Atrial impairment as a marker in discriminating between Takotsubo and acute myocarditis using Cardiac Magnetic Resonance.

Purpose: The purpose of this study was to comprehensively compare the left and right atrium strain and strain rate (SR) parameters by cardiac magnetic resonance (CMR) between patients with Takotsubo (TS) and patients with acute myocarditis (AM).

Method: We retrospectively enrolled three groups of patients: TS (n=18), AM (n=14) and 11 healthy subjects. All the patients had a complete CMR data for features tracking assessment. Differences in Reservoir, Conduit strain (ε_e), conduit strain rate (SRe) and Booster phase of bi-atrial strain were analyzed between the groups using ANOVA and MANCOVA analysis. Intra- and inter-observer reproducibility was assessed for all strain and SR parameters using intraclass correlation coefficients (ICCs) and Bland-Altman analysis.

Results: Atrial strain were feasible in all patients and controls. In TS, LA reservoir strain (ε_s), Reservoir SR, ε_e, and SRe were significantly lower compared with the other groups (p = 0,001 for all). MANCOVA analysis showed association of these parameters after correction for age and gender. While LA booster deformation (ε_a and SRa) strain parameters were preserved. LA SRe proved to have excellent sensitivity in differentiating patients with TS from those with AM (AUCs of 0.903, 95% confidence interval [C.I.] 0.81–0,99).
Bi-atrial strain and SR parameters showed good (excellent) intra- and inter-observer reproducibility (ranged between 0,61 - 0,96 and 0,50 -0,90, respectively).

Conclusion: Compared to AM, patients with TS showed significantly decreased LA reservoir, conduit strain and SR parameters. Therefore, LA strain assessment may have a role in discriminating between TS and AM.

Keywords: Atrial strain; Takotsubo; CMR; Myocarditis.

Abbreviations

STEMI ST elevated myocardial infarction

TS Takotsubo syndrome

AM Acute myocarditis

ACS acute coronary syndrome

LV left ventricle

CMR-FT cardiac magnetic resonance feature tracking

LA left atrium

RA right atrium

ε_s Reservoir strain

SRs Reservoir strain rate

ε_e Conduit strain

SRe Conduit strain rate

ε_a Booster strain

SRa Booster strain rate

STE Speckle tracking echocardiography

Highlights

- CMR-FT represent a feasible and reproducible tool to assess atrial strain.
- TS patients showed LA atrial impairment in comparison with AM group
- CMR-FT may be a novel parameter in discriminating between TS and AM, providing new insight into in Takotsubo cardiomyopathy

Introduction

Acute chest cardiac pain represents a common symptom in daily clinical practice and can be caused either by ischemic or non-ischemic disease. Whereas early detection of a ST elevated myocardial infarction (STEMI) is usually possible even in a preclinical setting, further differential diagnosis, in cases where a STEMI was ruled out, remains challenging. Discriminating between different non-ischemic causes of acute chest-pain, namely between Takotsubo syndrome (TS) and acute myocarditis (AM), represents a common diagnostic dilemma. Although the clinical presentation with a possible trigger as well as different demographics data may be different between these entities, the clinical phenotypes of TS may closely resemble AM, that includes beyond chest pain, dyspnea and syncope also similar cardiac signs, laboratory and electrocardiography changes[1]. In particular, TS is a well-recognized cardiomyopathy characterized by a pattern of left ventricular (LV) dysfunction, mainly presenting as apical ballooning and hyperkinesis of basal segments [1]. Less common variants can involve mid-ventricular, basal, focal LV segments or the whole LV or both ventricles (apical LV and right ventricle (RV)), or just the RV [1,2]. Recently, Stieirmaier *et al* reported a transient deterioration of left atrium (LA) strain parameters during acute/subacute phase of TS using cardiac magnetic resonance (CMR) [3].

These wall motion abnormalities and clinical symptoms are usually transient with complete recovery within several weeks.[3] Prognosis of TS is in most of the cases favorable, but recent studies have shown possible complications and death[4].

Because of different clinical course, management and outcome between TS and AM, differential diagnosis is crucial.

CMR has become the reference standard in evaluation of cardiac function and morphology in several clinical settings and diseases[5]. In addition, CMR has demonstrated high ability to diagnose and characterize acute and chronic myocardial diseases, and currently CMR is the gold standard to diagnose AM. Diagnostic accuracy in detection and rule out of AM is of special importance in the acute setting, since AM represents an exclusion criterion for TS according current international diagnostic criteria[6–8].

Recently, myocardial strain analysis has been used for ventricle function assessment using CMR[9,10], showing a potential role to discriminate between TS and AM[11]. CMR feature-tracking (CMR-FT) analysis allows assessment of regional myocardial abnormalities as well as detection of compensatory increase in other strain parameters [11]. Besides ventricular function evaluation, also atrial function has been investigated using CMR-feature tracking[12,13].

