Could CMR tissue-tracking and parametric mapping distinguish between Takotsubo syndrome and acute myocarditis? A pilot study

Abstract

Rationale and Objective: Takotsubo syndrome (TS) is a transient and often misdiagnosed form of left ventricular dysfunction. Acute myocarditis (AM) is usually included in TS differential diagnosis. The aim of this study is to assess the role of cardiac magnetic resonance imaging coupled with tissue-tracking technique (CMR-TT) and parametric mappings analysis in discriminating between TS and AM.

Materials and Methods: We retrospectively enrolled 3 groups: patients with TS (n=12), patients with AM (n=14), and 10 healthy controls. All the patients had a comprehensive CMR examination, including the assessment of global and segmental longitudinal strain (LS), circumferential strain (CS), radial strain (RS) and parametric mapping.

Results: The analysis of variance was used to compare the different groups. In TS patients, basal RS, global T1 mapping, global T2 mapping, mid T2 mapping, apical T1 and T2 mapping were statistically significantly different compared with the other groups. MANCOVA analysis confirmed that the association between myocardial strain data and parametric mapping was independent on age and sex. Apical T1 and T2 mapping proved to have a good performance in differentiating TS from AM (AUCs of 0.908 and 0.879, respectively).

Conclusion: Basal RS and apical tissue mapping analysis are the most advanced CMR-derived parameters in making a differential diagnosis between TS and AM.

Acronyms

TS Takotsubo syndrome

AM acute myocarditis

CMR cardiac magnetic resonance

TT tissue-tracking

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

ROC receiver-operating characteristic

AUC area under the curve

LVG left ventriculography

Keywords: CMR; Takotsubo syndrome; Myocarditis; T1 mapping; T2 mapping; Myocardial strain.

Background

Takotsubo syndrome (TS) is characterized by a transient left ventricular (LV) dysfunction and a specific pattern of contractility, characterized by apical akinesia and dilatation, with or without mid-ventricular involvement, associated with basal hypercontractility. Alternative patterns were described, with mid-ventricular, basal, and focal LV wall motion abnormalities [1,2]. TS cardiomyopathy is often misdiagnosed, though it is likely to be responsible for about 2% of the cases initially presenting as a suspected acute coronary syndrome [1,3] **.**

Concerning TS, several diagnostic criteria were suggested, and each of them highlights the crucial role of cardiac magnetic resonance (CMR) in quantifying LV and right ventricular (RV) global and regional contractility, assessing TS complications, and characterizing myocardial tissue. In addition, CMR is helpful to rule out other diseases, such as acute myocarditis (AM). The latter is included in the differential diagnosis of TS, according with the majority of the existing diagnostic criteria[1,4,5]**.** The two diseases should be differentiated as earlier as possible, given the fact that their clinical course, management, outcomes, and prognoses are different.

Myocardial strain analysis with tissue-tracking (TT) CMR has not been clinically validated yet. However, global strain has proved to have a high sensitivity in the early detection of subclinical LV dysfunction , with the potential to overcome the usual limitations of ejection fraction (EF) [6]**.** Moreover, regional variability of myocardial strain can be used as an additional tool in making a differential diagnosis among different cardiovascular diseases. [7]

Parametric mapping techniques, such as T1 mapping and T2 mapping, are quantitative imaging methods that offer an objective evaluation of myocardial tissue properties, thus providing researchers with a quantitative assessment of myocardial tissue alterations rather than just a semi-quantitative or qualitative assessment of the same. So, parametric mapping increases CMR diagnostic accuracy [8,9]**.**

In this pilot study, we tested CMR-TT and tissue mapping ability in highlighting the differences between TS and AM.

Material and method

Study population

In this retrospective and single-centre study, 12 patients with a diagnosis of TS, 14 patients with a diagnosis of AM, and 10 healthy controls were enrolled from March 3rd, 2017 to September 7th,2020 .

TS diagnosis was made by using the definition reported in the Position Statement of the European Society of Cardiology Heart Failure Association[5] **.**

The diagnosis of AM was made clinically, in accordance of what reported in the Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Endomyocardial biopsy (EMB) was not performed[10] .

Exclusion criteria included: subjects < 18 years old; patients with a different diagnostic suspicion after CMR.

CMR

Imaging protocol

All CMR scans were performed at 4.1± 2.6 days (median = 1 day, range = from 1 to 10 days) after admission to hospital by using a Philips Achieva dStream 1.5 T scanner system (*Philips Healthcare, Best, The Netherlands*). Anterior coil arrays were used. Cine-CMR examinations were electrocardiogram triggered and performed during breath-hold. Thirty phases were derived for each cardiac cycle. Our CMR protocol was based on functional sequences, such as cine white blood

steady-state free precession (SSFP) on the short axis and long axes (2 chambers, 3 chambers and 4 chambers) and tissue morphological and characterization sequences such as T2 STIR on both short and long axes, pre- and post-contrast T1 mappings, T2 mapping and LGE sequences.

