformation Analysis (CMR-HDA) can assess the myocardial tissue characteristic and strain of cardiomyopathy. Whether they can assess cardiac abnormality of hypothyroidism (HT) is unknown. We aim to analysis left ventricular (LV) T1 values and strain of patients with overt HT (OHT) and subclinical HT (SHT) with CMR-based T1 mapping and HDA. This study prospectively included 32 OHT patients, 23 SHT patients and 27 healthy controls who underwent CMR. LV T1 mapping was obtained with a Modified Look-Locker Inversion Recovery sequence while LV circumferential strain (LVCS) and radial strain (LVRS), LV longitudinal strain (LVLS) were respectively analyzed on the short-axial and four-chamber cines with HDA. LV Eject Fraction among three groups were similar ($p=0.676$). LV myocardial T1 correlated with LVCS ($r=0.734$, $p<0.001$) and LVRS ($r=-0.340$, $p=0.011$). LV myocardial T1 of OHT patients significantly increased in comparison with SHT patients ($t=5.403$, $p<0.001$) and normal controls ($t=10.197$, $p<0.001$), meanwhile, LV myocardial T1 of SHT patients were higher than that of controls ($t=2.629$, $p=0.013$). Compared with SHT patients ($t=1.925$, $p=0.031$) and normal controls ($t=2.875$, $p=0.006$), LVCS of OHT patients reduced while LVCS of SHT patients were lower than that of normal controls ($t=2.451$, $p=0.020$). LVRS of SHT patients were higher than OHT patients ($t=2.778$, $p=0.008$), but comparable to normal controls ($t=1.134$, $p=0.266$). LVLS of SHT and OHT significantly impaired in comparison with normal control. The increased LV myocardial T1 value and reduced strain were found in HT. CMR-based LV myocardial T1 and stain analysis are useful to evaluate myocardial tissue characteristic and mechanics in both overt and subclinical hypothyroidism.

Keywords Hypothyroidism · Cardiovascular magnetic resonance imaging · T1 mapping · Heart deformation analysis · Strain

Abbreviations

CMR	Cardiovascular magnetic resonance
HDA	Heart deformation analysis
HT	Hypothyroidism
OHT	Overt hypothyroidism
SHT	Subclinical hypothyroidism
LVCS	Left ventricular circumferential strain
LVRS	Left ventricular radial strain
LVLS	Left ventricular longitudinal strain
LVSS	Left ventricular shear strain
LVEF	LV eject fraction
TSH	Thyroid-stimulating hormone
FT4	Free thyroxine
FT3	Free triiodothyronine
Tg-Ab	Antithyroglobulin
TPO-Ab	Antithyroid peroxidase antibody
TE	Echo time
TR	Repetition time
MOLLI	Modified look-locker inversion recovery
SSFP	Steady state free precession
ESV	End diastolic volume
EDV	End systolic volume
SV	Stroke volume
ECV	Extracellular volume fraction

✉ Min Liu
mikie0763@126.com

[1] Department of Radiology, China-Japan Friendship Hospital, 2 Yinghua Dong Street, Hepingli, Chao Yang District, Beijing 100029, China

[2] Collaborations NE Asia, Siemens Healthcare, Wang JingRoad No.9, Beijing 100019, China

[3] Department of Endocrinology, Beijing Chaoyang Hospital of Capital Medical University, Bai jia zhuang Road No.8, Beijing 100020, China

Introduction

Hypothyroidism (HT) is a pathological condition defined by increased serum thyroid-stimulating hormone (TSH). Clinically, serum thyroid hormones including free thyroxine (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH), are biomarkers to evaluate hypothyroidism. According to serum thyroid hormones, HT is classified into the overt hypothyroidism (OHT) and subclinical hypothyroidism (SHT) [1]. OHT is a state of decreased serum FT4 and FT3 with increased TSH while SHT is a generally asymptomatic condition defined as normal FT3 and FT4 with elevated TSH. Cardiovascular system is the major target organ for thyroid hormone action [2].Hypothyroidism leads to impaired cardiovascular function and possibly heart failure, Once OHT is confirmed, oral l-thyroxine replacement therapy starts as soon as possible. Serum thyroid hormones are clinically used to evaluate treatment effect, however rat's model with surgical thyroidectomy suggest serum thyroid hormone levels may not accurately reflect thyroid tissue levels and cardiac function in mild hypothyroidism [3]. Otherwise, since evidence of myocardial abnormality of SHT was not enough, currently, oral L-thyroxine replacement therapy for SHT patients is controversial.

Ventricular function or mechanics of HT have been assessed with echocardiography [4, 5]. Cardiovascular magnetic resonance imaging (CMR) is the gold standard of cardiac function quantification. CMR-based Heart deformation analysis (CMR-HDA) is a new developed imaging processing technique for quantification of global or regional myocardial function and mechanic on cine images of CMR without the need for myocardial tagging [6, 7]. CMR-based T1 mapping is an emerging clinical biomarker for the quantification of myocardial tissue characterization. Researches [8, 9] documented that myocardial T1 increased with myocardial edema or fibrosis. Gao et al. [10] showed left ventricular (LV) T1 of OHT patients increased and LV Eject Fraction (LVEF) was comparable to the normal controls. Yao et al. [11] found that LV T1 values increased in SHT patients. At present, the correlation of LV myocardial T1 and strain of HT has not been assessed by CMR. Therefore, this study aimed to assess LV myocardial T1 and strain of patients with OHT and SHT, and to determine the correlation between LV myocardial T1 and mechanics.