The atria play a key role on maintaining left ventricular filling. Several articles have highlighted a significant pathophysiological contribution of atria in different cardiovascular diseases, including TS [3,14–16]. Backhaus et al reported an alteration of LA strain measurements in TS patients during the acute phase of the disease. In the setting of myocarditis, an impairment of LA strain measurements as well as an involvement of the right atrium have been described [15,16]. However, little is known about the difference of atrial mechanism in the pathophysiology of these two entities. Consequently, the purpose of this study was to evaluate LA and right atrium (RA) strain as an alternative marker to discriminate between TS and AM using CMR.

Material and Method

Study population

In this retrospective single-center study we searched in our database all patients who underwent CMR between March 3rd, 2017, and February 7th,2021 and with a suspected diagnosis of AM or apical ballooning TS based on clinical parameters and CMR findings.

TS diagnosis was made using current definition reported in the Position Statement of the European Society of Cardiology Heart Failure Association[7]. Criteria include regional wall motion abnormalities not limited to a single epicardial vascular distribution usually preceded by a stressful trigger, an absent of culprit atherosclerotic coronary 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.

The diagnosis of AM was made clinically according current guidelines reported in the Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases [17]. Endomyocardial biopsy was not performed. Some of the patients under analysis were published in our previous works. [11,18] Exclusion criteria included: subjects < 18 years old; contraindication to CMR (implantable devices, severe claustrophobia), or a history of renal disease with a current eGFR < 30 mL/min/1.73 m2; and coronary artery disease.

The control group comprised healthy subjects who had CMR to exclude scar related ventricular tachycardia without known cardiovascular risk factors, and had negative studies, were used as negative controls. Informed consent was waived because of the retrospective nature.

CMR acquisition

CMR scans were performed after hospital admission for acute chest pain and/or dyspnoea using a 1.5 T scanner system (Philips Achieva dStream , Philips Healthcare, Best, The Netherlands). An 8 channels anterior cardiac coil arrays were used. Cine-CMR examinations were electrocardiogram triggered and performed during breath-hold manoeuvres.

Thirty phases were derived for each cardiac cycle. CMR protocol included functional sequences, such as cine bright blood steady-state free precession (SSFP) on the short axis and long axes (2 chambers,

3 chambers and 4 chambers); and morphological and tissue characterization sequences, such as T2 Short Tau Inversion Recovery (STIR) on both short and long axes, pre- and post-contrast T1 mappings, T2 mapping and Late gadolinium enhancement (LGE) acquisitions. LGE imaging was performed 10-12 minutes after contrast media injection (Gadovist, Bayer Healthcare, Berlin, Germany) with a dose of 0.15 ml per kg body weight using phase-sensitive inversion recovery sequences acquired in both short and long axis. The correct inversion time was determined using the Look-Locker technique.

CMR image post-processing

A commercially available software, Circle CVI42 (CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada), was used for CMR-FT data analysis. CMR-FT analyses of atrial deformation were conducted offline. LA and RA endocardial borders were manually traced on long axis view of the cine images when the atrium was at its minimum volume. In particular, the four-, three-, and two-chamber views were used to derive LA longitudinal strain. Atrial appendage and pulmonary veins were excluded from segmentation. RA longitudinal strain was based on the four-chamber view only. After manual segmentation, the software automatically tracked the myocardial borders throughout the entire cardiac cycle. The quality of the tracking and contouring was visually validated and manually corrected by a radiologist with 3 years of experience in cardiac imaging. There are three peaks in the strain curve, including reservoir, conduit, and booster strain. Accordingly, their corresponding strain rate (SR) parameters were included.

For intra-observer analysis, one observer (RC), with 3 years of experience in cardiovascular imaging, performed SR analysis, repeating all measurements twice 1 month apart in random order to avoid recall bias. For inter-observer analysis, a second blinded observer (GC), with 2 years of experience in cardiovascular imaging, performed the SR analysis in a random set of 15 patients and healthy

subjects. Both observers were blinded to all clinical data, prior test results, and diagnosis as well as to the interpretation of the other observer.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Kolmogorov-Smirnov tests were used to check continuous variables for normal distribution. Comparisons of continuous data were performed using independent samples t test or Mann-Whitney U test analysis. Categorical variables were compared using chi-square or Fisher's exact test, according to data distribution.

Comparisons between groups were performed using the one-way ANOVA for continuous variables with normal distributions, and the Kruskal-Wallis test for continuous variables with skewed distributions. A post-hoc Tukey multiple comparison test was performed to look for statistically significant differences among each group. A general linear model analysis was performed including age and gender as covariates (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.

Intra-observer and inter-observer variability were assessed by intraclass correlation coefficients (ICCs) and Bland-Altman analysis. Correlation was assessed using the Pearson r and Spearman rho coefficient according data distribution. A p-value <0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA)

Results

Patient demographics and CMR parameters.