T2 mapping sequences were acquired prior to contrast agent injection in end-diastole in 3 short axis slices (apical, mid, basal) using multi-echo sequences. T1 mapping was 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 respectively 53 ± 3 ms and 1030 ± 30 ms, respectively.

In parametric mapping, the apical slice is often source of inaccurate measurements due to the high probability of inclusion of voxels outside the true myocardium. We have selected a not too apical slice in all the patients, in order to avoid partial volume effects in apical mapping.

Late gadolinium enhancement (LGE) imaging was performed 10-12 minutes after contrast agent injection (*Gadovist, Bayer Healthcare, Berlin, Germany*) using phase-sensitive inversion recovery sequences 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-TT data analysis. Offline CMR-TT analyses were conducted for the evaluation of peak global longitudinal strain (GLS), global radial strain (GRS),

and global circumferential strain (GCS) in a 16-segment software-generated model. Regarding GLS, data on myocardial strain were obtained from two-, three- and four-chambers long-axis views. Regarding GRS and GCS, data on myocardial strain data were acquired from apical, mid-ventricular and basal short-axis views in all patients. On all the acquired images, the epi- and endocardial borders were traced in the end-diastolic phase. After that, with an automatic computation, the software algorithm automatically tracked the myocardial borders 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. 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 normal distribution. Categorical variables were compared by using the chi-square test or Fisher's exact test, as appropriate.

Comparisons between groups were performed using the 1-way ANOVA for continuous variables with normal distributions, and the Kruskal-Wallis test was used for continuous variables with non-normal distributions. The post-hoc Tukey multiple comparison test was performed to look for statistically significant differences among each group. A general linear model (GLM) analysis was performed with age and gender as covariates (MANCOVA).

Again, a receiver-operating characteristic (ROC) analysis was performed to calculate optimal thresholds and areas under the curves (AUCs). The Youden index was used to identify optimal cut-off values from the ROC curves. Sensitivities and specificities were calculated for these cut-off values with 95% confidence intervals. 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) and MedCalc (MedCalc Software, Mariakerke, Belgium).

Results

Regarding the 12 patients with TS, 11 were females and one was male, with an average age of 67 ± 9 years. Among the 10 patients with AM, 6 were males and 4 females, with an average age of 43 ± 15 years. As for the healthy controls, 6 were females and 4 males, with an average age of 51 ± 8 years. The demographics characteristics and CMR parameters of the subjects enrolled in the study are summarized in **Table 1**.

Analysis of variance was used to compare the different groups. In the global strain analysis, there was a statistically significant difference between the groups as determined by one-way ANOVA. In particular, GLS, GCS and GRS were significantly lower in TS and AM group compared with control patients ($p<0.01$, $p=0.03$, $p=0.02$, respectively). Differences in basal, mid and apical strain analysis are summarized in **Table 1.** In particular, we found that all LS, apical CS, basal and apical RS were statistically significant difference between the groups under analysis.

Regarding parametric mapping, all T1 and T2 mapping parameters were significantly higher in AM and TS group compared to controls, as summarized in **Table 1**

A Tukey post hoc test revealed that, in TS patients, criteria such as age, basal RS, global T1 mapping, global T2 mapping, mid T2 mapping, and apical T1 and T2 mapping were statistically significantly different compared with the other groups (**Table 2 and Figure 1**)

MANCOVA analysis confirmed that the association of basal RS and parametric mapping were independent of age and gender (**Table 3).**

Apical T1 and T2 mapping proved to have a good sensitivity in differentiating patients with TS from those with AM (AUCs of 0.908 and 0.879 respectively, while related CI were 0.61–0.96 and 0.57–0.95, respectively). Optimal apical T1 and T2 mapping cut-off values to identify TS were >1,143 and >64 ms with sensitivities/specificities of 83/87 and 82/83%, respectively (**Figure 2)**

Discussion

Invasive coronary angiography with left ventriculography (LVG) is the 'gold standard' in making the diagnosis of TS [1,11]**.** However, this procedure is invasive and potentially at risk of the onset of life-threatening events[12]. Conversely, a few non-invasive imaging techniques proved to be helpful in the work-up of patients with TS. For example, echocardiography plays a key role as first-line imaging modality but, at the same time, its diagnostic value is often limited by inadequate soft tissue characterization and suboptimal field-of-view in the setting of poor acoustic windows, such as in overweight and obese patients [13,14]**.**

CMR is excellent for functional studies aimed at assessing regional wall motion abnormalities as well as for morphological studies with the goal of identifying the presence of reversible and irreversible myocardial injuries[15,14,16] **.** An important hallmark in the acute phase of TS is myocardial inflammation[15,17–19]. In the past, detection of myocardial oedema with T2-STIR was possible in patients with AM and TS [20] **,** but with widely recognized limitations [21]**.** Diagnostic accuracy increases by using parametric mappings techniques[22]**.** In particular, T2 mapping is able to identify acute myocardial oedema and has several advantages compared with traditional T2-weighted imaging, including higher signal-to-noise ratio and shorter breath-holds intervals, thus leading to less breathing-related motion artifacts. On the other hand, native T1 is sensitive to intracellular and extracellular changes in the free water content and its relaxation time increases during acute inflammation, vasodilation, and hyperemia [9,23]**.**