Materials and methods

Subjects

From January 2015 to September 2017, female patients with untreated HT due to Hashimoto's thyroiditis were included prospectively. The inclusion criteria were age ($20 < age < 60$ years) and increased serum TSH, antithyroglobulin (Tg-Ab) and antithyroid peroxidase antibody (TPO-Ab). Only patients who underwent CMR were included in the analysis .The exclusion criteria were male patient, pregnancy, secondary HT, hyperthyroidism, idiopathic cardiomyopathy, hepatic or renal dysfunction, and malignancy. The control group was composed of age-matched females from a population of healthy volunteers with normal serum FT3, FT4, TSH, Tg-Ab, TPO-Ab and normal thyroid ultrasound findings. None of the subjects received medications that can alter serum thyroid hormone concentrations. The study complies with the Declaration of Helsinki. The protocol was approved by the Research Ethics Committee of our Hospital and all participants provided written informed consent.

Thyroid hormones test

All participants underwent thyroid hormone test including TSH, FT3, FT4 as well as Tg-Ab and TPO-Ab test in the same day with CMR. Serum FT3, FT4, and TSH were assessed using the microparticular enzyme immunoassay method (Axsym, Abbott, USA) and normal limits were assumed as 1.71–3.71 pg/ml, 0.7–1.48 ng/dl and 0.35–4.94 μIU/ml for FT3, FT4 and TSH, respectively. Tg-Ab and TPO-Ab were assessed using radioimmunoassay with the normal limits as 0–4.11 IU/ml and 0–5.61 IU/ml, respectively.

CMR

CMR studies were performed on the clinical 3T MR system (Magnetom Trio, Siemens Healthcare, Erlangen, Germany). A 12-elements phase array coil with six anterior and six posterior elements was used for data acquisition. After localization, Cardiac cine images were acquired as a series of single breath-hold balanced steady-state free precession images including multiple short-axis stacks. Each slice was 8 mm thick with a 1.6-mm gap and was retrospectively gated with echo time (TE)/repetition time (TR) = 44.2 ms/1.4 ms, flip angle = 50°, temporal resolution = 40 ms. For cardiac T1-map, prototype Modified Look-Locker Inversion recovery (MOLLI) maps were generated from the matched short-axis cines with the following acquisition

parameters: TE/TR = 314.9/1.1 ms, flip angle = 35°, field of view = 340 × 255 mm^2, matrix size = 192 × 144, 107 phase-encoding steps, interpolated pixel size = 0.9 × 0.9 mm^2, GRAPPA = 2, 24 reference lines, cardiac delay time TD = 500 ms, 206 ms acquisition time for a single image, phase partial Fourier 6/8. Each slice was 8 mm thick with a 1.6 mm gap. To generate a pixed-wise myocardial T1-map, single-shot SSFP images were acquired at different inversion times and registered prior to a non-linear least-square curve fitting. If necessary, shimming and center frequency adjustments were performed to generate images with minor off-resonance artifacts.

CMR analysis

LV myocardial T1 and strains including circumferential strain (LVCS), radial strain (LVRS) as well as shear strain (LVSS) in the matched short-axial mid-ventricular slice were respectively assessed by two residents blinded to the clinical information. LV Eject Fraction (LVEF) and longitudinal strain (LVLS) were measured by the 3rd residents independently. Cardiac T1-maps and cines were transferred to a Syngo Multi Modality workstation (Siemens Healthcare, Erlangen, Germany) and short-axis T1 maps were manually contoured to outline the endo- and epicardium on the mid-ventricular slice to measure an average native T1 value of short-axial mid-ventricular slice. With use of Argus software (Siemens Healthcare, Erlangen, Germany), the LV endo- and epicardial borders were traced on consecutive short-axis cine images at end-systole and end-diastole for LVEF. Short-axial midventricular and four-chamber cines were transferred to a HDA prototype software (Trufi Strain Version 1.0, Siemens Corporation, Princeton, NJ). After the epi-cardial and endocardial border were manually drew, LVCS, LVRS and LVSS were automatically displayed on the short-axial cine images. Left ventricle on 4-chamber cines were manually defined on a single end-diastolic phase before being automatically propagated through all cardiac phases and LVLS were derived from deformation fields on 4-chamber cine images. Care was taken to avoid LV cavity blood pool and potential partial volume effects at the endo- and epicardial borders.

Statistical analysis

Data were analyzed using SPSS 11.0 (SPSS Inc; Chicago, IL, USA). All data are expressed as means ± standard deviation or median, unless otherwise specified. One-way ANOVA test and the LSD-t test or Mann–Whitney U test was used to compare clinical data among three groups and Spearman's correlation analysis was used to correlate LV T1 with serum thyroid hormone levels and strain. Two-sided $p < 0.05$ was considered statistically significant.

