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REVIEW

Advanced Cardiovascular Magnetic Resonance Imaging in Takotsubo Syndrome: Update on Feature Tracking and Tissue Mapping

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Abstract

Backgrounds Takotsubo syndrome (TTS) is an intriguing clinical entity characterized by transient myocardial dysfunction. The precise pathophysiological mechanism of TTS is still unknown, but recent evidence suggests a central role of systemic inflammation associated with adrenergic discharge. Although initially considered benign, TTS has shown several potential short-term and long-term complications and adverse outcomes. To improve understanding and management, advanced cardiovascular magnetic resonance (CMR) techniques, such as feature tracking (FT) and parametric mapping, have gained attention.

Purpose of Review The purpose of this review is to summarize the current literature on the clinical applications of CMR-FT and mapping in TTS. Additionally, the most significant and recent findings will be discussed.

Recent Findings FT-CMR enables the parametric quantification of myocardial deformation, allowing a comprehensive evaluation of left ventricular, right ventricular, and atrial function. It provides an accurate definition of areas of myocardial dysfunction and potentially serves as a superior prognostic tool compared to ejection fraction. Tissue mapping techniques enable precise and comprehensive tissue characterization by quantifying areas of oedema, and myocardial fibrosis.

Summary FT-CMR and mapping techniques serve as valuable prognostic tools both in the acute and chronic phases of TTS. They can detect subtle alterations and pan-cardiac involvement, while also providing important insights into the complex underlying mechanisms of the syndrome.

Keywords Takotsubo · Cardiovascular Magnetic Resonance · Feature Tracking · Mapping

Introduction

Takotsubo syndrome (TTS) is a cardiac disorder characterized by transient myocardial dysfunction that mimics acute myocardial infarction [1]. Despite initially considered a benign condition [2, 3], growing evidence suggests that the prognosis of TTS is not always favourable, with potential complications such as heart failure, cardiogenic shock, and death [4–9]. In fact, some studies have reported that TTS carries a similar or even higher risk of adverse outcomes compared to acute coronary syndrome [4, 10–13]. Importantly, this unfavourable prognosis extends beyond the acute phase [14–16]. This highlights the need for better understanding of the pathophysiology of TTS and the development of more effective management strategies.

The diagnosis of TTS is based on clinical, electrocardiographic, and echocardiographic findings. However, the role of cardiovascular magnetic resonance (CMR) imaging in the diagnosis and management of TTS has been increasingly recognized in recent years [17]. CMR is considered the gold standard for the evaluation of myocardial structure and function. In the context of TTS, it is recommended to perform CMR during the acute phase whenever possible. This allows for a

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comprehensive assessment of the disease providing useful clinical information for patient management [18]. New CMR techniques are continuously emerging and finding applications in many clinical settings, thanks to advances in related software and hardware techniques. Two techniques that have garnered considerable interest in recent years are CMR feature-tracking (CMR-FT) for myocardial strain analysis and parametric T1 and T2 mapping for myocardial tissue characterization.

In the present review, we will summarize and discuss the most recent findings regarding CMR-FT and mapping in TTS. Additionally, we will explore their significance and potential clinical applications.

Cardiovascular Magnetic Resonance Feature Tracking

Myocardial strain, also known as myocardial deformation imaging, is a technological advancement that has been developed to objectively quantify regional myocardial function beyond ejection fraction [19, 20].