This retrospective study shows that tissue mapping techniques can improve CMR sensitivity in differentiating TS from AM. In fact, these two diseases show characteristic patterns which are detectable with parametric mappings and are related to their different pathophysiology[1,10]**.** We found significantly higher apical T1 and T2 values in patients with TS compared to those with AM **(Figure 3).** T1 and T2 mapping had raised values even in myocardium apparently normal and not involved in wall motion abnormalities, thus showing an involvement of the whole LV. On the contrary, T2 mapping decreased gradually from the apical to the basal regions. According to Neil et al., in TS patients, inflammation is particularly localised at the apical cavity [19]**.**

Another hallmark of TS is represented by the typical regional wall motion abnormalities, i.e. mid-cavity to apical ballooning and akinesia, sparing the basal LV segments, although the latter may sometimes be hyperkinetic as well. It is the so called classic "bull-eye" appearance[15]**.** In this scenario, CMR is the gold standard in assessing cardiac structure and function[24]**.** Many studies demonstrated that myocardial strain reflects subtle changes in the underlying myocardial substrate[25–27]**.** In the most frequent type of TS, myocardial strain decreases from the base to the apex, thus indicating a more severe involvement of the LV apical and mid-ventricular segments compared to the basal [11,28]**.** Two hypotheses may explain this difference: one is that according to the apical myocardium is more responsive to sympathetic stimulation than the other ventricular regions. According to the second theory, regional differences in myocardial blood flow (with a reduced apical flow) might be present in the setting of catecholamine-mediated microvascular dysfunction[29,30]. Conversely, several studies reported that all myocardial strain parameters are significantly impaired in patients with AM[31–33].

Our study suggests that, in patients with TS, basal LS is preserved compared to mid-cavity and apical strain, while in patients with AM the whole LV is involved**.** These findings may be explained by a partial recovery of myocardial strain, in accordance with previous reports which

showed an improvement of LS from LV base to the apex with time [34]**.** Again, the higher value of basal RS may be explained by the transient LV hyperkinetic contractility of the basal segments, as already reported by Kobayashi et al.[35].

The assessment of the myocardial function is a crucial aspect in the evaluation of TS, because of its diagnostic and prognostic implications[1]. Strain analysis provides with an extensive quantification of all myocardial deformation components[6] . Moreover, it is able to detect even a focal (segmental) LV abnormality as well as the compensatory increase in other myocardial strain parameters aimed at maintaining EF within the normal range [36]. One of the usual CMR-TT limitations is that it is time-consuming, although it is also a post-processing technique that does not require additional time for images acquisition in the scanner[6]**.** CMR-TT contributes to the differential diagnosis between TS and AM, which require a different therapy.

With its advanced tools, CMR is a non-invasive method offering the opportunity to detect the presence of myocardial damage and assess whether myocardial injury is reversible or irreversible [17,37]**.**

A major limitation of this research is the relatively small sample size. However, the study reflects a case series of selected consecutive patients with an uncommon disease. The retrospective design of the study and the relatively reduced number of patients will certainly be improved in the future by using a prospective study methodology and a larger cohort. In addition, we included only patients with a clinical diagnosis of AM. EMB was not used. Moreover, the impairment of myocardial strain in TS patients would probably have been different if CMR had been performed sooner, ideally the same day of admission to hospital. This is because the temporal evolution of TS is usually rapid and an improvement in contractility may occur in the first 24 hours since the first appearance of symptoms[1,38].

Conclusion

Our findings show that basal radial strain (RS) and parametric mapping can differentiate between TS and AM, through the detection of different types of myocardial impairment, which are linked with their peculiar pathophysiology. CMR-TT and tissue mapping proved to be pivotal tools in assessing the evolution of myocardial injury. Further longitudinal prospective studies, with a larger number of patients, are needed to confirm the usefulness of these advanced CMR tools in this setting.