We included 18 patients with TS (17 females, mean age 68.7 ± SD 10 years.), 14 patients with AM (6 females, mean age 43,2 ± SD 15,9 years) and 11 healthy subjects (7 females, mean age 49,8 ± SD 9,2 years). One patient with the diagnosis of TS had to be excluded due to insufficient image quality.

Baseline characteristic and CMR parameters in the patients enrolled are summarized in **Table 1**.

Feasibility of bi-atrial CMR-FT

CMR scans were performed after admission with a mean delay of 4.1 ± SD 2.6 days.

CMR-FT of bi-atrial myocardium strain could be assessed and analysed successfully in all patients. Tracking quality was sufficient in all cases, based on visual checking and manual corrections.

CMR-FT of both atria

Changes in RA and LA deformation parameters are reported in **Table 1**. LA reservoir and conduit functions demonstrated a significant difference between the groups under analysis (LA ε_s: p=0,001, LA SRs: p=0,001, LAε_e: p=0,001 and LA SRe: p=0,001).

Comparison of LA strain analysis between groups showed significant differences as shown in **Table 2** and **Figure 1.**A Tukey post hoc test revealed that reservoir strain (LA ε_s: p=0,04), LA reservoir SR (LA SRs: p=0,007), LA conduit strain (LAε_e: p=0,01), and LA conduit SR (LA SRe: p<0,001) were significantly lower in the TS group compared to AM and healthy groups. Conversely, LAε_a, and RA strain parameters did not show any significant difference between the groups. MANCOVA analysis confirmed that association of LA deformation parameters were independent of gender and age **(Table 3)**

Association with clinical and CMR parameters

LA conduit strain and strain rate measurements demonstrated the highest correlation with LVEF (r =0,396, p=0,009; r= -0,422, p= 0,005, respectively). Correlation between LA reservoir strain and strain rate parameters are weak (r =0,312, p=0,019; r= -0,22, p= 0,032, respectively)

There was no other statistically significant correlation between atrial strain measurement and LVEF. LA and RA strain functions did not demonstrate a significant correlation between the extent of late gadolinium enhancement (expressed in both percent and grams) and atrial strain parameters in AM patients. Finally, there was not statistically significant correlation between troponin values and atrial strain measurement.

ROC analysis

LA SRe proved to have excellent sensitivity in differentiating patients with TS from those with AM (AUCs of 0.903, 95% confidence interval [C.I.] 0.81–0,99). Optimal cut-off for LA SRe values to identify TS was > - 1,75 with sensitivity, specificity, positive predictive value and negative predictive value of 94 %, 63 %, 60% and 94 % respectively (Figure **2)**

Inter and intra- observer analysis

Intra-observer and inter-observer ICC coefficients ranged between 0,61 - 0,96 and 0,50 - 0,90, respectively, as shown in **Table 4.** Bland-Altmann plots showed no systematic errors and minimal differences for LA reservoir and conduit strain as shown in **Figure 3.**

Discussion

We investigated the feasibility and diagnostic value of atrial strain assessment using CMR to discriminate patients with TS and AM. Compared to patients with AM and control group, patients with TS demonstrated a significantly lower LA strain, with a dysfunction of both reservoir and conduit phase of left atrium function. **Figure 4** and **5** showed a representative example of left and right atrial strain, respectively. Moreover, LA conduit strain rate demonstrated an excellent AUC to discriminate TS with a sensitivity of 94 % and specificity of 44%.

Eitel *et al*. reported specific CMR criteria for TS diagnosis that include the combination of typical contraction pattern, oedema, and absence of LGE [19]. Recently, ventricular myocardial strain has been evaluated as an additional useful diagnostic marker in patients with TS [11,20,21].

Despite CMR is excellent both for functional and morphological studies aimed to assess typical regional wall motion abnormalities and reversible and irreversible myocardial injuries [5,11,22], TS is often misdiagnosed due to an nonspecific clinical manifestation which could resemble other cardiovascular diseases, such as acute coronary syndrome and myocarditis.[1,23]

Our results showed that atrial strain assessed on routinely acquired SSFP cine images, could help clinicians for the challenging differential diagnosis of TS, as an alternative marker beyond the traditional CMR parameters. In particular, we found a different atrial strain impairment between TS and AM patients.

The atria have a key role in maintaining ventricular filling and can be subdivided into three consecutive phases: reservoir, conduit and booster. Over the past decade, the focus has been on LA enlargement [24], but LA size does not provide a complete overview of the LA function during the cardiac cycle. In this scenario, atrial strain analysis enables to overcome usual limitations of the sole use of LA volumetric measurement.

