This is the Author's [*accepted*] manuscript version of the following contribution: Cau, R., Masala, S., Manelli, L., Porcu, M., Scaglione, M., D'Angelo, T., Salgado, R. and Saba, L. (2024), Cardiovascular Magnetic Resonance Imaging of Takotsubo Syndrome: Evolving Diagnostic and Prognostic Perspectives. Echocardiography, 41: e15949.

The publisher's version is available at:
https://doi.org/10.1111/echo.15949

When citing, please refer to the published version.

Cardiovascular magnetic resonance imaging of Takotsubo syndrome: evolving diagnostic and prognostic perspectives

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Abstract

Takotsubo syndrome (TS) is a temporary form of left ventricular (LV) dysfunction characterized by a distinct pattern of LV impairment, often triggered by a physical or emotional stressful event. Historically, TS was considered a benign condition due to its prompt restoration of myocardial function and generally excellent outcomes. However, recent studies have shown that complications similar to those seen after myocardial infarction can occur, necessitating careful monitoring of these patients.
Among non-invasive imaging techniques, cardiovascular magnetic resonance (CMR) is becoming increasingly important in evaluating patients with TS. CMR offers a unique ability to non-invasively assess myocardial tissue characteristics, allowing for the detection of the typical features of TS, such as specific wall motion abnormalities and myocardial edema. Beyond its well-established diagnostic utility in the clinical management of TS, CMR has also proven valuable in prognosis and risk stratification for these patients. Advances in CMR, including myocardial strain and parametric mapping have expanded its role in the diagnosis, prognosis, and follow-up of these patients. This review aims to provide a comprehensive overview of the potential applications of CMR in the diagnostic and prognostic evaluation of TS patients. It explores the emerging use of novel CMR imaging biomarkers that may enhance diagnosis, improve prognostic accuracy, and contribute to the overall management of these patients.

Introduction

Takotsubo syndrome (TS) is an acute myocardial dysfunction that mimics the clinical presentation of acute myocardial infarction, typically preceded by a physical or emotional stressful event (1–3). TS is characterized by distinctive left ventricular (LV) wall motion abnormalities that extend beyond the distribution of a single epicardial coronary artery, and primarily affecting the apical segments (4). Although TS was initially considered benign due to its self-limiting nature, growing evidence indicates that its prognosis is not always favorable. Hemodynamic and electrical instability during the acute phase can lead to acute life-threatening complications such as heart failure, cardiogenic shock, and death(5–13). Importantly, this unfavorable prognosis can persist

beyond the acute phase(14,15), highlighting the need for a better understanding of TS pathophysiology and the development of more effective management strategies.
The diagnosis of TS is based on clinical, electrocardiographic, and echocardiographic findings(1,16). According to recent ESC guidelines, cardiovascular magnetic resonance (CMR) is becoming increasingly important in the evaluation of TS patients(17–19). CMR is capable to provide myocardial tissue characterization together with a comprehensive assessment of functional and morphological changes occurring during TS(20,21).
For this reason, CMR is recommended during the acute phase to confirm the diagnosis and rule out other cardiovascular differential diagnoses(22–27). Moreover, recent evidence has demonstrated that the role of CMR may extend beyond the diagnosis, offering crucial prognostic information (8). Table 1.
This review aims to provide a comprehensive overview of the current and potential applications of CMR in the diagnostic and prognostic evaluation of TS patients. It explores the emerging use of novel CMR imaging biomarkers that may enhance diagnosis, improve prognostic accuracy, and contribute to the overall management of these patients.

CMR imaging techniques and protocol

CMR sequences enable precise assessment of cardiac morphology and function, blood flow quantification and myocardial tissue characterization. The key sequences for identifying distinctive imaging features of TS include cine images, T2-weighted sequences, and late gadolinium enhancement (LGE) (4,16).**Figure 1**.
Cine images are obtained using steady-state free precession (SSFP) techniques, which are not limited by acoustic windows and provide multiplanar imaging with complete coverage of both the left and right cardiac chambers(28,29). The high blood-myocardial contrast resolution of cine CMR allows for precise delineation of the endocardial and epicardial borders by producing a clear contrast between the darkened myocardium and the bright blood pool. This capability enables accurate tracking of endocardial and epicardial borders in both end-systolic and end-diastolic phases, making CMR the reference standard imaging modality for evaluating cardiac morphology and function(28,30). Additionally, cine-images can be post-processed using feature-tracking software to evaluate myocardial strain patterns(31,32). Indeed, the recently introduced CMR feature-tracking provides an objective and quantitative assessment of both regional and global transient impairments in myocardial contractility, even when ejection fraction is preserved or recovered in TS patients, and without requiring additional CMR sequences (8).