References

1. Ghadri J-R, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. *Eur Heart J*. 2018;39(22):2047—2062. doi:10.1093/eurheartj/ehy077

2. Ono R, Falcão LM. Takotsubo cardiomyopathy systematic review: Pathophysiologic process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy. *Int J Cardiol*. 2016;209:196—205. doi:10.1016/j.ijcard.2016.02.012

3. Bybee KA, Prasad A, Barsness GW, et al. Clinical characteristics and Thrombolysis In Myocardial Infarction frame counts in women with transient left ventricular apical ballooning syndrome. *Am J Cardiol*. 2004;94(3):343-346. doi:https://doi.org/10.1016/j.amjcard.2004.04.030

4. Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. *Herz*. 2010;35(4):240-244. doi:10.1007/s00059-010-3339-x

5. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(1):8-27. doi:https://doi.org/10.1002/ejhf.424

6. Scatteia A, Baritussio A, Bucciarelli-Ducci C. Strain imaging using cardiac magnetic resonance. *Heart Fail Rev*. 2017;22(4):465-476. doi:10.1007/s10741-017-9621-8

7. Williams LK, Forero JF, Popovic ZB, et al. Patterns of CMR measured longitudinal strain and its association with late gadolinium enhancement in patients with cardiac amyloidosis and its mimics. *J Cardiovasc Magn Reson*. 2017;19(1):61. doi:10.1186/s12968-017-0376-0

8. Mavrogeni S, Apostolou D, Argyriou P, et al. T1 and T2 Mapping in Cardiology: "Mapping the Obscure Object of Desire." *Cardiology*. 2017;138(4):207-217. doi:10.1159/000478901

9. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol*. 2018;72(24):3158-3176. doi:https://doi.org/10.1016/j.jacc.2018.09.072

10. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34(33):2636-2648. doi:10.1093/eurheartj/eht210

11. Bossone E, Lyon A, Citro R, et al. Takotsubo cardiomyopathy: an integrated multi-imaging approach. *Eur Hear J - Cardiovasc Imaging*. 2014;15(4):366-377. doi:10.1093/ehjci/jet167

12. Lee H-H, Lee W-H, Chiu C-A, et al. The Current Status of Performing Left Ventriculography in Taiwan. *Acta Cardiol Sin*. 2016;32(1):49—54. doi:10.6515/acs20150520b

13. Kalisz K, Rajiah P. Computed tomography of cardiomyopathies. *Cardiovasc Diagn Ther*. 2017;7(5):539-556.

doi:10.21037/cdt.2017.09.07

14. Cau R, Bassareo P, Saba L. Cardiac Involvement in COVID-19—Assessment with Echocardiography and Cardiac Magnetic Resonance Imaging. *SN Compr Clin Med*. Published online June 10, 2020. doi:10.1007/s42399-020-00344-7

15. Bratis K. Cardiac Magnetic Resonance in Takotsubo Syndrome. *Eur Cardiol*. 2017;12(1):58-62. doi:10.15420/ecr.2017:7:2

16. Cau R, Bassareo PP, Mannelli L, Suri JS, Saba L. Imaging in COVID-19-related myocardial injury. *Int J Cardiovasc Imaging*. Published online 2020. doi:10.1007/s10554-020-02089-9

17. Fernández-Pérez GC, Aguilar-Arjona JA, de la Fuente GT, et al. Takotsubo Cardiomyopathy: Assessment With Cardiac MRI. *Am J Roentgenol*. 2010;195(2):W139-W145. doi:10.2214/AJR.09.3369

18. Eitel I, Lücke C, Grothoff M, et al. Inflammation in takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging. *Eur Radiol*. 2010;20(2):422-431. doi:10.1007/s00330-009-1549-5

19. Neil C, Nguyen TH, Kucia A, et al. Slowly resolving global myocardial inflammation/oedema in Tako-Tsubo cardiomyopathy: evidence from T2-weighted cardiac MRI. *Heart*. 2012;98(17):1278 LP - 1284. doi:10.1136/heartjnl-2011-301481

20. Abdel-Aty H, Boyé P, Zagrosek A, et al. Diagnostic Performance of Cardiovascular Magnetic Resonance in Patients With Suspected Acute Myocarditis: Comparison of Different Approaches. *J Am Coll Cardiol*. 2005;45(11):1815-1822. doi:https://doi.org/10.1016/j.jacc.2004.11.069

21. Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. *J Cardiovasc Magn Reson*. 2011;13(1):13. doi:10.1186/1532-429X-13-13

22. Sebastian B, K. RU, K. LG, et al. Performance of T1 and T2 Mapping Cardiovascular Magnetic Resonance to Detect Active Myocarditis in Patients With Recent-Onset Heart Failure. *Circ Cardiovasc Imaging*. 2015;8(6):e003073. doi:10.1161/CIRCIMAGING.114.003073

23. Pan JA, Lee YJ, Salerno M. Diagnostic Performance of Extracellular Volume, Native T1, and T2 Mapping Versus Lake Louise Criteria by Cardiac Magnetic Resonance for Detection of Acute Myocarditis: A Meta-Analysis. *Circ Cardiovasc Imaging*. 2018;11(7):e007598-e007598. doi:10.1161/CIRCIMAGING.118.007598

24. Petersen SE, Aung N, Sanghvi MM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson*. 2017;19(1):18. doi:10.1186/s12968-017-0327-9

