Research Square

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Cardiac Magnetic Resonance Tissue-Tracking and Parametric Mapping in Characterizing Takotsubo Syndrome: A Pilot Study

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Research Article

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Abstract

Aims: The aims of our pilot study were to evaluate the application of cardiac magnetic resonance tissue tracking (CMR-TT) and tissue mapping in characterizing TS.

Methods: Two groups were retrospectively enrolled: patients with apical ballooning TS (n=19) and healthy controls (n=10). We assessed global and regional bi-ventricular function, including longitudinal (LS), circumferential (CS), and radial strain (RS) analysis. Tissue characterization by T1, T2 mapping, and LGE was performed as well to detect the possible presence of myocardial injuries.

Results: LS was reduced in patients with TS compared to healthy controls. LS dysfunction was detected mainly at mid- and apical cavity (p=0.001 for both). Again, basal RS was higher in TS patients compared to the control group. No other statistically significant differences in myocardial strain were detected. TS patients had higher T1 and T2 values, with greater involvement of the LV apex compared with controls. In a multivariate analysis, there was a statistically significant difference between TS and controls regarding parametric mapping and myocardial strain after controlling for gender and age. T1-native and T2 mapping proved to have an excellent performance in differentiating TS patients from controls (AUCs of 0.94 and 0.96, respectively)

Conclusion: Our study suggests that myocardial strain impairment and parametric mappings could help in refining the evaluation of TS patients.

Highlights

Takotsubo is a transient and often misdiagnosed form of left ventricular dysfunction

Cardiac magnetic resonance allows to evaluate TS and rule out others cardiovascular disease

Cardiac magnetic resonance tissue-tracking and parametric mapping helps clinicians in refining Takotsubo diagnosis and understanding pathophysiology.

Background

Takotsubo syndrome (TS) is a transient form of left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning and hyperkinesis of basal segments (typical form). In atypical TS variants, however, myocardial stunning can involve mid-ventricular, basal, focal left ventricle (LV) segments or the whole LV or both ventricles (apical LV and right ventricle (RV)), or just the RV [1,2]. According to the current literature, about 90% of TS patients are women with an average age of 67–70 years [1]. The most common TS symptoms are acute chest pain, dyspnoea, or syncope, hence clinically indistinguishable from those of acute coronary syndrome (ACS)[1,2]. For this reason, TS cardiomyopathy is often misdiagnosed [3]. It is estimated to represent approximately 2% of the cases initially presenting as suspected ACS [4]. Initially, TS has been considered as a benign entity, but later it proved to be associated

with complications and death in about 4–5% of cases [2]. Although differential diagnosis from ACS requires coronary angiogram with ventriculography, several non-invasive imaging modalities are useful in the work-up of patients with TS as well. Among the most recent techniques, cardiac magnetic resonance imaging (CMR) is the key diagnostic modality for patients with suspected TS[1,5,6]. Not only it allows to assess wall motion abnormalities, but also to differentiate between reversible and irreversible myocardial damage, in order to rule out other cardiac diseases[6, 7–9,10]. In TS, traditional LV ejection fraction (EF) could be normal owing to a regional compensatory balance. In this scenario, myocardial strain analysis can detect regional wall motion abnormalities [11].

Several studies in echocardiography showed abnormalities in global and regional strain parameters in TS patients[12,13]. For example, as reported by Dias et al., myocardial strain analysis assessed with speckle tracking (STE) could identify early systolic dysfunction[13].

Recently, cardiac magnetic resonance tissue tracking (CMR-TT) has been introduced as a new tool to assess LV dysfunction similarly to speckle tracking at echocardiography. CMR-TT proved also to be a strong prognostic marker in different cardiovascular diseases.[14,15]

Again, T1 and T2 mapping are quantitative imaging methods which provide an objective evaluation of myocardial tissue characteristics, leading to an increase in CMR accuracy [16,17]. In particular, T1 mapping is able to identify change in free water content and its values increases during acute inflammation, vasodilatation and hyperemia [17].Conversely, T2 mapping is sensitive to detect acute myocardial oedema [17].