It is a dimensionless index of the length change between two given points, reflecting the degree of myocardial deformation. The formula to calculate strain (ε) is (L – L0)/L0, where L0 is the baseline length (usually end-diastole), and L is the instantaneous length at the time of measurement (usually at end-systole). The amount of deformation is expressed in percentages. Negative strain means shortening, thinning, and contraction, while positive strain means lengthening, thickening, and relaxation. Myocardial mechanics can be investigated in all directions of myocardial movement: longitudinal shortening, circumferential shortening, and radial thickening. Initially, echocardiography was utilized to evaluate myocardial deformation. However, over time, several CMR techniques have been introduced as alternative approaches. These include myocardial tagging, displacement encoding, and strain encoded imaging. Each technique has its limitations, such as the need for additional acquisitions, low signal-to-noise ratio, lack of standardization, and demanding post-processing requirements [21–23]. FT-CMR is a novel technique that uses a block-matching approach to identify anatomic features in CMR images along the myocardial boundaries and track them along the cardiac cycle by searching for the most comparable image pattern in the successive image [24, 25]. In many previous studies, FT-CMR has demonstrated excellent reproducibility and good correlation with tagging [26–28]. Compared to CMR tagging, CMR-FT is easier to perform without the need for dedicated acquisition and complex post-processing, as it can be applied to standard CMR cine Steady State Free Precession (SSFP) sequences, and it is highly reproducible [29, 30]. Thus, FT-CMR potentially has an important role in TTS because acute myocardial dysfunction is a prominent feature of the condition and the extent of dysfunction is one of the major prognostic factors in the short and long term [7]. Moreover involvement can extend beyond the distinctly akinetic areas of the left ventricle (LV) [31], affecting both the right ventricle (RV) [32] and left atrium (LA) [33].

Left Ventricle Strain

Assessing LV dysfunction in patients with TTS is crucial for accurate diagnosis and management. Hypokinesia, akinesia, or dyskinesia of the apical, midventricular, and basal segments are common patterns of LV dysfunction observed in TTS patients. While the apical ballooning pattern is the most recognizable and frequently observed, atypical patterns such as focal TTS can be more challenging to identify and diagnose using standard cardiovascular imaging methods [4, 34]. By detecting subtle abnormalities and accurately quantifying the extent of myocardial dysfunction, CMR-FT provides a more comprehensive and detailed evaluation of ventricular performance. During the acute phase of TTS, segmental analyses of peak circumferential and peak longitudinal strain provide objective assessments of regional LV contraction abnormalities, enabling discrimination of different ballooning patterns [35•]. Furthermore, FT-CMR evaluation of LV rotational mechanics reveals transient dyssynchrony, particularly pronounced in the subset of TTS patients with stressful triggers, comorbidities, and higher mortality risk [36•].

The extent of myocardial dysfunction has a well-established role in short- and long-term prognoses for TTS patients [37, 38]. Notably, typical apical ballooning is associated with more pronounced alterations of global circumferential and longitudinal strain and is linked to more severe LV dysfunction and increased mortality [35•, 38]. Stiermaier and colleagues have shown that strain values, including global circumferential, longitudinal, and radial strain, are significantly lower in TTS patients than in healthy subjects or in those with non-ST-segment elevation myocardial infarction (NSTEMI), but similar to those with ST-segment elevation myocardial infarction (STEMI) [35•]. In clinical practice, measurement of ejection fraction (EF) is the most popular method for assessing ventricular performance. However, in TTS, EF is often only moderately reduced since regional hypercontraction balances pronounced wall motion abnormalities. As a result, EF may not adequately reflect the extent of LV systolic dysfunction. Deformation indices, such as CMR-FT-derived strain, may provide superior prognostic markers in TTS. In this regard, LV

longitudinal strain has emerged as a superior clinical outcome marker when compared to EF in a group of TTS patients. Specifically, observed long-term mortality rates were significantly higher in patients with FT-derived global longitudinal strain values greater than about -11% [39•]. Moreover, while myocardial dysfunction in TTS was previously believed to be entirely reversible, recent studies have shown that patients may experience long-term echocardiographic wall motion abnormalities, despite apparent recovery of EF [40••].

Right Ventricle Strain

Right ventricular (RV) involvement has been observed in a significant number of TTS patients and has been associated with worse outcomes, including prolonged hospitalization and increased short- and long-term adverse events [32, 41–43]. Typically, RV wall motion abnormalities are concentrated in the apical segments, while mid and basal RV contraction remains preserved or hyperkinetic [44•].