25. Dorit K, Anne-Catherine P, M. SA, et al. Dyssynchrony, Contractile Function, and Response to Cardiac Resynchronization Therapy. *Circ Hear Fail*. 2011;4(4):433-440. doi:10.1161/CIRCHEARTFAILURE.111.962902

26. Smedsrud MK, Pettersen E, Gjesdal O, et al. Detection of Left Ventricular Dysfunction by Global Longitudinal Systolic Strain in Patients with Chronic Aortic Regurgitation. *J Am Soc Echocardiogr*. 2011;24(11):1253-1259.

doi:https://doi.org/10.1016/j.echo.2011.08.003

27. Kutty S, Rangamani S, Venkataraman J, et al. Reduced global longitudinal and radial strain with normal left ventricular ejection fraction late after effective repair of aortic coarctation - a CMR feature tracking study. *J Cardiovasc Magn Reson*. 2012;14(Suppl 1):O59-O59. doi:10.1186/1532-429X-14-S1-O59

28. Heggemann F, Weiss C, Hamm K, et al. Global and regional myocardial function quantification by two-dimensional strain in Takotsubo cardiomyopathy. *Eur J Echocardiogr*. 2009;10(6):760-764. doi:10.1093/ejechocard/jep062

29. Nef HM, Möllmann H, Elsässer A. Tako-tsubo cardiomyopathy (apical ballooning). *Heart*. 2007;93(10):1309-1315. doi:10.1136/hrt.2006.101675

30. Ako J, Takenaka K, Uno K, et al. **Reversible Left Ventricular Systolic Dysfunction -Reversibility of Coronary Microvascular Abnormality**. *Jpn Heart J*. 2001;42(3):355-363. doi:10.1536/jhj.42.355

31. Lee JW, Jeong YJ, Lee G, et al. Predictive Value of Cardiac Magnetic Resonance Imaging-Derived Myocardial Strain for Poor Outcomes in Patients with Acute Myocarditis. *Korean J Radiol*. 2017;18(4):643-654. doi:10.3348/kjr.2017.18.4.643

32. Løgstrup BB, Nielsen JM, Kim WY, Poulsen SH. Myocardial oedema in acute myocarditis detected by echocardiographic 2D myocardial deformation analysis. *Eur Hear J - Cardiovasc Imaging*. 2016;17(9):1018-1026. doi:10.1093/ehjci/jev302

33. Hsiao J-F, Koshino Y, Bonnichsen CR, et al. Speckle tracking echocardiography in acute myocarditis. *Int J Cardiovasc Imaging*. 2013;29(2):275-284. doi:10.1007/s10554-012-0085-6

34. Kim S-A, Jo S-H, Park K-H, Kim H-S, Han S-J, Park W-J. Functional recovery of regional myocardial deformation in patients with takotsubo cardiomyopathy. *J Cardiol*. 2017;70(1):68-73. doi:https://doi.org/10.1016/j.jjcc.2016.09.006

35. Kobayashi Y, Okura H, Kobayashi Y, Fukuda S, Hirohata A, Yoshida K. Left ventricular myocardial function assessed by three-dimensional speckle tracking echocardiography in Takotsubo cardiomyopathy. *Echocardiography*. 2017;34(4):523-529. doi:https://doi.org/10.1111/echo.13492

36. Stokke TM, Hasselberg NE, Smedsrud MK, et al. Geometry as a Confounder When Assessing Ventricular Systolic Function: Comparison Between Ejection Fraction and Strain. *J Am Coll Cardiol*. 2017;70(8):942—954. doi:10.1016/j.jacc.2017.06.046

37. Eitel I, Behrendt F, Schindler K, et al. Differential diagnosis of suspected apical ballooning syndrome using contrast-enhanced magnetic resonance imaging. *Eur Heart J*. 2008;29(21):2651-2659. doi:10.1093/eurheartj/ehn433

38. Weiner MM, Asher DI, Augoustides JG, et al. Takotsubo Cardiomyopathy: A Clinical Update for the Cardiovascular Anesthesiologist. *J Cardiothorac Vasc Anesth*. 2017;31(1):334-344. doi:https://doi.org/10.1053/j.jvca.2016.06.004

Figure Legend

Figure 1 Box-plot chart of differences myocardial strain and tissue mapping among Takotsubo, Acute Myocarditis and control.

Figure 2 ROC Curves for apical T1 and apical T2 mapping to identify the patients with Takotsubo.

Figure 3 Example of parametric mapping with AHA segmentation in (a) patients suffering from myocarditis and (b) patients with Takotsubo syndrome.