The purpose of this study was to investigate the application of CMR-TT and parametric mapping in evaluating TS.

Material And Method

Study population

In this study we included 19 patients admitted to our University hospital due to acute chest pain and/or dyspnoea with a diagnosis of apical ballooning TS and 10 healthy controls. The diagnosis of TS was defined according to the Position Statement of the European Society of Cardiology Heart Failure Association [18]. These include regional wall motion abnormalities not limited to a single epicardial vascular distribution usually preceded by a stressful trigger, an absent of culprit atherosclerotic carotid disease assessed by invasive catheterization, new ECG abnormalities, elevated serum natriuretic peptide and small increase in cardiac troponin, and recovery of LV dysfunction at follow-up.

Exclusion criteria included: subjects < 18 years old; contraindication to CMR (such as implantable devices, severe claustrophobia), history of renal disease with a current eGFR < 30 mL/min/1.73 m2; coronary artery disease.

The control group comprised 10 healthy subjects without any known cardiovascular disease or risk factors.

Informed consent was obtained from each patients and controls.

CMR

Imaging protocol

All CMR were performed at 4.1 ± 2.6 days (median = 1 day, range = 1–10 days) after admission to hospital by a Philips Achieva dStream 1.5 T scanner system (*Philips Healthcare, Best, The Netherlands*). Anterior coil arrays were used. ECG-triggered cine-CMR examinations were carried out and performed during breath-hold. Thirty phases were derived for each cardiac cycle. The CMR protocol was based on functional sequences, such as cine white blood steady-state free precession (SSFP) on the short and long axes (2 chambers, 3 chambers and 4 chambers). Other images and clips which were acquired included tissue morphological and characterization sequences such as T2 STIR on both short and long axes, T1 pre- and post-contrast mappings, T2 mapping, and late gadolinium enhancement (LGE).

T2 mappings were acquired prior to inject the contrast agent in end-diastole in 3 short axis slices (apical, mid, basal) using multi-echo sequences. T1 mappings were obtained before and 10 minutes after the administration of contrast agent in end-diastole in 3 corresponding short axis slices (apical, mid, basal) using a balanced steady-state free precession based 3–3–5 modified Look-Locker inversion recovery scheme.

The reference values of our scanner for T1 and T2 mapping are 53 ± 3 ms and 1,030 ± 30 ms, respectively.

The apical slice in parametric mapping is often linked with inaccuracy in measurements due to the high probability of inclusion of voxels outside true myocardium. We selected a not too apical slice in all patients to avoid partial volume effects in apical mapping.

LGE technique was performed 10–12 minutes after contrast agent injection (*Gadovist, Bayer Healthcare, Berlin, Germany*) using phase-sensitive inversion recovery acquired in both short and long axis. The correct inversion time was determined using the Look-Locker technique

Image analysis

A radiologist (RC with 3 years of experience in cardiovascular imaging) assessed tissue-tracking and parametric mapping on CMR examinations. We used the commercially available software system Circle CVI42 (*CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada*) for CMR-FT data analysis. Offline CMR-FT analyses were conducted for evaluation of peak global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS) in a 16-segment software-generated model. Concerning GLS, data on myocardial strain were derived from two-, three- and four-chambers long-axis views. Regarding GRS and GCS, data on myocardial strain was derived from apical, mid-ventricular, and

basal short-axis views in all the patients. On all images, the epi- and endocardial borders were outlined in end-diastole. Subsequently, an automatic computation was triggered, by which the applied software algorithm automatically outlined the border throughout the cardiac cycle. The quality of the tracking and contouring was visually validated and manually corrected when needed.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median [interquartile range]. Comparisons of continuous data were performed using the independent samples t test or Mann-Whitney U test; Kolmogorov-Smirnov tests were used to check continuous variables for the normal distribution. Categorical variables were compared using the chi-square testor Fisher's exact test, as appropriate. Correlation was assessed using the Pearson r and Spearman rho coefficient as appropriate. A p-value < 0.05 was considered statistically significant. A general linear model (GLM) analysis was performed with age and gender as covariate (MANCOVA). A receiver-operating characteristic (ROC) analysis was performed to calculate optimal thresholds and areas under the curves (AUCs). The Youden index was used to depict optimal cut-off values from the ROC curves. Sensitivities and specificities were calculated for these cut-off values with 95% confidence intervals.