The visualization and assessment of the extent of regional abnormalities in the RV are challenging with echocardiography due to its complex geometry. Similar to the left ventricle, hypercontractile segments may partially compensate for dysfunctional segments, resulting in a less sensitive detection of the extent of RV systolic dysfunction through EF measurements. FT-CMR evaluation of longitudinal RV strain has been shown to outperform subjective visual assessment of RV involvement [44•]. Additionally, it has demonstrated a correlation between LVEF and long-term risk stratification, enabling more accurate identification of high-risk individuals [32, 44•, 45]. Patients with biventricular involvement may be particularly prone to a severe clinical course with heart failure and/or cardiogenic shock due to the higher degree of LV dysfunction, which is further compromised by reduced LV preload resulting from RV dysfunction. However, further studies are needed to determine if these hemodynamic alterations can impact long-term prognosis.

Atrial Strain

Although the most obvious manifestations in TTS are seen in the LV, atrial involvement has also been described [33]. FT-CMR allows for the evaluation of both left and right atrial performance by quantifying the atrial reservoir, conduit, and booster functions based on absolute strain values and corresponding strain rates [46]. Reservoir function refers to the collection of pulmonary venous return in the atrium during ventricular systole, while conduit function represents the early diastolic blood passage during ventricular filling. Booster pump function is responsible for the late diastolic augmentation of ventricular filling. During the acute phase of TTS, both LA reservoir function and LA conduit function are significantly impaired and tend to recover completely at follow-up [47•, 48]. In contrast, LA booster pump function is normal or even increased within the acute phase [47•]. It is likely that LA reservoir function and conduit function are reduced due to increased LV filling pressures resulting from LV diastolic dysfunction. Increased LA contractility, along with prolonged myocardial relaxation, may be a compensatory response to decreased LV diastolic filling, and helps maintain adequate antegrade flow. A recent invasive hemodynamic study has indeed demonstrated severe diastolic dysfunction of the left ventricle in patients with TTS compared to a control group without cardiovascular diseases. Specifically, the invasive assessment of pressure–volume loops revealed prolonged myocardial active relaxation (an energy-dependent process) and normal ventricular compliance (passive ventricular filling) [49]. Further studies are needed to better understand the intricate hemodynamic alterations responsible for diastolic dysfunction in TTS.

A recent study investigating LA strain using FT-CMR demonstrated that impaired LA function during the acute phase was associated with long-term mortality, independent of traditional cardiovascular risk factors and LVEF [47•].

Table 1 summarizes recent findings on FT-CMR and provides an interpretation of its clinical utility.

In summary, FT-CMR has emerged as a promising tool for the assessment of TTS patients, providing an accurate and comprehensive evaluation of myocardial function. Specifically, FT-CMR allows for the detection of global myocardium involvement, even beyond areas of visually assessed abnormal wall motion. This has important clinical implications for the diagnosis, management, and long-term risk stratification of TTS patients. While further studies are needed to fully establish the role of FT-CMR in TTS, the current evidence suggests that it has great potential in improving our understanding and management of this complex syndrome.

Parametric Mapping

Accurate non-invasive tissue characterization is crucial for the diagnosis and management of TTS as it enables differentiation from other conditions. Moreover, it provides valuable insights into the underlying mechanisms of TTS.

In recent years, advanced techniques have been continuously developing to enhance the assessment and quantification of myocardial tissue properties. One of these techniques is mapping, which entails the acquisition of a series of images using various contrast weightings or imaging