Myocardial edema can be assessed using T2-weighted sequences such as short tau inversion recovery (STIR) and parametric sequences like T2-mapping. T1-mapping has also shown to provide similar information despite with less specificity(33–37). The widespread introduction of parametric mapping in Takotsubo syndrome offers significant benefits by providing quantitative tissue characterization, which overcomes some limitations of traditional visual or semi-quantitative approaches(7,27). While parametric mapping offers valuable insights, the technique is still developing and not yet fully standardized across clinical practices. As such, it is critical to ensure that the implementation of any parametric mapping method is both precise and reliable. This requires stringent quality control measures at the local CMR facility, particularly before it can be applied confidently in clinical diagnostics. Establishing a reference range for healthy individuals within each center is essential, and these local values should be compared with established, published benchmarks. Adhering to the Society for Cardiovascular Magnetic Resonance (SCMR) Standardized CMR Imaging Protocols is recommended to ensure best practices in clinical application(28).

LGE imaging represents the cornerstone of CMR imaging (38). This technique involves the intravenous administration of gadolinium, which distributes differently in fibrotic tissue compared to healthy myocardium. In particular, there's a delay of contrast distribution within the fibrotic tissue, as well as a prolonged clearance, resulting in enhanced contrast between scarred and healthy myocardium (39). In LGE imaging, it is important to consider both the contrast dose and type. We typically administer 0.15 mmol/kg of gadolinium contrast media in TS patients. Lower doses of contrast media may reduce the diagnostic performance of LGE imaging, particularly at 1.5 T, as demonstrated in the international multicenter study conducted by Kim et al(40).

Optional CMR sequences that can provide additional information are phase-contrast, early gadolinium enhancement (EGE) and perfusion sequences.

In particular, phase-contrast and EGE sequences enable accurate assessment of TS complications, such as LV outflow tract obstruction and LV thrombi, respectively.

LV outflow tract obstruction is a not so uncommon complication during the acute phase of TS that can precipitate hemodynamic instability(41). CMR can accurately evaluate the gradient across the stenosis using phase contrast sequences and evaluate some associated imaging features including systolic anterior movement or mitral regurgitation(28,41).

The occurrence of LV thrombi ranges from 1.3% to 5% during the acute phase of TS, primarily due to transient LV regional akinesia and elevated catecholamine levels, especially in the apical ballooning TS pattern(42). CMR, particularly through EGE sequences performed 1–3 minutes after contrast injection with a high inversion time, offers greater diagnostic accuracy for detecting LV thrombi compared to echocardiography(43).

Finally, first-pass perfusion CMR utilizes the dynamic inflow of a contrast agent into the myocardium to quantify myocardial blood flow and myocardial perfusion reserve both at rest and during pharmacological stress. Growing body of research suggests that abnormalities in microvascular flow can precipitate TS and can correlate with the extent of myocardial injuries(44–46).

Figure 2 provides a suggested CMR protocol in patients with clinical suspicion of TS.

CMR in the diagnosis of TS

In recent years, CMR has become increasingly important in diagnosing suspected TS. Its unique ability to detect subtle myocardial abnormalities makes it superior to other imaging modalities for identifying TS. Accurate identification of TS and distinguishing it from other cardiovascular diseases are crucial in clinical practice, significantly impacting patient prognosis and survival.

According to the 2023 European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies, non-invasive imaging modalities, including CMR, are fundamental in diagnosing cardiomyopathies, such as TS, especially when echocardiography provides poor image quality. This approach is given a Class I, Level B recommendation for the initial assessment of suspected patients(18).