Table 1 Clinical data of study population

Clinical data	Control (n = 27)	Subclinical HT (n = 23)	Overt HT (n = 32)
Age (years)	35.1 ± 6.3	36.1 ± 9.9	36.7 ± 8.3
TPO-Ab (IU/ml)*	3.1	1591.7	1488.6
TG-Ab (IU/ml)*	0	159.1	416.6
FT3 (pg/ml)	2.48 ± 0.14	2.47 ± 0.09	1.68 ± 0.12
FT4 (ng/dl)	1.18 ± 0.08	0.90 ± 0.05	0.48 ± 0.03
TSH (μIU/ml)	2.19 ± 0.19	32.57 ± 8.68	89.40 ± 6.83

TPO-Ab and Tg-Ab are expressed as *Median value; other data were expressed as means ± standard deviation; *HT* hypothyroidism, *TPO-Ab* antithyroid peroxidase antibody, *Tg-Ab* antithyroglobulin, *FT4* free levothyroxine, *FT3* free triiodothyronine, *TSH* thyroid stimulating hormone

Results

Patient characteristics

32 OHT and 23 SHT patients as well as 27 healthy controls were included. Baseline clinical characteristics and laboratory findings were presented in Table 1. Ages among three groups were similar. TPO-Ab of the OHT group was significantly higher than the control group ($U = 41.0$, $p < 0.001$) and comparable to the SHT group ($U = 156.0$, $p = 0.805$). Similarly, Tg-Ab of the OHT group was significantly more than the control group ($U = 57.0$, $p < 0.001$), and comparable to the SHT group ($U = 160.5$, $p = 0.894$). FT3 of the OHT group was significantly lower than the SHT ($t = -8.326$, $p < 0.001$) as well as the control group ($t = -6.607$, $p < 0.001$) while FT3 of the SHT group was similar to control group ($t = 1.205$, $p = 0.233$). FT4 of the OHT group decreased significantly by comparison with the SHT ($t = -11.108$, $p < 0.001$) and control group ($t = -12.641$, $p < 0.001$) .FT4 of the SHT group was lower than the control group ($t = -3.532$, $p = 0.001$). TSH of the OHT group was higher than that in SHT ($t = 5.492$, $p < 0.001$) and control group ($t = 10.046$, $p < 0.001$) while TSH of SHT group was higher than that of control group ($t = 4.756$, $p < 0.001$).

CMR T1 mapping and strain

LV T1 maps, LVCS, LVRS and LVSS of OHT, SHT and normal controls on the matched short-axial mid-ventricular slice are respectively shown in Figs. 1, 2 and 3. LVLS of the four-chamber cines are shown in Fig. 4. FT3, FT4 and TSH respectively were 2.1 ± 0.7 pg/ml, 0.8 ± 0.3 ng/dl, and 51.2 ± 49.5 μIU/ml. Table 2 demonstrated LV myocardial T1, LVLS, LVCS inversely correlated with FT3, FT4 and positively correlated with TSH. LVRS weakly correlated with FT3 ($r = 0.209$, $p = 0.018$), but not with FT4 ($r = 0.076$, $p = 0.391$) or TSH ($r = -0.114$, $p = 0.199$). LVSS weakly