Table 1 Feature-tracking cardiovascular magnetic resonance findings in TTS

Strain measures	Chamber	Findings	Clinical Significance
• Longitudinal Strain: deformation along the longitudinal axis of motion • Circumferential strain: deformation along the circumference • Radial strain: radial deformation, representing the change in thickness of the myocardial wall during the cardiac cycle • Twist and torsion: rotation of the LV during the cardiac cycle (ventricular twist and torsional kinetics)	Left Ventricle	GLS, GCS, an GRS are significantly lower in TTS patients than in healthy subjects but similar to those with STEMI [35•] • FT-CMR evaluation of LV rotational mechanics reveals transient dyssynchrony in the acute phase of TTS [36•] • A GLS value higher than approximately -11% identifies patients at high long-term risk [39•]	• FT-CMR facilitates the differentiation of various patterns of ballooning • LV strain is a superior prognostic marker in both the acute and long-term phases compared to EF
	Right Ventricle	Longitudinal RV strain outperform subjective visual assessment of RV involvement [44•] Longitudinal RV strain correlates with EF and identifies individuals at high risk [44•]	RV strain is an excellent tool to identify patients with RV involvement and a promising instrument for risk stratification
	Left and Right Atrium	LA reservoir function and LA conduit function are impaired in the acute phase and tend to recover completely at follow-up [47•] LA booster pump function is normal or even increased within the acute phase [47•]	Impaired LA function reflects LV diastolic dysfunction and serves as a prognostic indicator

TTS TakoTsubo syndrome; *LV* left ventricular; *RV* Right ventricular; *LA* left atrial; *GLS* Global Longitudinal Strain; Global Circumferential Strain; *GRS* Global Radial Strain; *STEMI* ST-segment elevation myocardial infarction; *FT-CMR* Feature-tracking cardiovascular magnetic resonance

parameters, such as T1, T2, or T2* relaxation times. By analysing the signal intensity values in these images, parametric maps can be generated, which provide both qualitative (Fig. 1) and quantitative (Fig. 2) information about tissue characteristics, such as myocardial fibrosis or oedema. The signal intensity primarily depends on extracellular water content (T2 mapping), as well as fibrosis and infiltration of fat or amyloid (native T1 and ECV).

Pathophysiology

Although the precise underlying mechanisms of TTS remains incompletely elucidated, recent studies using advanced imaging techniques have indicated a notable involvement of inflammation in its pathogenesis. Catecholaminergic surge during stress has been linked to the activation of pro-inflammatory cytokines, suggesting a possible connection between systemic inflammation and TTS [50]. Inflammatory conditions like infections or surgeries can further contribute to systemic inflammation and its association with TTS [51]. Catecholamines affect systemic inflammation through adrenoreceptors on inflammatory cells, influencing blood and lymph flow as well as the distribution of pro-inflammatory cells [52, 53]. Mechanistically, factors such as endotoxins and catecholaminergic discharge can trigger nitrosative stress, leading to increased myocardial vascular permeability, plasma leakage, and infiltration of pro-inflammatory cells, can result in myocardial oedema [54–56]. Of note, oedema remains a relatively non-specific marker of myocardial involvement that characterizes cardiac injury in the course of several diseases, including myocardial infarction [57], myocarditis [58], and cardiomyopathies [59–61]. However, oedema and associated inflammatory features may vary according to the underlying disease, potentially marking differences in the pathogenic processes; in example, neutrophils surge, proportional to the extent of the myocardial oedema, characterizes the acute phase of myocardial infarction [62], whereas lymphocytes or eosinophils infiltrates are more common in acute myocarditis [63].

In this context, a significant clinical study has provided compelling evidence for the presence and features of local myocardial inflammation in TTS patients. This study utilized multiparametric CMR with ultra-small superparamagnetic particles of iron oxide (USPIO) to detect and characterize myocardial inflammation. The USPIO enhancement was higher in patients with TTS compared to a matched control group in both ballooning and not-ballooning LV myocardial segments. This increased enhancement indicated a significant infiltration of activated and phagocytic M1 type macrophages within the myocardial tissue of all TTS patients. Furthermore, patients with acute