Statistical analysis was performed using IBM SPSS Statistics version 22 (*SPSS Inc., Chicago, IL, USA*) and MedCalc (*MedCalc Software, Mariakerke, Belgium*).

Results

A total of 19 (18 females and 1 male) TS patients were compared with 10 healthy controls. TS patients had an average age of 68 years (range: 59–82 years), while controls (6 females and 4 males) had an average age of 51 years (range: 28–63 years).

The CMR parameters of the patients under analysis are shown in Table 1. The two groups did not show any significant difference concerning diastolic and systolic LV and RV volumes and EF. Apical ballooning was the most prevalent contraction pattern.

Table 1
Comparison of Demographic features and CMR LV and RV volume and function in Takotsubo and healthy subjects

	TS	Control	p
Age	68,6 ± 10,2	51 ± 8,8	0,001
Female	18/19 (93%)	6/10 (61%)	0,13
EDV/BSA LV	72,5 ± 15,4	78,4 ± 13,1	0,54
ESV/BSA LV	30,7 ± 10	32 ± 6,5	0,63
SV/BSA LV	41,5 ± 10,8	46,8 ± 9,3	0,30
LVEF	52,2 ± 9,1	57,2 ± 6,6	0,41
EDV/BSA RV	66,9 ± 16,3	77,83 ± 20,90	0,16
ESV/BSA RV	40,2 ± 8,49	34,52 ± 9,99	0,24
SV/BSA RV	41,36 ± 16,33	43,69 ± 12,29	0,07
RVEF	57,62 ± 5,66	55,86 ± 2,72	0,4
TS tako-tsubo syndrome; RV right ventricle; LV left ventricle, EDV end-diastolic volume; ESV end-sistolic volume; SV stroke volume; EF ejection fraction BSA body surface area Mean +/- DS			

LV GLS was significantly lower in TS compared to the control group (p = 0.001). In particular, LS impairment was mainly at mid- and apical cavity (p = 0.001 for both). Conversely, basal LS was not significantly different between the two groups under analysis. All apical myocardial strain parameters were significantly lower in TS with respect to healthy controls. Figure 1. Moreover, basal RS showed a higher value in TS group than in the control group (p = 0.01). On the contrary, RV myocardial strain did not show any significant difference between the two groups.

Differences in basal, mid, and apical strain analysis are summarized in Table 2.

Table 2
Comparison of CMR-TT and Parametric Mapping in Takotsubo and healthy subjects

TS		Control	p
GLS RV	-24,61 ± 3,88	-26,6 ± 3,2	0,4
GCS RV	-14,28 ± 1,32	-12,47 ± 4,41	0,06
RV Basal circumferential strain	-11,24 ± 1,67	-9,32 ± 7,00	0,3
RV Mid-cavity circumferential strain	-15,12 ± 3,71	-12,74 ± 4,32	0,21
RV Apical circumferential strain	-19,71 ± 3,07	-16,63 ± 5,46	0,11
RV Global radial strain	24,4 ± 5,9	21,72 ± 9,99	0,18
RV Basal radial strain	20,8 ± 3,27	18,64 ± 9,66	0,7
RV Mid-cavity radial strain	27,57 ± 9,11	21,16 ± 9,68	0,27
RV Apical radial strain	36,81 ± 10,1	31,21 ± 15,05	0,35
GLS LV	-12,86 ± 2,55	-17,8 ± 1,89	**0,001**
GCS LV	-16,02 ± 8,87	-20,9 ± 1,8	**0,006**
GRS LV	31,2 ± 8,1	37,5 ± 5	**0,011**
LV Basal longitudinal strain	-16,57 ± 3,72	-18 ± 1,8	0,98
LV Basal circumferential strain	-20,17 ± 2,59	-20,14 ± 3,12	0,35
LV Basal radial strain	43,4 ± 11,1	30,4 ± 18,7	**0,01**
LV Mid longitudinal strain	-13,31 ± 2,98	-17,9 ± 3,03	**0,001**
LV Mid circumferential strain	-17,90 ± 3,36	-20,17 ± 2	0,13
LV Mid radial strain	31,18 ± 8,57	28,3 ± 8,21	0,87
LV Apical longitudinal strain	-12,91 ± 2,59	-16,25 ± 3,52	**0,001**
LV Apical circumferential strain	-17,38 ± 4,8	-25,76 ± 1,23	**0,001**
LV Apical radial strain	24,65 ± 8,99	42 ± 22,89	**0,002**
Global T1 mapping	1161,8	1004,14	**0,001**
Basal T1 mapping	1109	1006,1	**0,004**
Mid-cavity T1 mapping	1138,48	999	**0,001**
Apical T1 mapping	1213,29	1009	**0,001**
Global T2 mapping	64,4 ± 5,04	54,2 ± 2,2	**0,001**
Basal T2 mapping	59,9 ± 4,56	54,2 ± 3,6	**0,002**