Beyond diagnosing TS, diagnostic CMR plays a crucial role in distinguishing TS from other conditions such as myocarditis, MINOCA, and myocardial infarction. Features like coronary distribution of wall motion abnormalities or myocardial edema, along with the subendocardial LGE pattern, suggest ischemic etiologies. In contrast, localized myocardial edema with and a non-ischemic LGE pattern supports a diagnosis of myocarditis(1,2,4,27).

The 2020 ESC guidelines suggest CMR as non-invasive imaging tool in the differential diagnosis of TS, myocarditis, and myocardial infarction allowing to avoid unnecessary invasive imaging(17). A recent randomized trial in patients with an unclear NSTEMI diagnosis explored the use of CMR as an initial imaging technique to reduce the need for invasive coronary angiography. The CMR-first strategy provided an alternative diagnosis for a significant proportion of patients and reduced the need for invasive coronary angiography compared to routine clinical care (87% reduction, p = 0.001), with similar outcomes (hazard ratio for CMR vs. routine care: 0.78 [95% confidence interval: 0.37 to 1.61])(47).

Additionally, non-contrast CMR sequences that assess myocardial strain are showing promise in the differential diagnosis of TS(23–25,48,49). Cau et al. investigated the base-to-apex gradient patterns of longitudinal strain (LS), circumferential strain (CS), and radial strain (RS) in 30 patients with apical ballooning TS and 50 patients with anterior myocardial infarction. The gradients were defined as the peak difference between averaged basal and apical LS, CS, and RS. The base-to-apex RS gradient was significantly reduced in patients with TS compared to those with myocardial infarction (14.04 ± 15.50 vs. -0.43 ± 11.59, P = 0.001). This gradient also served as an independent discriminator between TS and myocardial infarction, with an odds ratio of 1.28 (95% CI: 1.08–1.52, P = 0.006) in multivariate logistic regression analysis(23). Beyond ventricular strain parameters, atrial function assessed via CMR feature tracking has shown excellent sensitivity in differentiating patients with TS from those with other cardiovascular diseases, including acute myocarditis, with an area under the curve (AUC) of 0.903 (95% confidence interval: 0.81–0.99)(24).

Another advantage for the CMR diagnostic work-up of TS is represented by parametric mapping sequences. During the acute phase of TS, there is a notable increase of the myocardial native T1, T2, and extracellular volume (ECV) values, which can be utilized as non-contrast indicators for diagnosing the condition(50–52).

A recent prospective study by Sörensson et al. demonstrated the increased clinical value of tissue mapping in patients with myocardial infarction and non-obstructive coronary arteries (MINOCA) who underwent early cardiac magnetic resonance (CMR) imaging with parametric mapping. The integration of parametric mapping techniques into CMR protocols resulted in a higher rate of TS diagnosis compared to patients who did not undergo mapping sequences (35% vs. 19%; p = 0.002)(53).

Additionally, CMR may also be suited for assessing extracardiac structures that could trigger TS, such as pheochromocytoma, by means of the localizer sequences, mandatory before any CMR acquisition. **Figure 3** provides a practical example of pheochromocytoma detected through scout sequences.

CMR biomarkers as prognosticators of TS

The prognosis for patients with TS has traditionally been considered favorable, usually with full recovery of left ventricular function within three to six months. However, recent studies have indicated that short- and long-term mortality for TS patients is higher than in the general population(5,12). Furthermore, the outcomes are comparable to those of patients with acute coronary syndrome(54) and ST-segment elevation myocardial infarction(55).Therefore, obtaining an accurate prognostic stratification is essential.

Among non-invasive imaging modalities, echocardiography is the first-line method for evaluating heart function in TS patients. It provides detailed insights that are crucial for prognosis and are linked to adverse cardiovascular events, such as reduced LV ejection fraction, right ventricular involvement, and global longitudinal strain (11,12,56,57). However, its effectiveness can be limited by anatomical window constraints, suboptimal assessment of the right ventricle, and its inability to detect changes in myocardial tissue(16,58).

Conversely, CMR represents the reference standard for evaluating both left and right cardiac chamber volume and function. It also provides a comprehensive assessment of myocardial tissue abnormalities in TS, offering additional insights that are essential for prognosis.