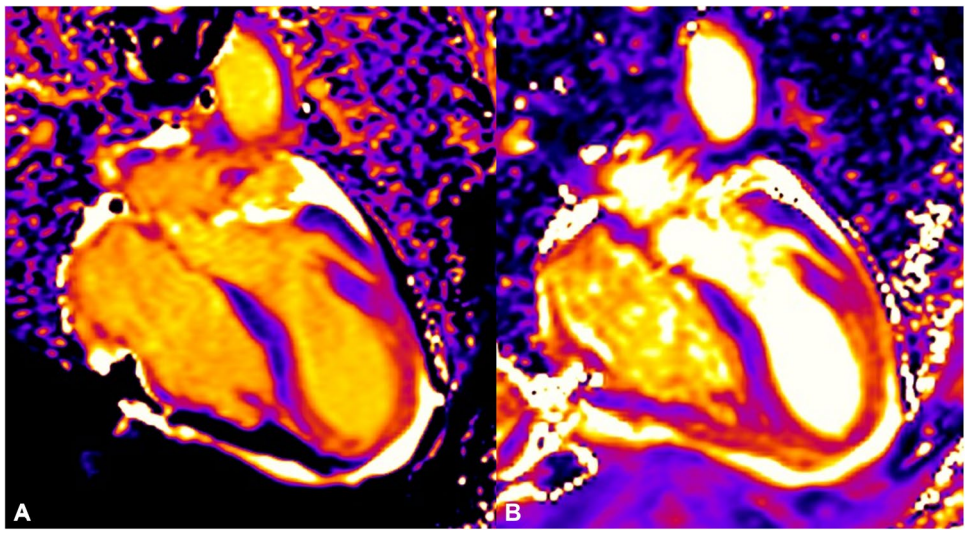

Fig. 1 Native T1 (panel A) and T2 (panel B) mapping images from 4-chamber long-axis view. An increase in signal intensity of native T1 as well as T2 mapping in mid-apical left ventricular segments is evident from visual inspection of the color-coded map

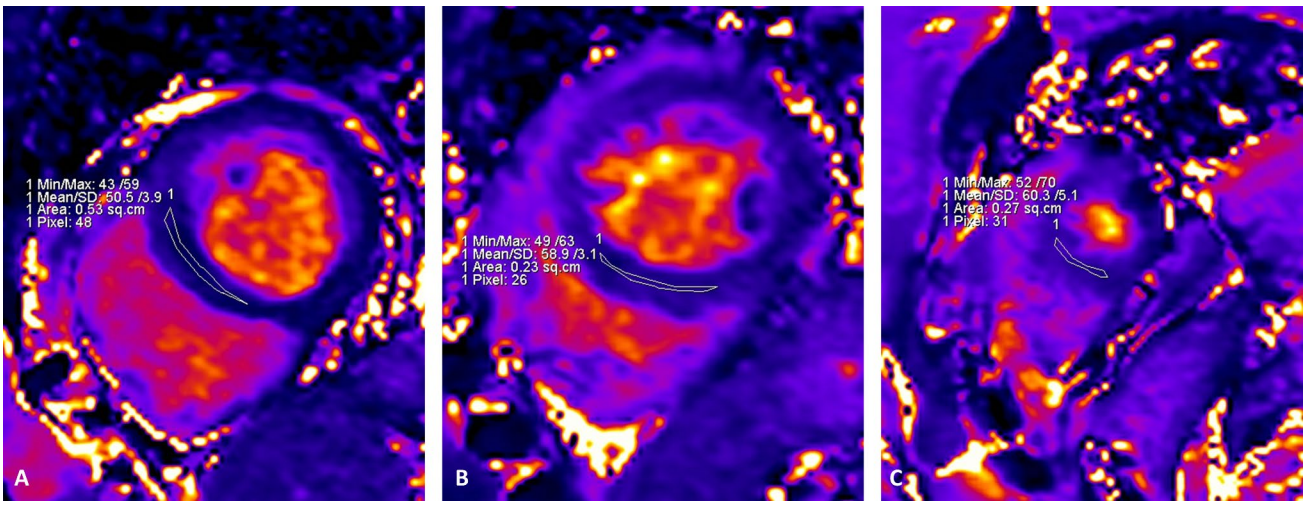

Fig. 2 Quantitative analyses of T2 mapping data in a patient with TTS. A progressive increase in T2 mapping values is observed from basal to apical segments. Of note, subtle myocardial edema is detected at basal segments too as indicated by border-line increase in T2 mapping value (50.5 ms, normal value for the scanner and sequence used is up to 50 ms)

TTS showed changes in peripheral monocyte subsets and increased systemic levels of pro-inflammatory cytokines, providing further support for the involvement of systemic inflammation and its correlation with the inflammatory response within the myocardium [64••].