TS		Control	p
Mid-cavity T2 mapping	63,7 ± 5,58	52,9 ± 2,3	**0,001**
Apical T2 mapping	71,14 ± 6,6	55 ± 3,2	**0,001**

TS tako-tsubo syndrome; AM acute myocarditis;, LV left ventricle, RV right ventricle; GLS global longitudinal strain; GCS global circumferential strain; GRS Global radial strain

Mean +/- DS

Regarding parametric mapping, T1 and T2 mapping were significantly higher in TS patients than in their healthy peers (p = 0.001 for both) with greater involvement of the apical slice (p = 0.001 for both). Figure 2.

MANCOVA analysis confirmed that the association of myocardial strain measurements and parametric mapping were independent of age and gender (Table 3).T1 and T2 mapping provided excellent performances in characterizing TS patients compared to healthy controls, with AUCs of 0.94 (95% CI, 0.85–1) and 0.96 (95% CI, 0.94–1) respectively. Optimal cut-off values of global native T1 and T2 to identify TS were > 1,085 and > 57.86 ms with sensitivities/specificities of 88/90% and 94/90%, respectively. Figure 3. None of the patients and controls had LGE.

Table 3
MANCOVA analysis

	Age	Sex
GLS LV	0,36	0,78
LV Mid longitudinal strain	0,28	0,97
LV Apical longitudinal strain	0,69	0,61
LV Apical circumferential strain	0,52	0,55
GCS LV	0,57	0,77
GRS LV	0,56	0,97
LV Basal Radial Strain	0,08	0,25
LV Apical radial strain	0,85	0,37
Global T1 mapping	0,24	0,29
Basal T1 mapping	0,28	0,42
Mid-cavity T1 mapping	0,43	0,34
Apical T1 mapping	0,48	0,26
Global T2 mapping	0,84	0,63
Basal T2 mapping	0,17	0,97
Mid-cavity T2 mapping	0,89	0,64
Apical T2 mapping	0,95	0,39

Discussion

Since its first report, TS has been increasingly diagnosed, with a current prevalence which is estimated at approximately 2% in all patients presenting with clinical manifestation of ACS and up to 10% if only women are considered. Other Authors think that TS prevalence is underestimated [19,20]. In fact, according to Minhas et al., TS incidence has been increasing over the years [21]. The diagnosis of TS remains a challenge due to its clinical manifestations, which may closely resemble ACS [1]. Coronary angiography with left ventriculography is considered the gold standard diagnostic tool for a definitive diagnosis of TS [22], but this procedure is invasive and at risk of the onset of life-threatening events. For these reasons, several non-invasive imaging modalities have been proposed in assessing TS [1].CMR is an excellent tool aimed at assessing the typical regional wall motion abnormalities, with precise quantification of RV and LV systolic function. CMR allows also to detect the presence of reversible and irreversible myocardial injuries [6]. Eitel et al. reported specific CMR criteria for TS diagnosis which include the combination of

typical contraction pattern, oedema, and absence of LGE [5]. Besides, CMR is better than other non-invasive imaging for the detection of RV involvement. [5,14] Right ventricular disfunction in TS has being recognized with an incidence from 13–50%, and it is associated with worse outcomes [14,23].