LV ejection fraction is an essential measure for diagnosing and managing patients with TS; however, it does not always reflect the underlying contributors to myocardial performance, such as end-diastolic volume (EDV) and end-systolic volume (ESV). Since EF is directly influenced by both EDV and ESV, understanding the relative roles of these volumes is crucial. Therefore, a more comprehensive approach may be useful in TS patients—one that considers these individual components alongside EF, rather than relying solely on EF as a singular indicator of ventricular function(59,60).

The information obtained from LV ejection fraction and its contributing factors can be complemented by myocardial strain analysis The newly implemented CMR feature tracking provides an objective and quantitative assessment of both regional and global transient impairments in myocardial contractility, even in TS patients who have preserved or recovered ejection fraction (31).

Stiermaier et al. assessed the prognostic value of left ventricular CMR feature-tracking in a multicenter cohort of 141 patients with TS. Their multivariate model revealed that patients with lower global longitudinal strain had a higher incidence of adverse cardiovascular events (HR 1.14, 95% CI 1.04–1.25, $P = 0.006$). The study found that patients with a global longitudinal strain greater than -14.75% experienced shorter event-free survival according to Kaplan-Meier analysis (log-rank, $P = 0.02$)(61).

The prognostic impact of global longitudinal strain was recently explored in a systematic review of five studies involving 564 TS patients, which reported that global longitudinal strain has incremental prognostic value compared to LV ejection fraction(8).

In addition to accurate visualization of regional wall LV motion abnormalities, CMR allows for direct assessment of right ventricular (RV). RV involvement represents a useful parameter in TS risk stratification, because has been linked to worse outcomes including longer hospital stays and a higher incidence of both short- and long-term adverse events(11,62–66).

Using CMR-based feature-tracking imaging can enhance sensitivity in detecting right ventricular involvement, allowing for a more detailed identification of subtle abnormalities in right ventricular contractility(64).

In the acute phase of TTS, myocardial abnormalities are not confined to the ventricular chamber; they also extend into the atria(24,67,68). A multicenter study that recruited 152 TS patients during the acute phase of the disease reported that the reservoir and conduit parameters of the left atrium were impaired, with recovery observed during follow-up. Conversely, the booster functions of the left and right atria were increased in the acute setting, reflecting a compensatory mechanism. Additionally, reservoir function accurately discriminated between low- and high-risk groups regarding adverse clinical events, even after adjusting for cardiovascular risk factors. Receiver operating characteristic analysis revealed that the reservoir was the best predictor of cardiovascular events (0.69, 95% CI 0.55–0.82), and the combination of reservoir and LV ejection fraction increased the prognostic ability (68).

The prognostic role of CMR in TS extends beyond the simple morphological assessment of cardiac chamber function and volume, allowing for detailed tissue characterization.

The prognostic impact of LGE in TS is controversial(38,69). Initially, the absence of LGE was considered essential for diagnosing TS(70). However, an increasing number of studies have shown that LGE can be present in patients with TS(2,69).

This presence may be linked to delayed contrast washout due to hyperemia and increased interstitial water(71). Naruse et al. explored the impact of LGE on the prognosis of TS patients, reporting that the presence of LGE was associated with cardiogenic shock, a longer duration of LV recovery, and ECG abnormalities (69).

However, further longitudinal studies are needed to confirm the relationship between the presence and extent of LGE and long-term prognosis.

Beyond LGE, parametric techniques may have prognostic value in TS due to its association with electrocardiographic abnormalities and potential complications(72,73).

Arcari et al evaluated the association between edema assessed trough parametric mapping, mechanical, and electrical abnormalities in the acute phase of TS, reporting an association between apicobasal T2 mapping gradient and negative T-wave voltage and QTc length (r = 0.499, P = 0.007 and r = 0.372, P = 0.047, respectively)(73).
The prognostic value of multiparametric CMR parameters for cardiovascular events is under investigation in ongoing multicenter EVOLUTION registry(7).