Recently, the atrial deformation has been recognized in several cardiovascular diseases as an important marker of adverse cardiovascular events and there is a growing body of evidence that LA and RA deformation are sensitive quantitative parameters in early state diseases[14,25]

Our findings showed significantly lower LA ε_s, LA SRs, LAε_e, and LA SRe values in TS patients compared to a cohort of myocarditis patients. On the other hand, LAε booster strain showed an opposite trend towards higher values in TS patients, although this difference was not statistically significant. Change in RA strain and SR parameters demonstrated a similar trend of LA, although the difference between the groups under analyses was higher for LA strain.

The observed values of atrial strain in patients with TS are in line with the current literature [26]. A potential explanation of atria dysfunction in TS patients has been recently suggested [26]. The role of diastolic impairment in TS has been evaluated in a few studies so far, highlighting a transient LA impairment with recovery during follow-up. Stiermar *et al*. reported an improvement in LA reservoir strain parameters from 42% during the acute phase to 51 % at follow-up, similar trends were observed for conduit and booster phase [3]. The result of our study suggested a potential role of diastolic impairment in TS pathophysiology, highlighting atrial conduit rate parameters as a sensitive diagnostic tool in discriminating between TS and AM.

Truong *et al*. showed that CMR-FT had good intra- and inter-observer reproducibility for analysis of atrial deformation in both LA and RA [12,13]. Quantitative parameters used in our study are robust, with good to excellent intra- and inter-observer reproducibility for atrial strain and SR parameters, and fair to good for LA booster strain. These results are in line with previous research by Dick *et al*. [15]. Reproducibility for RA strain was poorer than LA strain, likely because of RA measurements in one view only (4-Chambers) compared to LA measurements, which were done in three different views (3-Chambers, 2-Chambers, and 4- Chambers).

A major limitation of this research is the relatively small number of patients and the retrospective selection of the patients' cohort. However, we enrolled exclusively TS patients with the apical type. The promising results of our study prompt further prospective trials including larger cohorts to

confirm our findings. Moreover, the predictive value of atrial strain for adverse cardiovascular events has not been assessed in our study at follow-up. Finally, the impairment in atrial strain in patients with TS would have been probably different if CMR was performed within a shorter period of time, ideally the same day of hospital admission.

Conclusion

In the current study, patients with TS showed significant lower LA reservoir and conduit functions compared to AM group. Our study findings suggest that LA impairments can be an additional quantitative parameter to discriminate TS and AM, helping clinicians in the challenging differential diagnosis of these two entities.

Disclosure

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 and none of the paper's contents have been previously published.

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Some of the patients under analysis were published in one of our previous studies.

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The authors declare that they have no competing interests.

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Figure legends

Figure 1 : Box-Whisker plots representing the difference of left atrial strain and strain rate parameters between Takotsubo, controls and Acute Myocarditis.

Figure 2 : ROC Curves for LA conduit strain rate to identify the patients with Takotsubo**.**

Figure 3 : Bland-Altman plots for intra- and inter-observer reproducibility of LA reservoir and conduit strain

Figure 4: Contouring for left atrium strain and strain rate parameters . The figure showed a representative image of left atrial strain from 2-chambers view using CMR-FT in a TS patient (fig a), in control subject (b) and in AM patient (c) with corresponding strain and strain rate parameters.

Figure 5: Contouring for right atrium strain and strain rate parameters. The figure showed a representative image of left atrial l strain from 4-chambers view using CMR-FT in a TS patient (fig a), in control subject (b) and in AM patient (c) with corresponding strain and strain rate parameters.

Tables

Table 1: Comparison of demographics and CMR findings in AM and TS

	TS	AM	Control	p
Age	68,7 ± 10	43,2 ± 15,9	49,8 ± 9,2	**0,001**
Female	17/18 (94%)	5/14 (35%)	7/11 (63%)	**0,001**
LVEF	58,7 ± 8,9	58,2 ± 5	59,2 ± 4,9	0,9
RVEF	59,6 ± 5,8	57,2 ± 4,9	55,6 ± 2,9	0,06
LGE g	0	12,27 ± 9,01	0	/
LGE %	0	11,62 ± 9,51	0	/
Troponin	2936 ± 2446	3270 ± 1670	0	/
LA ε_s	24,8 ± 5,9	30,1 ± 7,2	35,6 ± 3,9	**0,001**
LA SRs	1,1 ± 0,3	1,4 ± 0,4	1,5 ± 0,2	**0,001**
LAε_e	10,6 ± 4,4	16,3 ± 6,2	21,5 ± 4,9	**0,001**
LA SRe	-0,9 ± 0,4	-1,9 ± 0,7	-1,8 ± 0,4	**0,001**
LAε_a	14,7 ± 6,2	12,3 ± 3,8	13,2 ± 2,2	0,38
LA SRa	-1,65 ± 0,5	-1,5 ± 0,4	-1,73 ± 0,3	0,45
RA ε_s	35,9 ± 22,6	28,2 ± 2,2	38,7 ± 9,1	0,25
RA SRs	1,9 ± 0,6	-1,6 ± 0,5	2,1 ± 0,7	0,28
RAε_e	21,3 ± 15,1	17,8 ± 7,3	24,3 ± 9,8	0,38
RA SRe	-2,2 ± 1	-1,4 ± 0,3	-1,6 ± 0,8	0,07