Tables

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

	TS	AM	Control	p
Age	66.8 ± 9.27	43.1 ± 15.95	51 ± 8,8	<**0.01**
Gender (Female)	11/12	4/14	6/10	<**0.01**
EDV/BSA LV	69.5 ± 19.7	90.4 ± 18.1	78.4 ± 13.1	**0.01**
ESV/BSA LV	29.8 ± 10.2	38.5 ± 11.5	32 ± 6,5	0.09
SV/BSA LV	40 ± 12	51.8 ± 7,3	46.8 ± 9.3	**0.03**
EF LV	56.8 ± 9.1	58.2 ± 5	59.2 ± 6.6	0.7
GLS	-12.09 ± 2.9	-12.4 ± 2.2	-17.8 ± 1.89	<**0.01**
GCS	-17.81 ± 3.7	-18.4 ± 2.6	-20.9 ± 1.8	**0.039**
GRS	30.7 ± 10.11	28.4 ± 7.3	37.5 ± 5	**0.029**
Basal longitudinal strain	-16.2 ± 5.2	-10.9 ± 3.1	-18 ± 1.8	<**0.01**
Basal circumferential strain	-20.7 ± 2.5	-18 ± 3	-20.14 ± 3.12	0.06
Basal radial strain	49.7 ± 7.3	35.6 ± 10	30.4 ± 18.7	<**0.01**
Mid longitudinal strain	-14.45 ± 3.25	-11.6 ± 2.23	-17.9 ± 3.03	**0.028**
Mid circumferential strain	-17.32 ± 3.67	-18.17 ± 2.87	-20.17 ± 2	**0.1**
Mid radial strain	19.6 ± 10.82	77.32± 8.21	28.3± 8.21	0.08
Apical longitudinal strain	-12.34 ±2.44	-13.85 ± 4.57	-16.25 ± 3.52	<**0.01**
Apical circumferential strain	-17.7 ± 3.2	-20.7 ± 2.13	-25.76 ± 1.23	<**0.01**
Apical radial strain	22.92 ± 9.60	27.4 ± 12.89	42 ± 22.89	**0.02**
Global T1 mapping	1161.8	1060.56	1004.14	<**0.01**

Basal T1 mapping	1121	1046,1	1006,1	**0.016**
Mid-cavity T1 mapping	1135,6	1055	999	**<0.01**
Apical T1 mapping	1227.25	1080.5	1009	**<0.01**
Global T2 mapping	65.2 ± 4.8	60 ± 5.7	54.2 ± 2.2	**<0.01**
Basal T2 mapping	59.3 ± 4.4	60.7 ± 5.7	54.2 ± 3.6	**<0.01**
Mid-cavity T2 mapping	64.9 ± 5.7	58.2± 6.3	52.9 ± 2.3	**<0.01**
Apical T2 mapping	71.5 ± 6.7	61.3 ± 6.5	55 ± 3.2	**<0.01**

TS tako-tsubo syndrome; AM acute myocarditis;, LV left ventricle, EDV end-diastolic volume; ESV end-systolic volume; SV stroke volume; EF ejection fraction BSA body surface area ; GLS global longitudinal strain; GCS global circumferential strain; GRS global radial strain.

Mean +/- DS

Table 2: Multiple Comparisons Tukey post hoc test between different group and CMR-TT parameters and parametric mapping

	p-value		
	TS vs AM	TS vs control	AM vs control
Global T2 mapping	**0.046**	**0.001**	**0.017**
Mid-T2 mapping	**0.022**	**0.001**	0.089
Apical T2-mapping	**0.001**	**0.001**	**0.038**
Basal radial strain	**0.024**	**0.004**	0.574
Global T1 mapping	**0.038**	**0.001**	0.26
Apical T1 mapping	**0.011**	**0.001**	0.25
Age	**0.001**	0.29	**0.015**

Table 3. MANCOVA analysis
Association of different group with ipsilateral symptoms

	Age	Sex
Basal Radial Strain	0.86	0.45
Global T1 mapping	0.42	0.97
Apical T1 mapping	0.55	0.58
Mid T2 mapping	0.29	0.87
Apical T2 mapping	0.51	0.33
Global T2 mapping	0.65	0.25