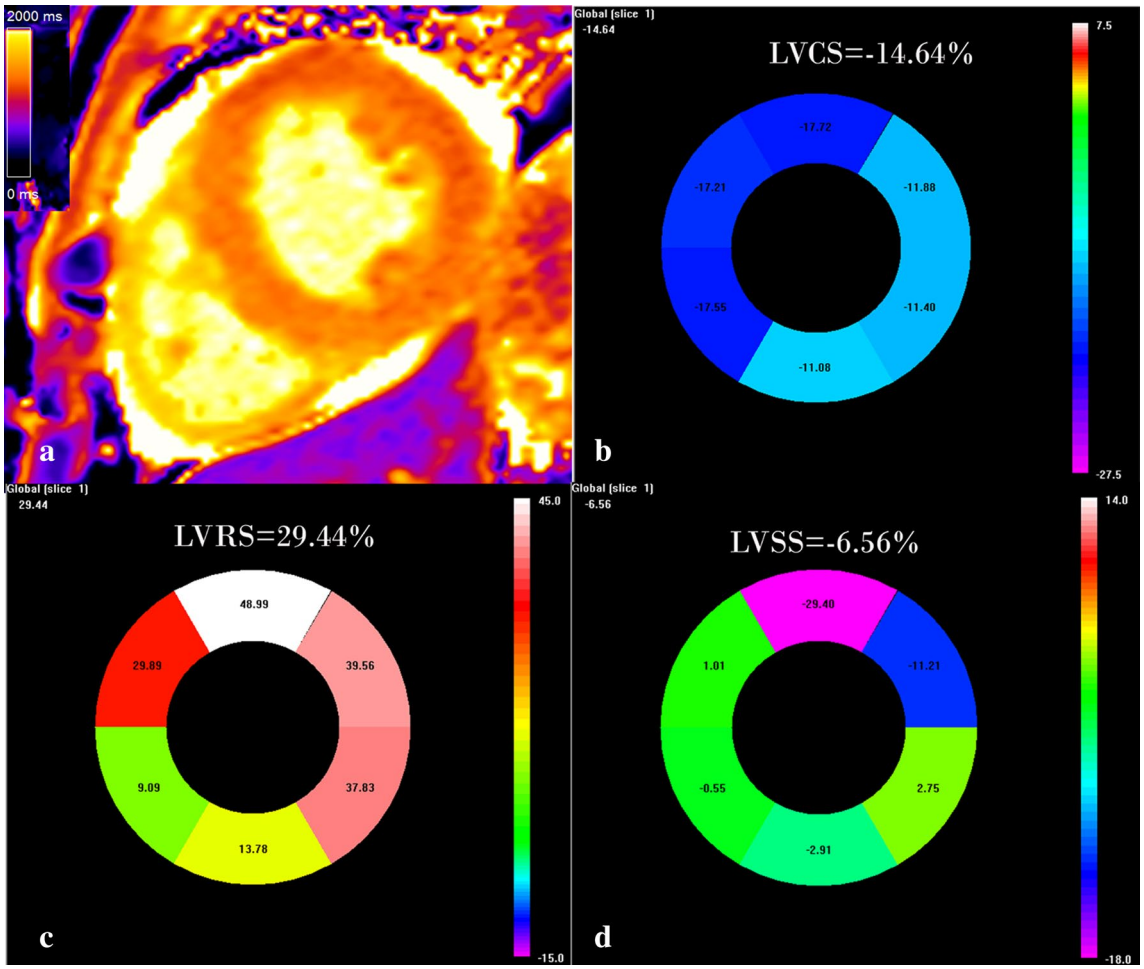

Fig. 1 CMR T1-map and strain from the short-axial mid-ventricular slice of a 37-year-old OHT patient: **a** native T1 map, LV T1 = 1319.8 ms; **b** LV circumferential strain = − 14.64%; **c** LV radial strain = 29.44%; **d** LV shear strain = − 6.56%

correlated with FT3 (r = 0.261, p = 0.003), but not with FT4 (r = − 0.173, p = 0.051) or TSH (r = − 0.158, p = 0.075). As shown in Fig. 5, LV myocardial T1 correlates with LVCS (r = 0.734, p < 0.001) and inversely with LVRS (r = − 0.340, p = 0.011). There was no significantly correlation between LV myocardial T1 and LVSS (r = 0.101, p = 0.423) in HT patients.

Table 3 demonstrated LVEF, ESV were comparable among three groups while EDV and SV increased in OHT and SHT in comparison of healthy controls. LV myocardial T1 of OHT patients was significantly increased in comparison with SHT patients (t = 5.403, p < 0.001) and normal controls (t = 10.197, p < 0.001), moreover, T1 of SHT patients was more than that of normal controls (t = 2.629, p = 0.013). Figure 6 showed LVLS of OHT and SHT significantly decreased in comparison of normal control. LVCS of OHT patients were decreased in absolute value in comparison with SHT patients (t = 1.925, p = 0.031) and normal controls (t = 2.875, p = 0.006) while LVCS of SHT patients was less in absolute value than that of normal controls (t = 2.451, p = 0.020). LVRS of SHT patients was comparable to normal controls (t = 1.134, p = 0.266), but more than OHT patients (t = 2.778, p = 0.008). LVSS were similar among the three groups (F = 0.926, p = 0.402).

Discussion

To our knowledge, this is the first study to assess cardiac abnormality with CMR-based T1 mapping and strain analysis with heart deformation analysis (HDA) of patients with hypothyroidism. There are several important findings in the current study: (I) LV myocardial T1, LVLS, LVCS inversely correlated with FT3. (II).LV myocardial T1 correlated with LVCS and LVRS. (III) Patients with OHT had the elevated LV myocardial T1 and impaired LVLS, LVCS as well as LVRS. (III) In comparison with normal controls,