This study shows that tissue mapping techniques and CMR-TT can improve the diagnosis of TS. Its main findings are as follows: (1) parametric mapping and CMR-TT allow to detect LV impairment in TS patients; (2) particularly, T1 and T2 mapping enable the objective assessment of regional LV myocardial tissue alteration with excellent performance; (3) GLS in TS is significantly lower than in healthy subjects; (4) all apical strain parameters in TS are significantly impaired with respect to controls; (5) basal radial strain (RS) in TS is significantly higher in comparison with healthy subjects. These findings highlight the potential of parametric mapping and CMR-TT in refining the diagnosis of TS.

Diagnostic value of parametric mapping in TS patients

T1 and T2 mapping are quantitative imaging methods that enable an objective assessment of myocardial tissue properties, thus increasing CMR diagnostic accuracy[16,17]

We found significantly higher T1 and T2 mapping values in patients with TS, according to the current literature in the field [24,25], mainly at the apex but even in remote and apparently normal myocardium in TS patients with involvement of the whole LV. T2 mapping decreased gradually from apical to basal regions. Our results showed a higher parametric mapping values in patients segments without wall motion abnormalities. The substrate for this widespread myocardial involvement is so far unexplained. Histological studies suggest several mechanisms in the onset of TS, including multi-vessel coronary spasm, increased catecholamine levels inducing myocardial toxicity and an excessive transient ventricular afterload induced by a peak of catecholamines.[26]

Wilson et al. in post-mortem examination demonstrated that macrophages, predominantly M1, are the leading cellular protagonist in the onset of myocardial inflammation in TS. In addition, the authors reported that similar inflammation changes were observed even in normal myocardium of post-mortem TS patients.[27]

Consistently with a previous study, T1 and T2 mapping provided excellent performances in TS patients compared to healthy controls [24,25]. Our study suggests that parametric mappings are robust markers in patients with TS and add information regarding the extent of myocardial tissue alterations in this setting.

Diagnostic value of CMR-TT in TS patients

Another specific CMR hallmark in TS are the typical regional wall motion abnormalities. Generally speaking, CMR is the gold standard for the assessment of cardiac function and volume quantification[28]. Many studies have demonstrated that myocardial strain reflects subtle changes in myocardium contractility [29–31]. At echocardiography, STE is a very useful tool for quantitative assessment of myocardial function, but it is limited in case of suboptimal acoustic views in the setting of poor acoustic

windows, such as in overweight and obese patients or in those with chest deformity or with chronic lung diseases [32]. Furthermore, echocardiography evaluation of RV is challenging and frequently limited to a subjective qualitative assessment.[33]

Myocardial strain analysis with CMR-TT, despite being time-consuming, could help in this setting.

In the commonest type of TS, i.e. that with apical ballooning, LS parameters decrease from the base to the apex[12]. Our results are in line with the current literature[12]. In particular, we found that basal longitudinal strain (LS) is preserved with respect to mid- and apical LS. These results require further evaluation and might be due to partial myocardial recovery, as reported by Kim et al., who showed an improvement of LS from LV base to apex with time[34]

In addition, the higher value of basal RS in TS could be explained by the transient LV hyperkinetic motion of the basal segments, as already reported by Kobayashi et al [35]. So, the hyperkinesis of basal segments is determined by an increase in RS, but not in LS and CS.

Finally, our findings did not show and significant RV involvement in the enrolled TS cohort.

Study limitations

A major limitation of this research is the relatively small number of patients. However, the study reflects a series of selected consecutive patients with a not so common disease. The relatively small sample size can certainly be improved in the future by enrolling a larger cohort. Moreover, the impairment in myocardial strain in TS patients would probably have been different if CMR had been performed within a shorter period of time, ideally the same day of admission to hospital.