RAε_a	14,9 ± 8,7	9,7 ± 5,5	13,4 ± 4,8	0,11
RA SRa	-2 ± 1,2	-1,6 ± 1	-1,4 ± 0,6	0,6

TS Takotsubo syndrome; LA left atrium; RA right atrium; ε_s Reservoir strain; SRs Reservoir strain rate; ε_e Conduit strain; SRe Conduit strain rate; ε_a Booster strain, SRa Booster strain rate
Mean +/- DS

Table 2: Multiple comparison Tukey post Hoc Test between different group and LA strain parameters

	TS vs AM	TS vs Control	AM vs control
LA ε_s	**0,04**	**< 0,001**	0,07
LA SRs	**0,007**	**0,003**	0,8
LAε_e	**0,01**	**< 0,001**	**0,04**
LA SRe	**< 0,001**	**<0,001**	0,9
Age	**< 0,001**	**0,001**	0,37
Gender	0,13	**0,01**	0,2

TS Takotsubo syndrome; LA left atrium; RA right atrium; ε_s Reservoir strain; SRs Reservoir strain rate; ε_e Conduit strain; SRe Conduit strain rate; ε_a Booster strain, SRa Booster strain rate
Mean +/- DS

Table 3. MANCOVA analysis

	Age	Gender
LA reservoir strain	0,81	0,54
LA reservoir strain rate	0,09	0,14
LA conduit strain	0,19	0,78
LA conduit strain rate	0,07	0,34

Table 4: ICCs for Intra- and inter-observer reproducibility of Atrial strain and SR parameters

	Intra-observer	Inter-observer
LA ε_s	0,85 (0,45-0,93)	0,81 (0,45-0,92)
LA SRs	0,93 (0,69-0,96)	0,89 (0,69-0.96)
LAε_e	0,90 (0,61-0,93)	0,85 (0,57-0,95)
LA SRe	0,85 (0,57-0,95)	0,86 (0,51-0,94)
LAε_a	0,84 (0,52-0,94)	0,78 (0,50-0,91)
LA SRa	0,61 (0,36-0,76)	0,57 (0,37-0,75)
RA ε_s	0,87 (0,61-0,96)	0,87 (0,61-0,95)
RA SRs	0,80 (0,41-0,93)	0,80 (0,41-0,93)
RAε_e	0,84 (0,55-0,95)	0,73 (0,37-0,90)
RA SRe	0,50 (0,48-0,83)	0,50 (0,48-0,83)
RAε_a	0,84 (0,52-0,94)	0,82 (0,50-0,91)
RA SRa	0,61 (0,14-0,87)	0,58 (0,38-0,78)

TS tako-tsubo syndrome; LA left atrium; RA right atrium; ε_s Reservoir strain; SRs Reservoir strain rate; ε_e Conduit strain; SRe Conduit strain rate; ε_a Booster strain, SRa Booster strain rate