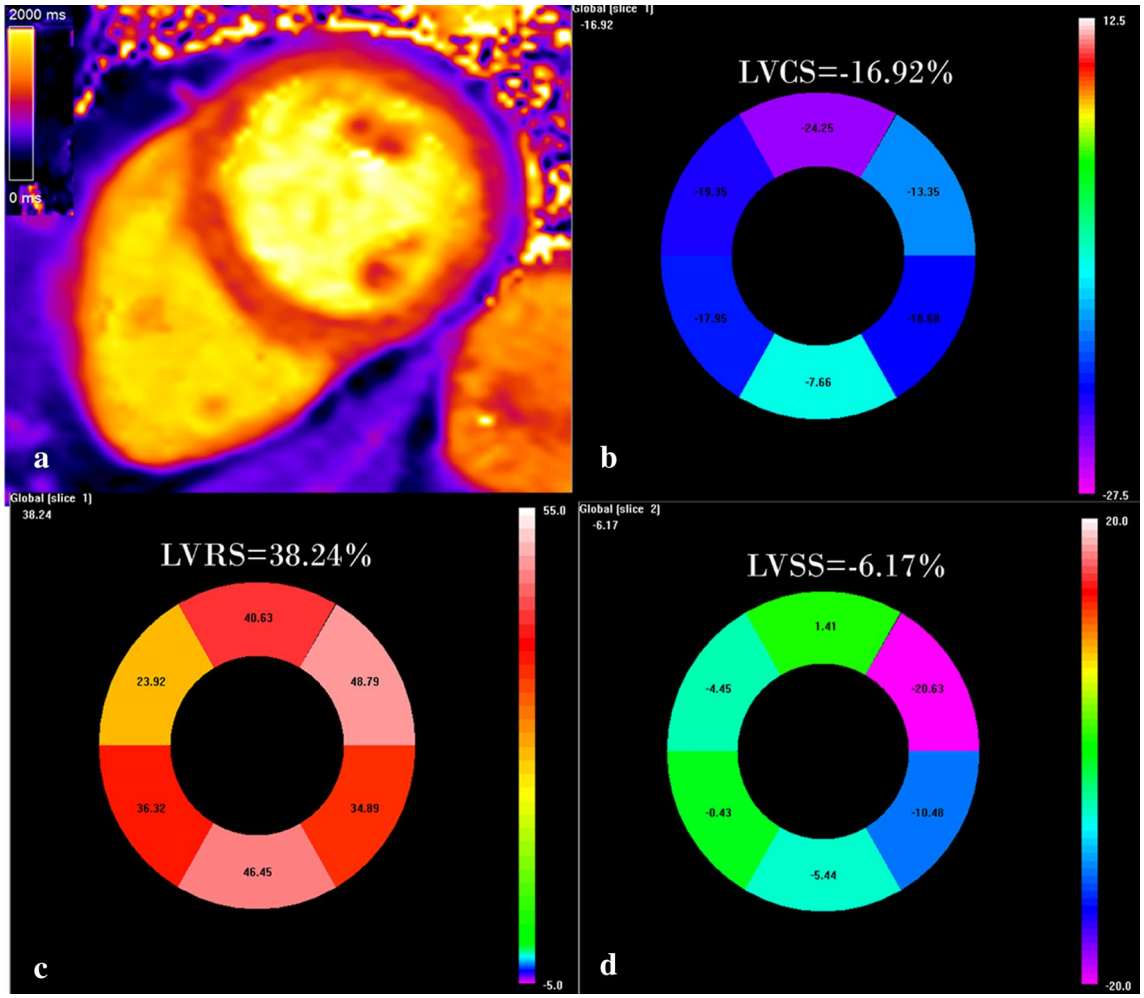

Fig. 2 CMR T1-map and strain from the short-axial mid-ventricular slice of a 37-year-old SHT patient: **a** native T1 map, LV T1 = 1184.6 ms; **b** LV circumferential strain = − 16.92%; **c** LV radial strain = 38.24%; **d** LV shear strain = − 6.17%

LV myocardial T1 of SHT patients increased while LVLS, LVCS were reduced.

CMR T1 mapping has the potential to quantify local or diffuse myocardial abnormality in a noninvasive way. OHT patients had an elevated LV myocardial T1 in comparison with healthy controls, which is consistent with Gao's findings [10]. Autopsy study [2] revealed myofibrillar swelling with diffuse interstitial fibrosis in HT. In OHT, elevated T1 may be related with the myogfibrillar swelling. LV myocardial T1 of SHT patients also increased compared to normal controls. Serum FT3 is the bioactive hormone that is known to affect tissue oxygen consumption and cardiovascular performance [12]. In SHT patients, increased LV myocardial T1 suggest myocardial injury might occur even whose serum FT3 were normal. SHT could alter collagen, myocardial fiber orientation, tissue water content, and capillary blood flow distribution [13], however, the mechanism of the elevation of LV myocardial T1 remains unclear. Thyroid hormone correlated with LV myocardial T1, indicating that decreased serum thyroid hormone might associate with the myocardial diffused abnormality and T1 value can be regarded as noninvasive surrogate of mild myocardial injury induced by HT.

Studies [5, 14, 15] have suggested that myocardial strain may provide earlier disease detection. Tissue tracking technologies [5, 15] such as speckle tracking echocardiography, CMR-based Feature (Tissue) Tracking and HDA [16] have enhanced the noninvasive assessment of the mechanics of cardiac chambers. Some echocardiographic studies [5, 15] have shown HT is associated with impaired cardiac strain. With HDA, our results showed that LVLS, LVCS and LVRS in OHT significantly reduced in comparison with normal control, which were consistent with the speckle tracking echocardiography study [15], suggesting the transmural myocardial dysfunction in OHT. Tadic et al. [5] showed LVLS and LVCS were significantly decreased in SHT patients before therapy in comparison with the controls or SHT patients after therapy. Our results showed that LVLS, LVCS of SHT was lower than that of normal control while