Conclusion

Our findings suggest that the pattern of LV regional strain abnormalities assessed using CMR-TT and parametric mapping can help in refining TS diagnosis and understanding pathophysiology. Additional studies, with a larger number of patients, are needed to confirm the usefulness of these advanced CMR tools in TS patients.

Abbreviations

TS Takotsubo syndrome

CMR cardiac magnetic resonance

TT tissue-tracking

STE Speckle Tracking echocardiography

ACS Acute coronary syndrome

RV right ventricle

LV left ventricle

EF ejection fraction

ESC European Society of Cardiology

STIR Short tau inversion recovery

GLS global longitudinal strain

GRS global radial strain

GCS global circumferential strain

LGE late gadolinium enhancement

Declarations

Disclosures

All authors agreed with the content and gave consent to submit.

All authors contributed equally as authors to this work.

The authors state that this work is not under consideration elsewhere

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Figures

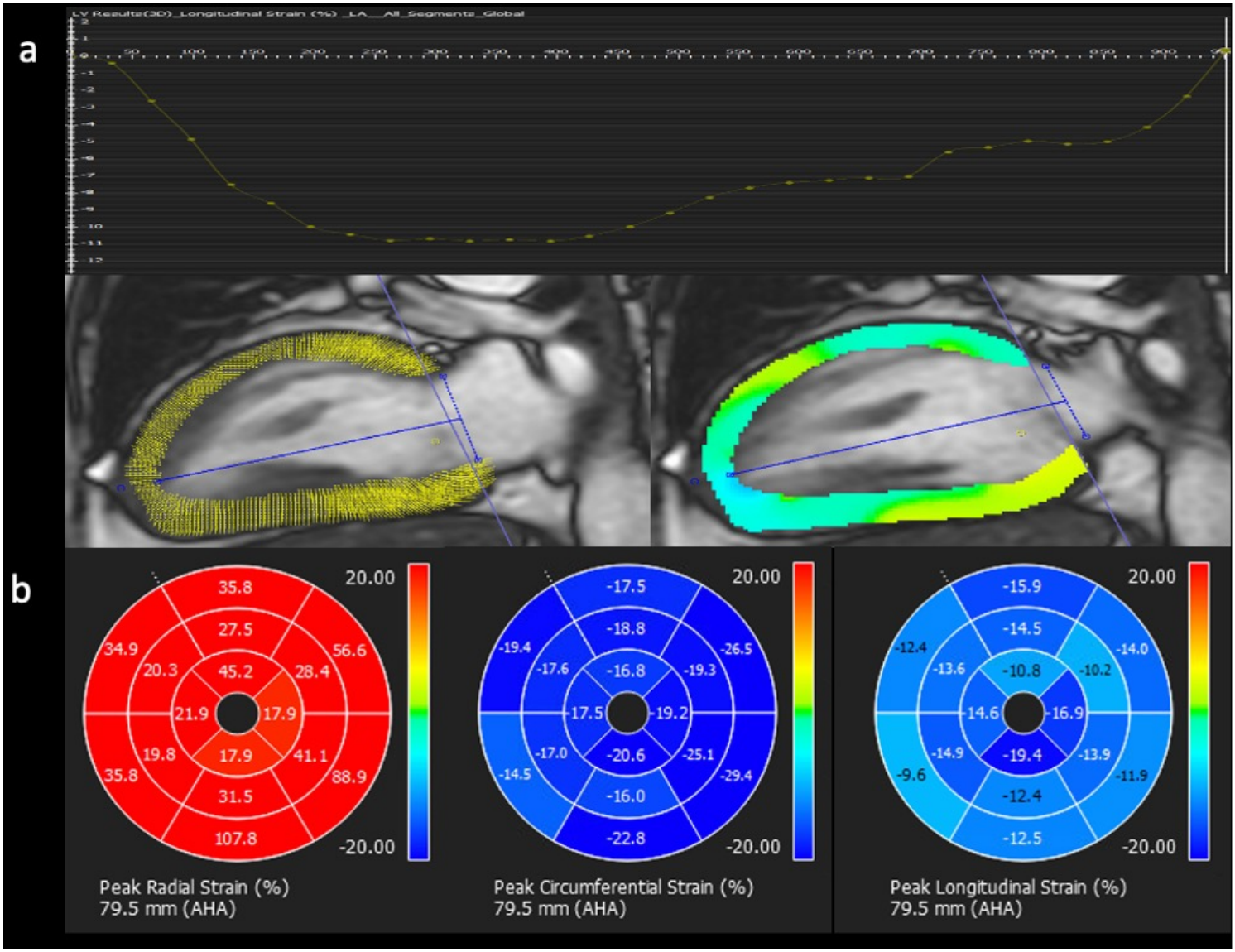

Figure 1

an example of Global longitudinal strain(a) and regional radial, circumferential and longitudinal strain in AHA segmentation (b)