Figures

Figure 1

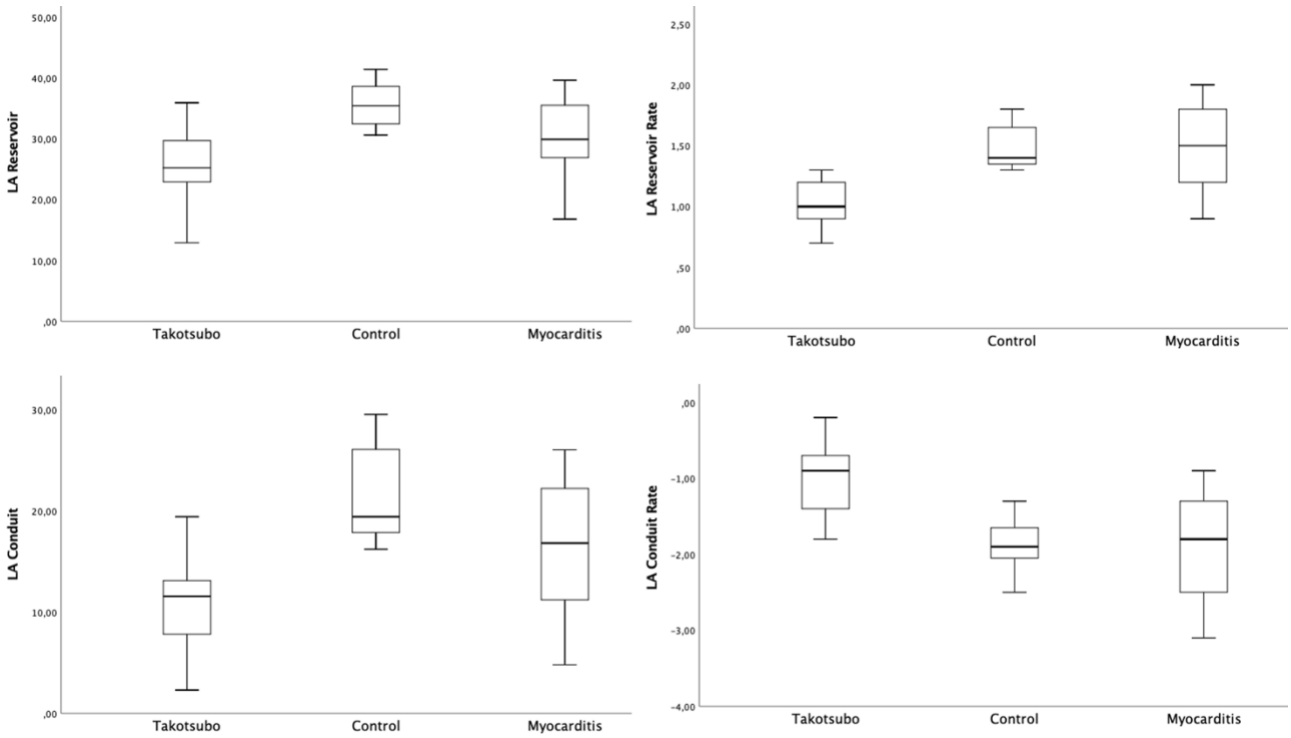

Figure 1: Box-Whisker plots representing the difference of left atrial strain and strain rate parameters between Takotsubo, controls and Myocarditis.