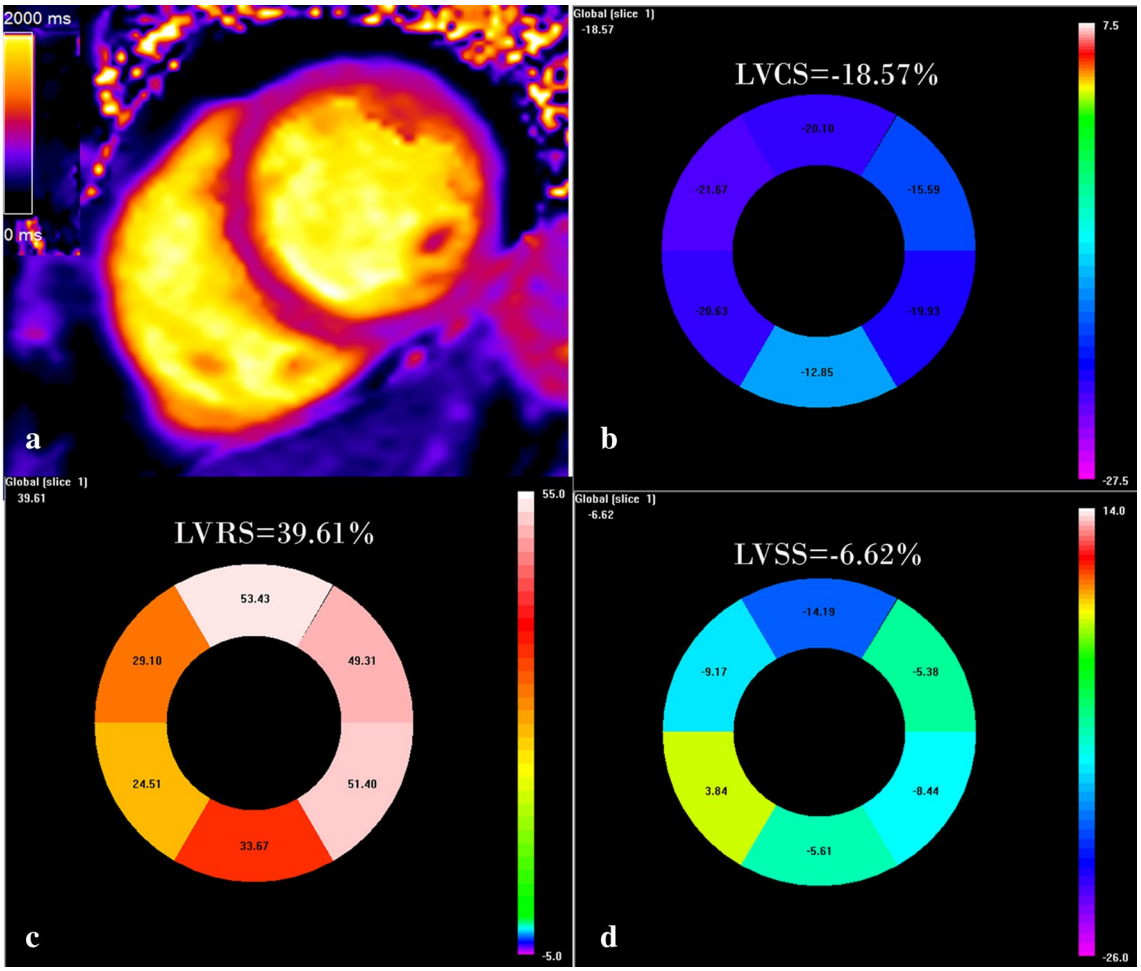

Fig. 3 CMR T1-map and strain from the short-axial mid-ventricular slice of a 37-year-old healthy volunteer: **a** native T1 map, LV T1 = 1012.8 ms; **b** LV circumferential strain = − 18.57%; **c** LV radial strain = 39.61%; **d** LV shear strain = − 6.62%

LVRS was comparable to normal control. Decreased LVLS and LVCS in both OHT and SHT suggest longitudinal and circumferential mechanic impairments even in early stage. However, LVSS were comparable among OHT, SHT and normal controls. Since myocardial rotation due to shearing forces created by sliding of myocardial fibers in the longitudinal-circumferential direction is dominated by the subepicardial layer because of the larger radius of rotation, shear strain reflect the force between slices. We speculate the regional LVSS on the short-axial mid-ventricular slice cannot reflect the shear strain for myocardial rotation between different slices.

The cardiac performance is sensitive to FT3. LV myocardial T1, LVLS and LVCS correlated with serum thyroid hormone levels, indicating that decreased thyroid hormone concentrations in the blood might be related to the myocardial interstitial lesions and impaired longitudinal and circumferential mechanics, in consistent with previous findings [17]. Native T1 could distinguish normal from abnormal myocardium and increase in edema [18] or fibrosis [19] which result in abnormal myocardial stiffness and contractility leading to cardiac mechanical dysfunction. LVLS and LVCS were reported to be significantly correlated with native T1 values in hemodialysis patients [20]. Homsi et al. [21] documented that right ventricular myocardial native T1 significantly correlated with right ventricular longitudinal strain in patients with pulmonary arterial hypertension with feature tracking. Our study demonstrated increased T1 and correlated with the impaired LVCS and LVRS in HT. Our findings supported that CMR-based T1 mapping and strain analysis could detect diffuse myocardial injury and impaired myocardial mechanics of HT. The results do contribute to our current understanding of the effect of hypothyroidism on the architecture and function of the left ventricular myocardium.

There are several limitations in current study. The major limitation is the small sample size, single-center study design, so T1-mapping and strain analysis for HT patients