Figure 1

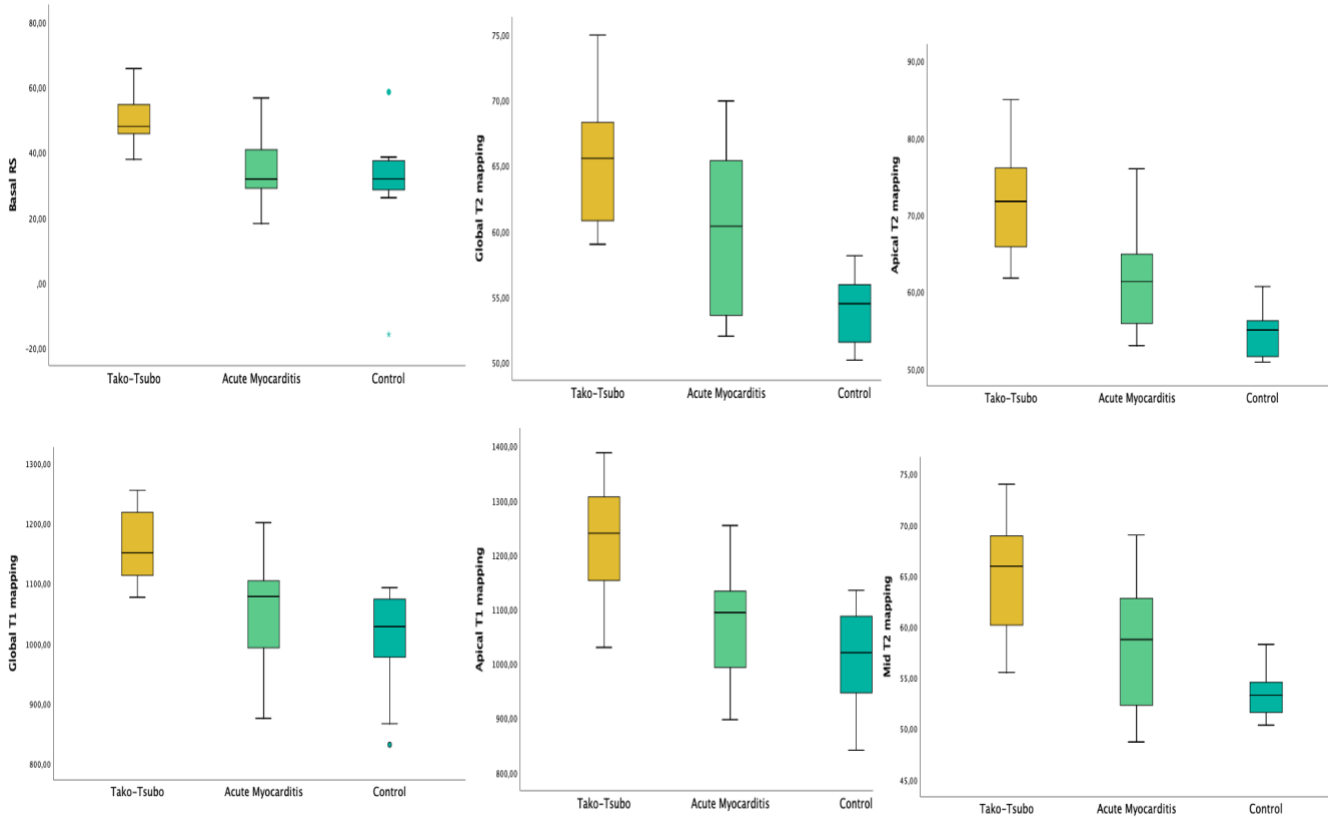

Figure 1 Box-plot chart of differences myocardial strain and tissue mapping among Takotsubo, Acute Myocarditis and control.