Figure 2

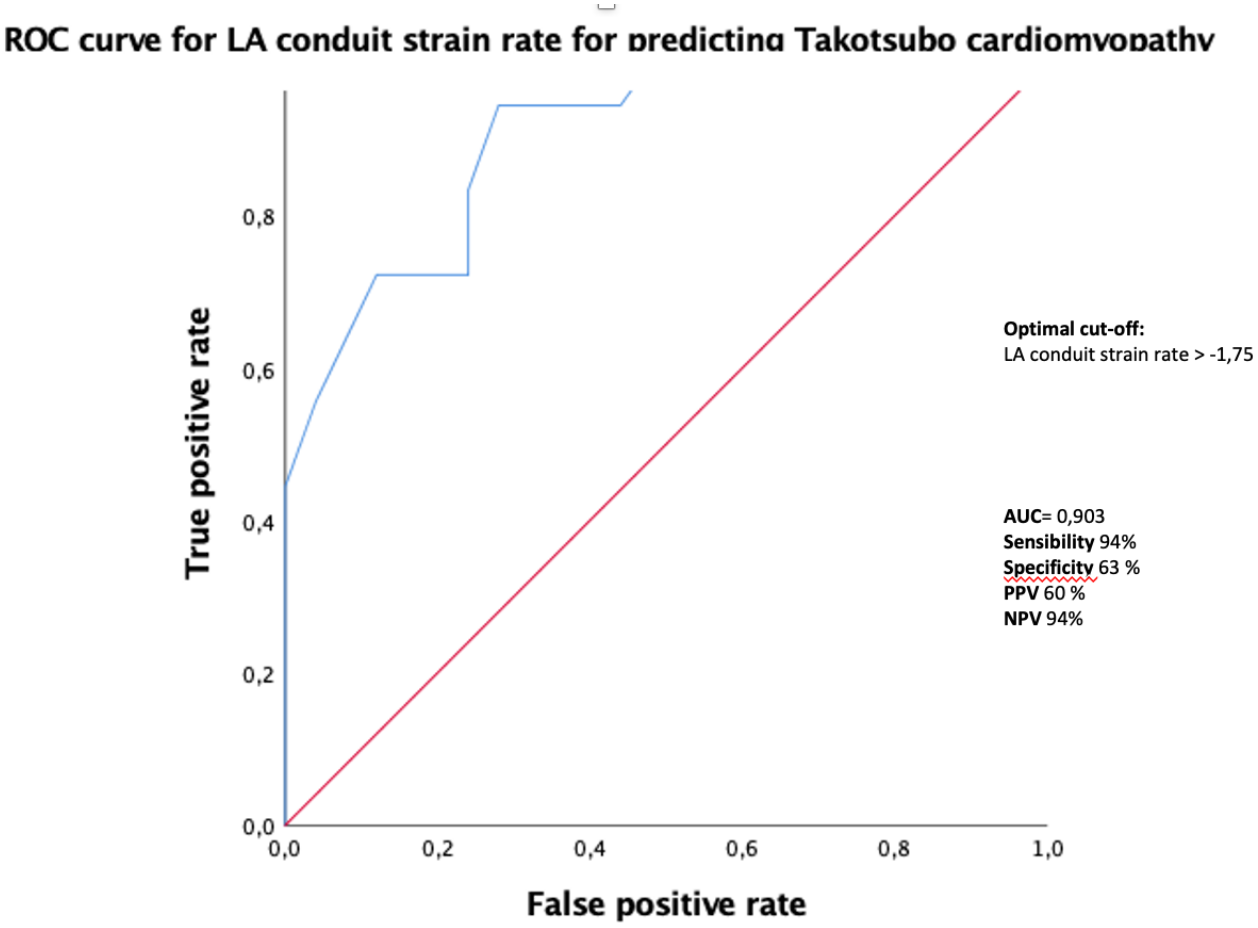

Figure 2: ROC Curves for LA conduit strain rate to identify the patients with Takotsubo**.**

Figure 3

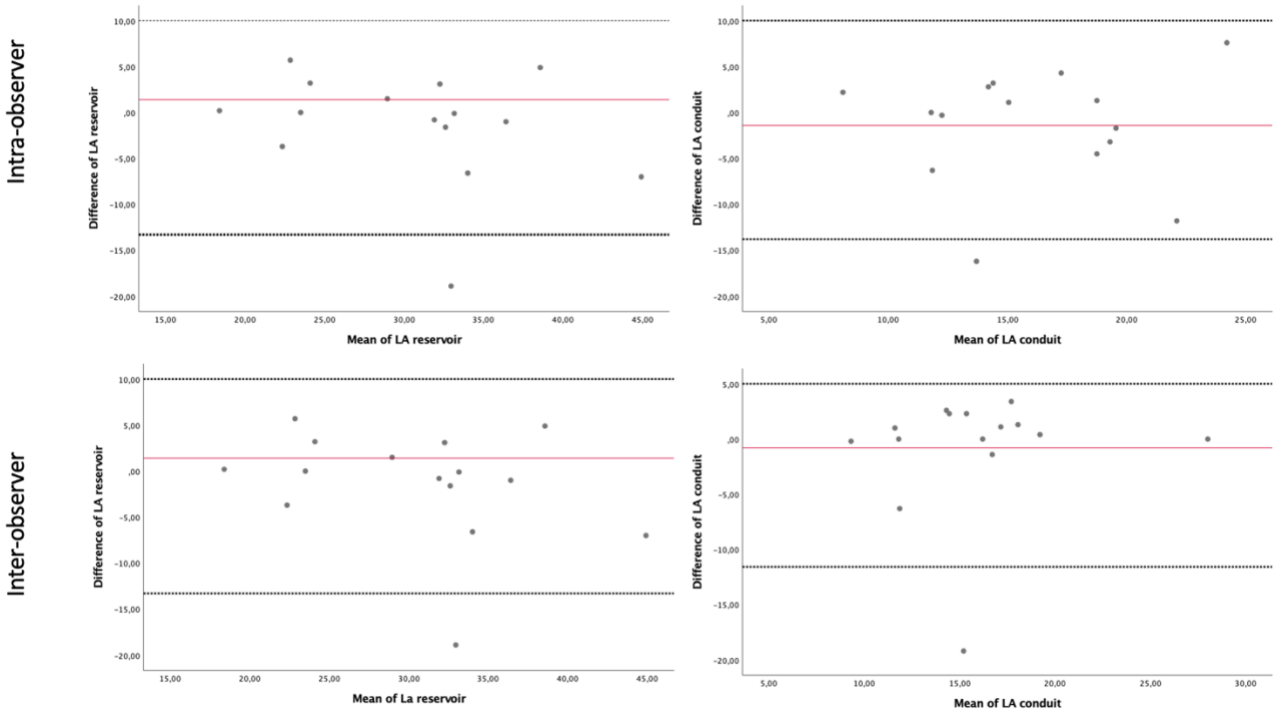

Figure 3: Bland-Altman plots for intra- and inter-observer reproducibility of LA reservoir and conduit strain