Future perspective

Artificial intelligence (AI) is playing an increasingly prominent role in the medical field, particularly in cardiovascular medicine. AI techniques have proven effective in detecting, diagnosing, and managing a range of cardiovascular diseases, which enhances disease classification and stratification(26,49,74–78). In clinical practice, AI is widely used in various applications, including automated image acquisition, reconstruction, and analysis. Recently, radiomics features have become a valuable tool for characterizing imaging features by extracting voxel-based information from images. This approach captures the inherent heterogeneity of pixels concerning their spatial context(79–81).
A recent systematic review, which included five studies with a total of 920 TS patients, demonstrated that AI-based models can increase the diagnostic rate of TS with higher sensitivity and specificity compared to human readers(82).
Cau et al. investigated five different tree-based ensemble learning methods to differentiate between TS and acute myocarditis in patients with acute chest pain using a CMR protocol without intravenous contrast. The methods included Random Forest, Extremely Randomized Trees, a plain bagging classifier of decision trees, and two boosting ensembles: Adaptive Boosting and Extreme Gradient Boosting. Among these, the Extremely Randomized Trees algorithm achieved the highest diagnostic performance, with a sensitivity of 92% (95% CI 78–100), specificity of 86% (95% CI 80–92), and an area under the ROC curve of 0.94 (95% CI 0.90–0.99) for diagnosing TS. Shapley analysis identified atrial strain parameters as the most effective discriminators for identifying TS. Furthermore, the use of AI-based models significantly reduced analysis time compared to human readers (586 seconds vs. 0.26 seconds, p = 0.001)(26).
Beyond the diagnostic capabilities of AI-based models in identifying TS, Mannil et al. explored the prognostic capabilities of an AI-based model built using radiomics data from CMR images to assess five-year outcomes, including major adverse cardiac and cerebrovascular events. These events were defined as a composite of death from any cause, myocardial infarction, stroke or transient ischemic attack, or recurrence of TS. The authors evaluated various AI models and conducted internal

validation using ten-fold cross-validation. They found that the Naïve Bayes model demonstrated superior predictive performance, with a sensitivity of 82.9% (CI 80–86.2), a specificity of 83.7% (CI 75.7–92), an AUC of 0.88 (CI 0.83–0.92), a precision of 0.88 (CI 0.83–0.92), and a precision-recall curve of 0.98 (CI 0.97–0.99)(83).

Conclusion

CMR has significantly enhanced our understanding, diagnostic, and prognostic abilities in patients with TS. Its multiparametric capabilities offer increasingly detailed insights into cardiac structure and pathophysiology, with the unique ability to noninvasively detect myocardial tissue changes by identifying inflammation and/or delayed gadolinium contrast washout, as well as transient impairments in myocardial contractility. Comprehensive assessments of TS patients using CMR could be pivotal in advancing personalized medicine and improving prognostic outcomes

Declaration of interest

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

All authors contributed equally to the work.

The authors state that this work is not under consideration elsewhere and none of its contents have been published previously.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

All authors read and approved the final manuscript.

The scientific guarantor of this publication is the corresponding author.

The authors declare that they have no competing interests.

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Table legends

Table 1: Summary of Diagnostic, Prognostic, and Management Implications of CMR imaging features in Takotsubo Syndrome, Including Sex-Specific differences

Abbreviations: CMR cardiovascular magnetic resonance; EF Ejection fraction; IR inversion recovery; LGE late gadolinium enhancement; LV left ventricle; GRE gradient echo; PSIR phase sensitivity inversion recovery; RV right ventricle; SSFP steady-state free precession; STIR short tau inversion recovery; TS Takotsubo syndrome

Figure legends

Figure 1: Practical Example of Traditional CMR Imaging Features in Takotsubo Syndrome: Cine-CMR images demonstrate typical left ventricular apical ballooning (Panel A: late systole, Panel B: late diastole). T2-weighted short tau inversion recovery sequences in both short-axis (Panels D-F) and long-axis (Panel C) views show increased signal in the mid and apical slices, with preserved basal signals. During the acute phase, a subtle transmural late gadolinium enhancement was observed in the akinetic segments (Panels G-I), which disappears at the 3-month follow-up (Panel J)

Figure 2: Overview of the Suggested CMR Protocol with Mandatory and Optional Sequences

Figure 3: Takotsubo Syndrome Triggered by Pheochromocytoma: Panels A and B demonstrate the characteristic wall motion abnormalities. In the scout sequences, an adrenal mass is observed (red arrows in Panel C), with heterogeneous enhancement in the LGE sequences (Panel D) and hyperintense T2 signals (Panel E). Computed tomography imaging confirmed a left heterogeneous adrenal mass with areas of necrosis (Panels F-H)