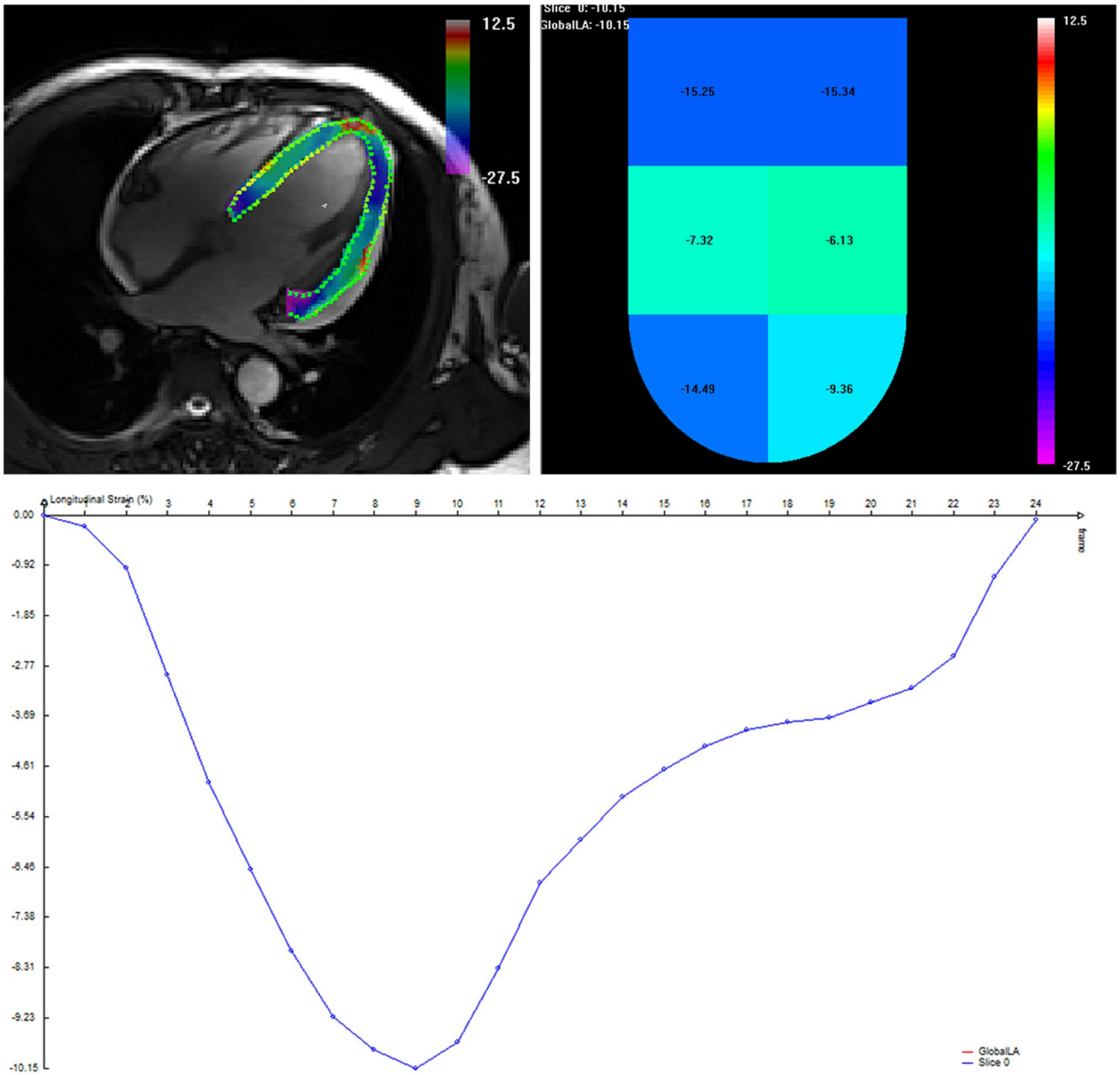

Fig. 4 LV longitudinal strain (LVLS) analysis from the four-chamber cine of a 37-year-old OHT patient is − 10.15%

Table 2 The correlation of left ventricular myocardial T1, strain and thyriod hormones

CMR T1-mapping and strain		FT3	FT4	TSH
LV T1 (ms)	1159.7 ± 101.6	R = − 0.401 p = 0.002	r = − 0.479 p < 0.001	r = 0.515 p < 0.001
LVLS (%)	− 14.6 ± 2.7	r = − 0.651 p < 0.001	r = − 0.357 p = 0.007	r = 0.678 p < 0.001
LVCS (%)	− 15.7 ± 4.3	r = − 0.551 p < 0.001	r = − 0.337 p < 0.001	r = 0.554 p < 0.001
LVRS (%)	31.6 ± 7.7	r = 0.209 p = 0.018	r = 0.076 p = 0.391	r = − 0.114 p = 0.199
LVSS (%)	− 6.3 ± 2.7	r = 0.261 p = 0.003	r = − 0.173 p = 0.051	r = − 0.158 p = 0.075