Recent studies have also investigated the role of epicardial fat in TTS. Epicardial fat is metabolically active visceral fat, and a recent CMR study has shown a correlation between the volume of epicardial fat and CMR markers of myocardial inflammation and subclinical contractile dysfunction in TTS patients [65].

CMR techniques have also been used to investigate alterations in myocardial metabolism and calcium handling in TTS. Acute impairment in energetic status [64••] and abnormal myocardial calcium handling [66] have been observed and can persist for at least three months, suggesting their involvement in the pathophysiology of the disease.

Overall, the integration of imaging techniques has provided valuable insights into the pathophysiology of TTS, highlighting the role of inflammation, metabolic abnormalities, and altered calcium handling.

Clinical and Prognostic Implications

The typical CMR appearance of TTS is characterized by widespread myocardial oedema without significant replacement fibrosis observed in late gadolinium enhancement (LGE) imaging [31, 67]. However, recent studies have indicated that LGE may be present in some TTS patients [68,

69]. When LGE is detected, it is typically of low intensity, less than 5 standard deviations, suggesting minimal myocardial injury or necrosis [31]. In other cases, incidental findings from chronic and unrelated co-pathologies can be considered too [70].

More recently, studies using T1 and T2 mapping tools in TTS were published. In the acute phase of TTS, a significant increase in native T1, T2, and ECV has been observed [40••, 71, 72]. Non-contrast T1 and T2 mapping have demonstrated high diagnostic accuracy in identifying acute myocardial injury in patients with mid-apical TTS without the need of gadolinium contrast [73]. It is important to highlight that there is a direct correlation between T2, native T1, and ECV [73]. The reason behind this direct correlation could be explained by the significant impact of extracellular myocardial oedema on the interstitial space during the acute phase [74, 75•]. Specifically, extensive and widespread oedema not only affects T2 but also T1 mapping-derived measurements, including native T1 and ECV [76]. Hence, the rise of ECV in the acute phase of TTS is expression two simultaneous processes: extensive oedema and remodelling of the extracellular matrix. Moreover, increased myocardial water content and extracellular volume are observed not only in regions with abnormal wall motion but also, to a lesser extent, in areas with normal kinesis compared to controls [75•]. This finding suggests that myocardial involvement extends beyond regions with wall motion abnormalities, including the RV. The added clinical value of tissue mapping in this scenario has been highlighted by a recent prospective study of a cohort of patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) who underwent early CMR imaging with T1 and ECV: compared to patients with MINOCA imaged using CMR without mapping techniques, a higher rate of TTS diagnosis was obtained [67].

Quantification of oedema using parametric techniques holds potential prognostic value, as its presence and extent have been associated with both electrocardiographic abnormalities and potential complications in TTS [75•, 77, 78]. Higher T2 values within the initial days following the acute event have been found in TTS patients with delayed recovery [72] and are inversely correlated with LV systolic function [75•]. Additionally, a larger difference in T2 values between the apex and base of the LV, indicative of higher oedema dispersion and gradient, is associated with more pronounced T-wave inversion and a longer QTc interval, potentially explaining the electrical instability observed in TTS patients [75•]. However, it is important to note that data regarding mortality in relation to CMR mapping findings in TTS are still limited due to the small sample sizes of current studies.