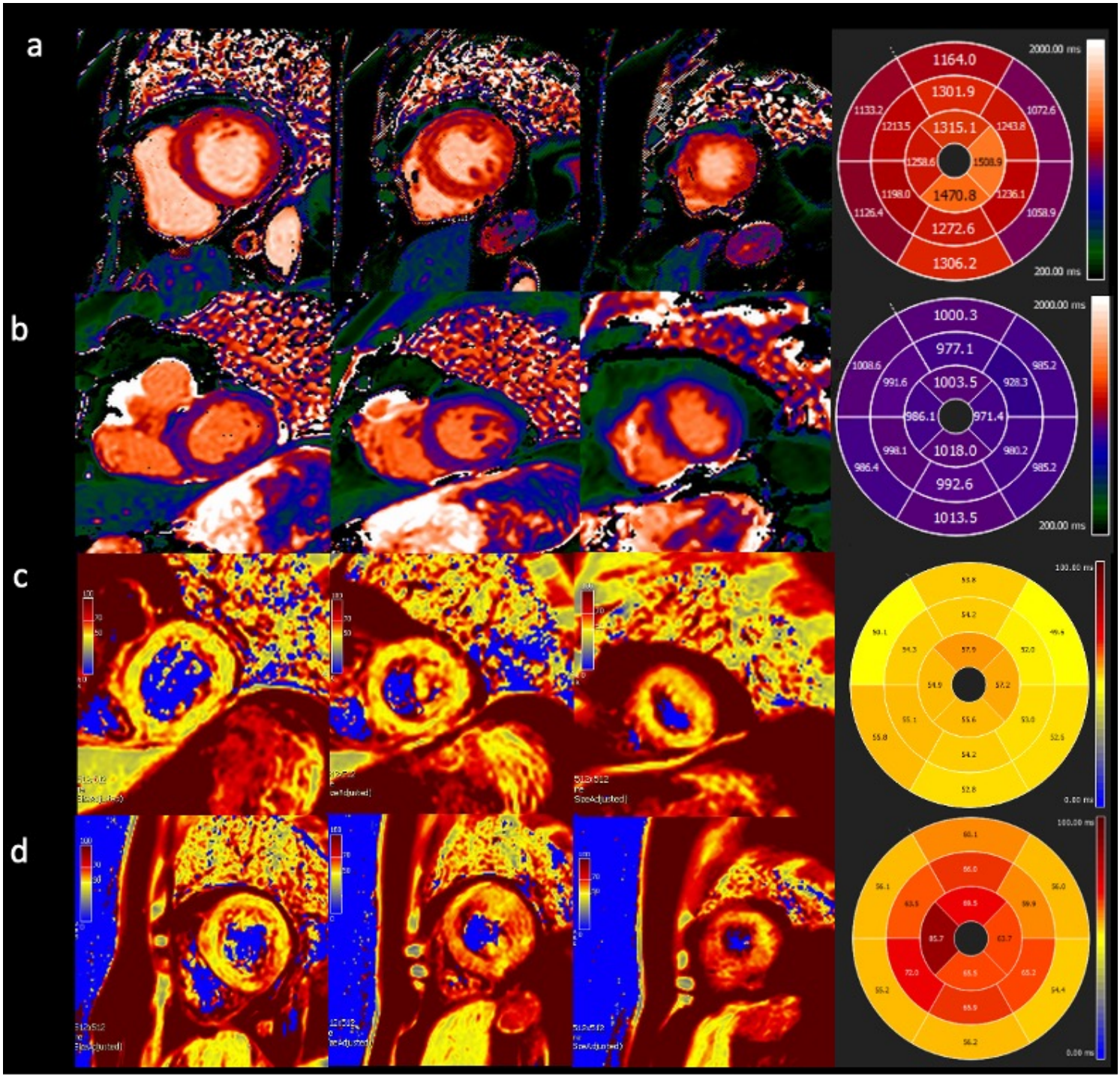

Figure 2

an example of parametric mapping in TS patients (a,d) and in healthy subjects (b,c)