Figure 2

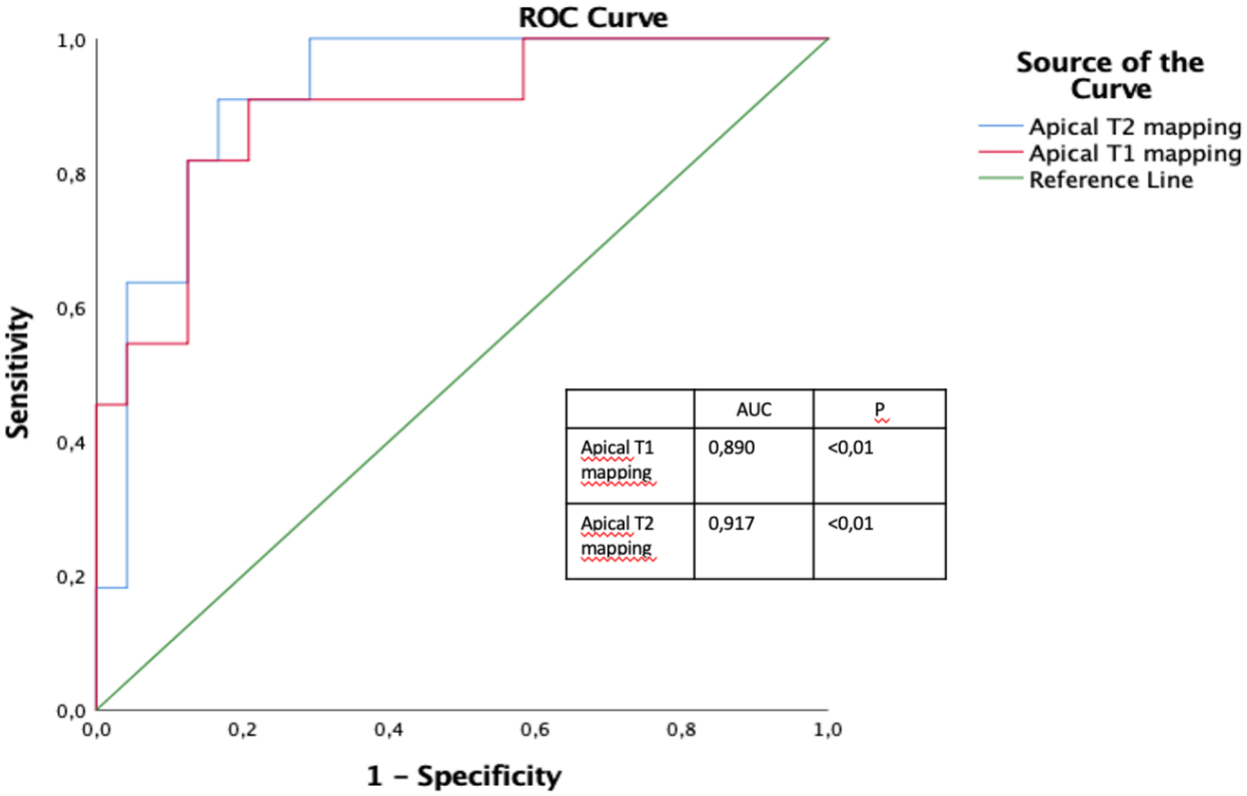

Figure 2 ROC Curves for apical T1 and apical T2 mapping to identify the patients with Takotsubo.

Figure 3

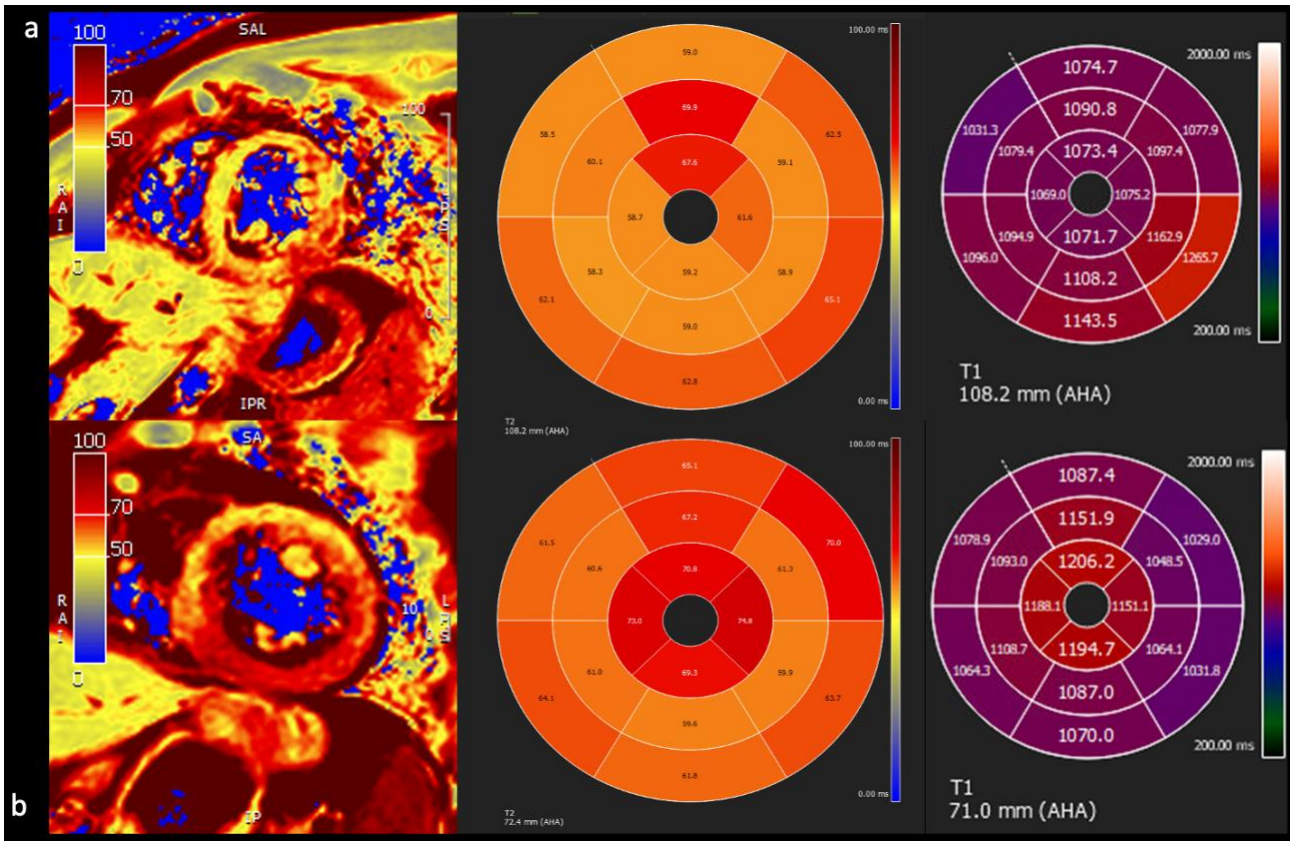

Figure 3 Example of parametric mapping with AHA segmentation in (a) patient suffering from myocarditis and (b) patient with Takotsubo syndrome.