During the recovery phase, mapping techniques can detect persistent abnormalities despite complete normalization of systolic function. T2 mapping values tend to normalize over the follow-up period, although they may remain slightly elevated for approximately 3–5 months after the acute phase [79, 80]. On the other hand, T1 values may remain elevated for a longer period. In recovered TTS patients, native T1 in the LV has been found to be persistently elevated compared to a matched control group, even more than 1 year after the acute event. This observation is accompanied by impaired cardiac deformation (despite preserved LVEF), higher levels of natriuretic peptides, and persistent cardiac limitations observed during exercise testing at cardiopulmonary stress tests [40••]. Despite the well-known technical limitations in performing tissue mapping in thin free wall of the RV, it was also demonstrated a persistent increase in ECV values in the RV of patients with previous TTS [80]. These findings suggest the presence of subtle long-term non-transitory abnormalities that may partly explain the persistence of symptoms and unfavourable prognosis of TTS patients [40••]. Moreover, magnetic resonance imaging with ultrasmall superparamagnetic iron oxide particles (USPIO) has shown signs of macrophage inflammatory infiltrate in the acute phase: though these changes regressed at a 5 months follow-up, signs of systemic inflammation persisted [64••]. Altogether, this supports the notion that persistent myocardial inflammation can be present even after the complete recovery of systolic function. According to this hypothesis, the long-term increase of certain biomarkers associated with inflammation, including BNP, has been demonstrated [50, 81, 82]. However, it cannot be excluded that such abnormalities were pre-existent the TTS attack, especially when considering the large comorbid burden that characterizes these patients [83].

The evaluation of interstitial fibrosis or ongoing inflammatory processes using mapping techniques appears potentially useful for prognostic stratification and guiding therapy, however, studies supporting these findings as well as clinical trials in this context are still limited.

Table 2 summarizes mapping techniques for TTS tissue characterization. Each technique is described along with its specific features. Additionally, the table includes the most significant findings and their clinical significance in different phases of the disease.

Conclusions

FT-CMR and mapping techniques have emerged as valuable tools for evaluating TTS, a complex clinical condition that extends beyond a benign and transient

Table 2 Magnetic Resonance Imaging mapping techniques and their respective findings in TTS

Mapping Technique	Description	Findings and Clinical Significance
T2 mapping	Allows quantification of myocardial oedema (even in regions without wall motion abnormalities)	• ***Acute phase***: The quantification of oedema, its extent, and dispersion have prognostic significance • ***Chronic phase***: Tends to normalize after 3–5 months
Native T1 and ECV mapping	Both techniques provide information regarding on the extent of extracellular remodelling. Boths parameters are influenced by the content of extracellular water	• ***Acute phase***: They are typically elevated due to the influence of myocardial oedema • ***Chronic phase***: They can remain persistently elevated due to the presence of interstitial fibrosis and are associated with symptom persistence
T2* mapping with USPIO-enhancement	Can detect and characterize myocardial inflammation, indicating an infiltration of activated and phagocytic M1 type macrophages	• ***Acute phase***: It is increased in both ballooning and non-ballooning LV myocardial segments • ***Chronic phase***: It can remain slightly elevated, indicating ongoing low-grade inflammation

ECV Extracellular Volume. *USPIO* ultra-small superparamagnetic iron oxide. *LV* left ventricle

LV systolic dysfunction. These imaging techniques allow for the detection of subtle abnormalities, such as pan-cardiac involvement or mild alterations in regional systolic function, despite complete normalization of LVEF. Moreover, they provide insights into long-term myocardial abnormalities, including interstitial fibrosis or ongoing inflammation, potentially guiding therapeutic strategies during follow-up. However, there are certain limitations to consider, including variability in image acquisition and analysis, limited sample sizes, and technical challenges that impact the accuracy and clinical applicability of these modalities. Future directions involve standardization and multicentre collaborations to establish protocols and cut-off values, integration of novel imaging techniques [84], longitudinal studies for prognostic evaluation, and therapeutic monitoring for personalized medicine. By addressing these limitations and exploring these perspectives, the clinical utility of mapping and FT-CMR in TTS can be enhanced, leading to improved diagnosis, characterization, and patient management.

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Declarations

Conflict of Interest Matteo Sclafani, Giacomo Tini, Beatrice Musumeci, Alessandro Cianca, Viviana Maestrini, Luca Cacciotti and Luca Arcari declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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