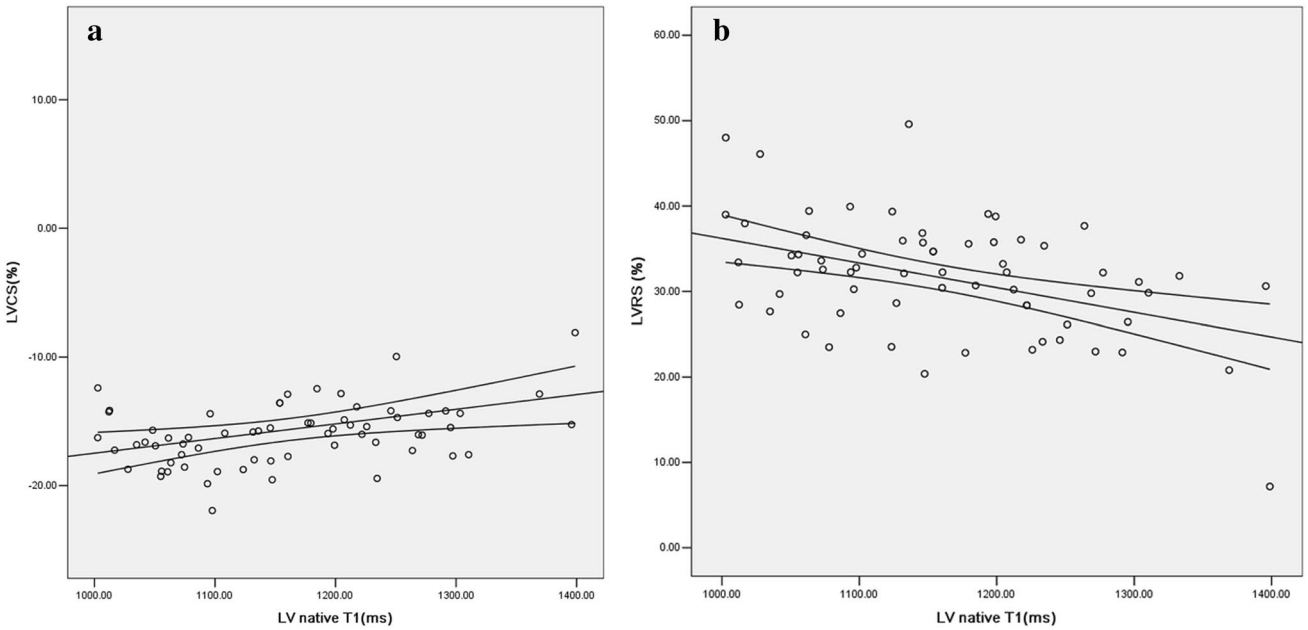

Fig. 5 Correlation of LV T1 with CMR-based strain: **a** LV myocardial T1 correlated with LV circumferential strain; **b** LV T1 inversely correlated with the LV radial strain

Table 3 Left ventricular myocardial T1 and strain in subclinical HT, Overt HT and controls

CMR findings	Controls	Subclinical HT	Overt HT	F▲	P
LV T1 (ms)	$1064.2 \pm 32.3^{\#}$	$1112.4 \pm 80.9^{\Delta}$	1297.9 ± 71.2*	49.41	< 0.001
LVCS (%)	$-19.8 \pm 0.4^{\#}$	$-16.3 \pm 0.6^{\Delta}$	-13.2 ± 1.0*	6.96	< 0.001
LVRS (%)	35.7 ± 7.7	$32.4 \pm 8.4^{\Delta}$	28.4 ± 6.4*	3.34	0.039
LVSS (%)	-6.6 ± 2.2	-7.0 ± 2.0	-6.8 ± 2.0	0.93	0.402
LVLS (%)	$-19.1 \pm 1.9^{\#}$	$-14.9 \pm 1.6^{\Delta}$	-12.7 ± 2.7*	27.39	< 0.001
LVEF (%)	63.1 ± 5.2	60.9 ± 3.1	61.1 ± 10.1	0.40	0.676
EDV (ml)	51.8 ± 4.1	$55.9 \pm 7.1^{\Delta}$	63.7 ± 8.9*	4.95	0.041
ESV (ml)	26.1 ± 1.5	27.7 ± 2.8	24.6 ± 3.1	2.53	0.232
SV (ml)	25.0 ± 2.3	$25.1 \pm 4.6^{\Delta}$	38.7 ± 2.9*	5.04	0.032

▲ one-way ANOVA test among Overt HT, Subclinical HT and normal control

HT hypothyroidism, *LVCS* left ventricular circumferential strain, *LVRS* left ventricular radial strain, *LVSS* left ventricular shear strain, *LVLS* left ventricular longitudinal strain, *LVEF* left ventricular eject fraction, *EDV* end diastolic volume, *ESV* end systolic volume, *SV* stroke volume

$^{\#}p < 0.05$ for Control vs subclinical HT; $^{\Delta}p < 0.05$ for overt HT vs subclinical HT; *$p < 0.05$ for overt HT vs control

need a further verification. LV myocardial T1 and strain before and after levothyroxine treatment need a further comparison. Because T1-mapping on the four-chamber slice were not obtain, the correlation of T1 with LVLS on the matched four-chamber slice remains unclear. Extracellular volume fraction (ECV) is a marker of myocardial fibrosis, however, it was not assessed since delay enhancement and post-contrasted T1 mapping were not performed in our research. In further studies, post-contrast T1 and ECV will be evaluated in HT patients as well as ECV with levothyroxine therapy.

In conclusion, LV myocardial T1 correlates with LV strain in HT. The combination of CMR-based T1 mapping and stain analysis has the potential to provide qualification of tissue characteristic and mechanic abnormality of HT even in early stage and may be used to guide and evaluate the treatment.

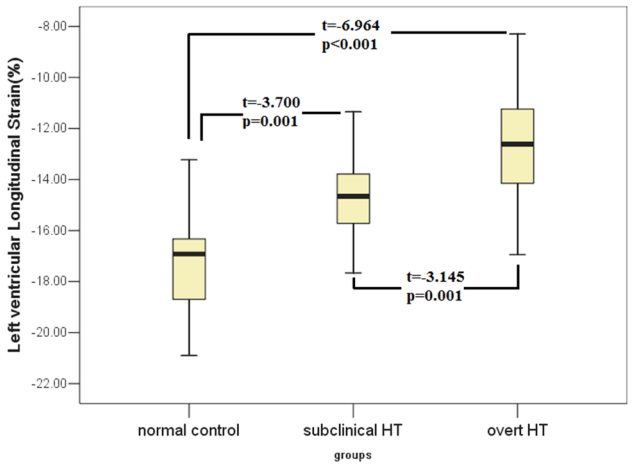

Fig. 6 LVLS of OHT and SHT significantly decreased in comparison of normal control

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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