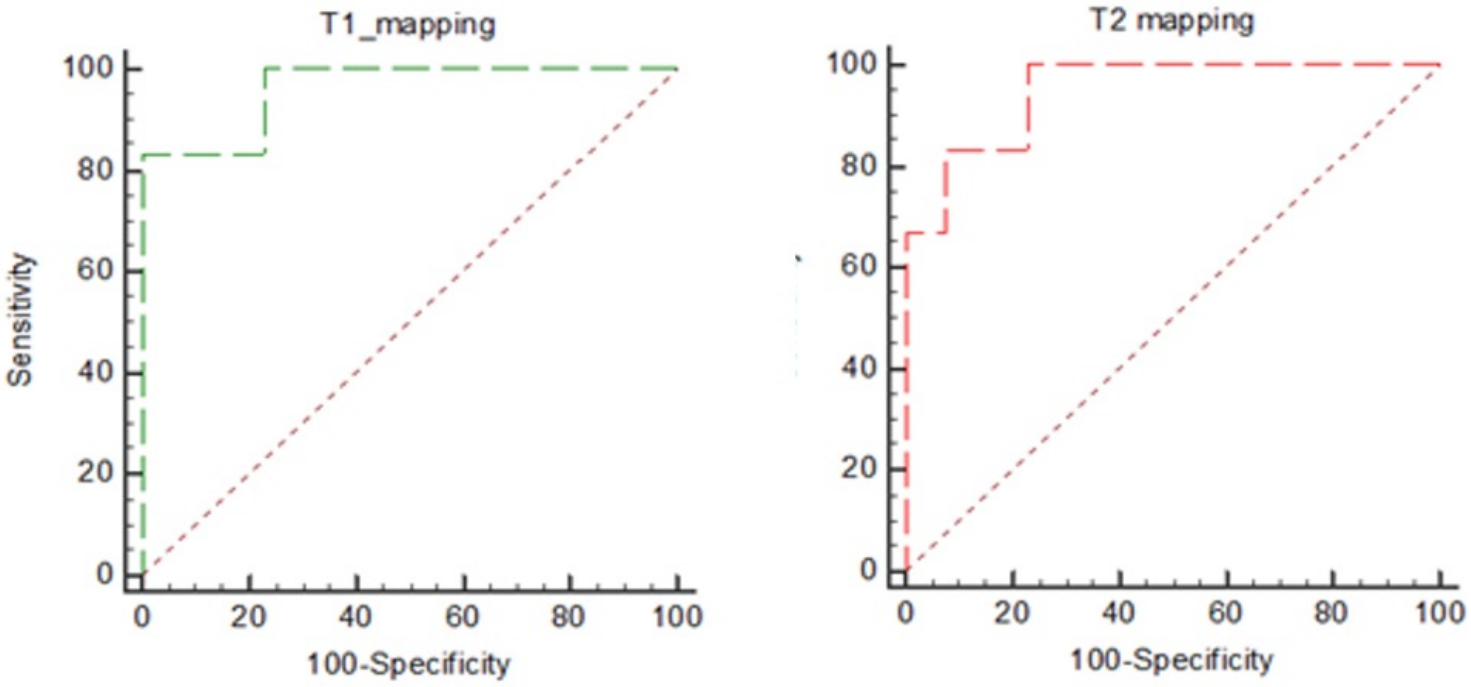

Figure 3

ROC Curves for T1 and T2 mapping in patients with Takotsubo.