Figure 4

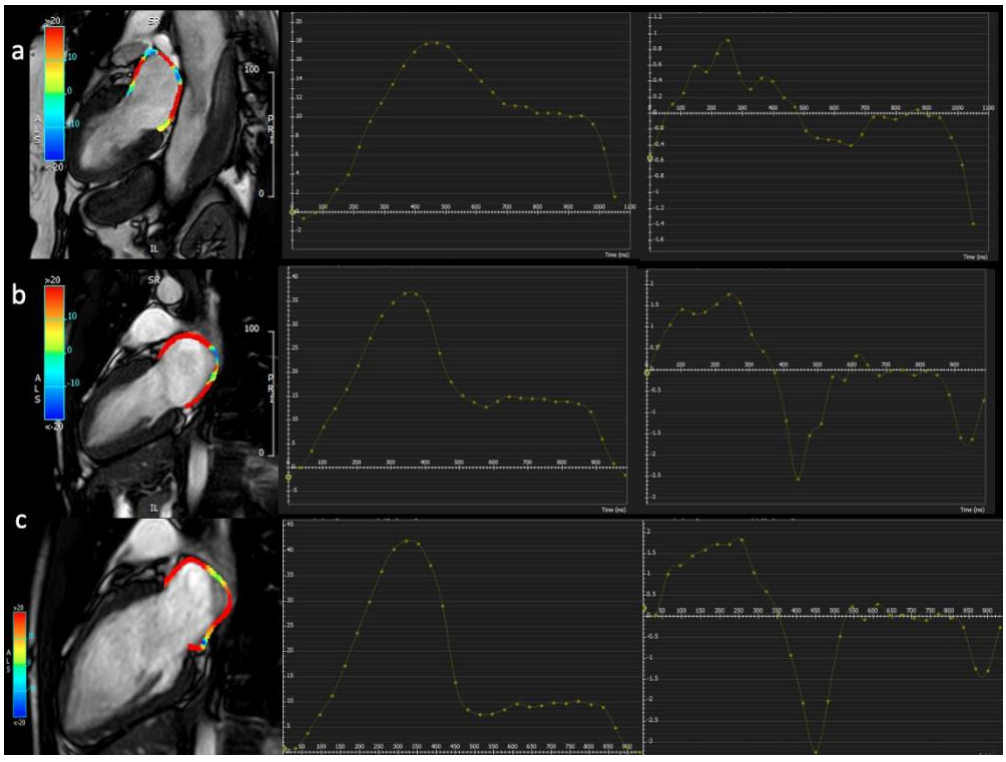

Figure 4: Contouring for left atrium strain and strain rate parameters. The figure showed a representative image of left atrial strain from 2-chambers view using CMR-FT in a TS patient (fig a), in control subject (b) and in AM patient (c) with corresponding strain and strain rate parameters.

Figure 5

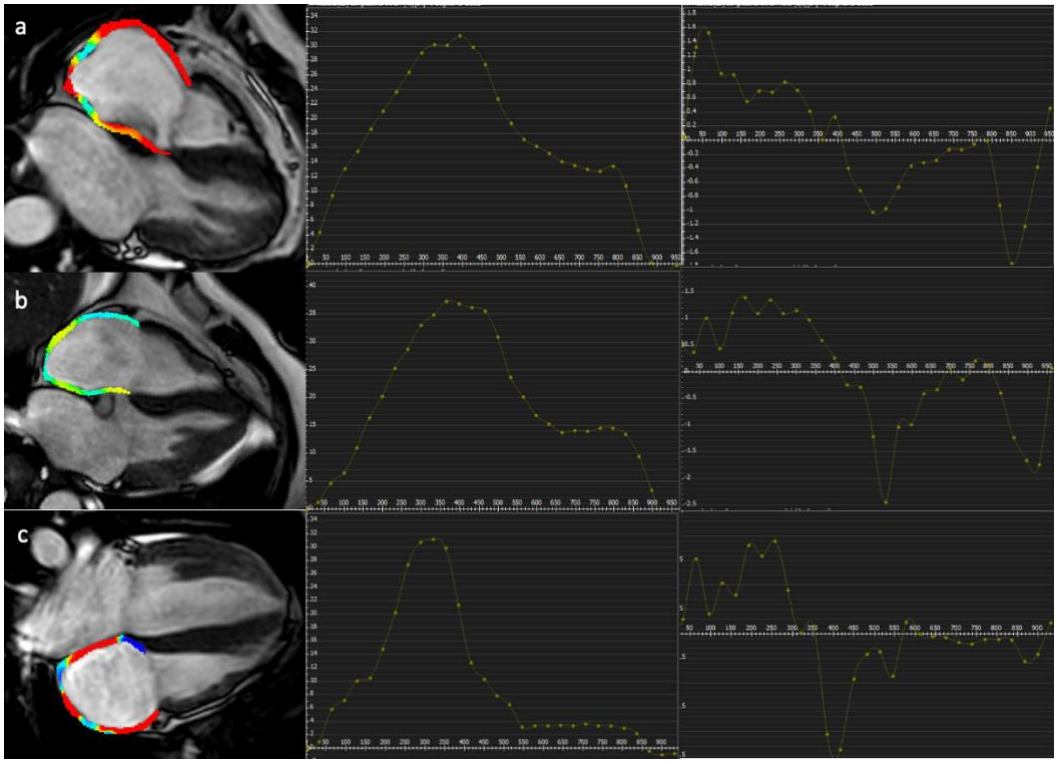

Figure 5: Contouring for right atrium strain and strain rate parameters . The figure showed a representative image of left atrial l strain from 4-chambers view using CMR-FT in a TS patient (fig a), in control subject (b) and in AM patient (c) with corresponding strain and strain rate parameters.