

Discovering Takotsubo Syndrome with Cardiac Magnetic Resonance

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Abstract

Reversible left ventricle dysfunction is a key feature of Takotsubo syndrome (TTS), but the differentiation between acute cardiac syndromes at admission could be a significant challenge. Despite the wide accessibility of echocardiography, cardiac magnetic resonance (CMR) is emerging as unique tool to accurately assess this entity, through its detailed morphological, functional and tissue characterization. Typical wall motion abnormalities, pattern and distribution of edema and even of low-intensity late gadolinium enhancement are singular findings of TTS on CMR. Therefore, it should be considered to perform CMR during hospitalization and at follow-up, facilitating the differential diagnosis with myocarditis and acute myocardial infarction, and consequently patient management. Despite all the imaging advances made so far, evaluation of coronary anatomy remains mandatory in patients with ST-segment elevation.

Keywords: Takotsubo syndrome; Stress-induced cardiomyopathy; Cardiac magnetic resonance; Myocardial edema; Late gadolinium enhancement; myocarditis; Acute myocardial infarction. Abbreviations: ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; CMR: Cardiac Magnetic Resonance; ECV: Extracellular Volume Fraction; FPP: First-Pass Perfusion; LGE: Late Gadolinium Enhancement; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; MI: Myocardial Infarction; MVO: Microvascular Obstruction; RV: Right Ventricle; SD: Standard Deviation; T2-STIR: T2-Weighted Short-Tau Inversion Recovery; T2W: T2-Weighted; TTS: Takotsubo Syndrome; WMA: Wall Motion Abnormalities

Introduction

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, is an acute syndrome characterized by transient left ventricle (LV) dysfunction, in the absence of obstructive coronary artery disease [1]. Accounting for 1-2% of all patients admitted with a presumed diagnosis of acute coronary syndrome (ACS), it typically occurs in postmenopausal women and is often triggered by an emotional or physical stressful event [2]. Distinguishing between ischemic and nonischemic etiology can be a challenge, due to the similar clinical presentation, electrocardiographic and echocardiographic abnormalities [3,4].

Advanced imaging modalities are becoming increasingly important in the management of cardiac diseases. Cardiac magnetic resonance (CMR) has become a first-line modality for noninvasive assessment of patients with TTS, providing a unique morphological, functional and tissue characterization. Due to its high spatial resolution and inter-observer consistency, it is particularly suitable to differentiate TTS from other forms of acute ventricular dysfunction associated with patent coronary arteries. Applications of CMR in patients with suspected TTS [2,5-7].

- Qualitative and quantitative assessment of regional wall motion abnormalities (WMA)
- Precise quantification of right and left ventricular function
- Tissue characterization-inflammation, edema, fibrosis, necrosis
- Assessment of additional abnormalities-pericardial effusion, pleural effusion and ventricular thrombi
- Detection of mechanical complications; • Differential diagnosis.

Ventricular Function and Wall Motion Abnormalities

CMR is the modality of choice to assess ventricular function and regional wall motion, and it can correlate the functional pattern to the tissue properties of the myocardium. The most common anatomical variant of TTS is characterized by hypo-/a- or dyskinesia of the apical and midventricular LV segments, associated with basal hypercontractility, resulting in the typical appearance of “apical ballooning” (Figure 1).

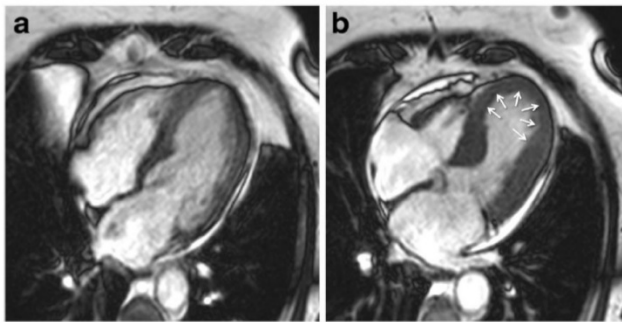


Figure 1: Cine CMR 4-chamber view in diastole (a) and Systole (b) Revealing apical ballooning in Takotsubo syndrome Plácido et al. [5].

However, other contraction patterns of TTS may be identified in up to 18% of the cases. These include mid-ventricular variant, characterized by circumferential mid-LV akinesia with basal and apical contraction, and the basal (reverse) variant, which demonstrates circumferential basal and mid-LV akinesia with hyperdynamic apical LV contraction. Focal, biventricular and isolated right ventricular variants have also been described [7-9].

Myocardial Inflammation

Myocardial inflammation is a key tissue property in the acute phase of TTS despite being nonspecific, since it can also be seen in acute myocarditis and acute myocardial infarction (AMI). Hallmark changes in inflammation include myocardial hyperaemia, edema and fibrosis, all of which can be evaluated with CMR imaging. Another indicator of the inflammatory process in TTS is the slight association between edema and pericardial effusion. Myocardial edema in TTS is a transient dynamic phenomenon, resolving in 2-3 months without myocardial scarring. T2-weighted (T2W) CMR is the standard imaging technique to detect acute myocardial edema, and T2-weighted short-tau inversion recovery (T2-STIR) is the most commonly used sequence to assess edema in clinical practice (Figure 2). However, T2STIR image quality is easily degraded with respiratory motion, tachyarrhythmia or slow-flow artifacts [2,7,10].

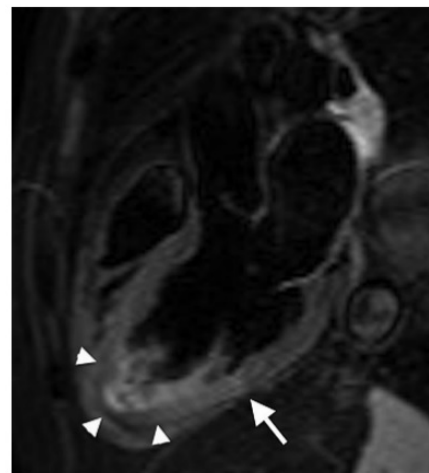


Figure 2: Three-chamber STIR image showing concentric increased signal in apical and mid-myocardium with normal myocardial signal at the base Abbas et al. [9].

It assumes a diffuse or transmural distribution, not restricted to a specific vascular territory. Those areas of edema typically match the dysfunctional ventricular contraction area observed with cine CMR sequences, involving all segments of apical portion, or alternatively mid or basal portions [5,7,10]. Joshi and colleagues showed that the T2 signal is higher in myocardial segments with the most impaired function, suggesting increased edema [11]. Higher apicobasal ratio of T2W signal intensity signify more severe apical myocardial edema [12].

More detailed evaluations with T2W imaging detected persistent myocardial dysfunction in segments with prolonged myocardial edema [1]. Interestingly, Zhong-Qun et al. also demonstrated that myocardial edema is associated with negative T waves, and that when the edema disappears, the negative T waves normalize [12].

Late Gadolinium Enhancement

As opposed to AMI, Late Gadolinium Enhancement (LGE) is generally absent in TTS [13]. However, recent studies revealed that LGE may be acutely identified in 10%-40% of TTS patients, when a lower threshold is used as a positive criterion for LGE (i.e., >3 standard-deviation (SD) above the mean signal intensity of remote myocardium) and when CMR is performed early in the disease course. Myocardial enhancement is nonspecific, but its location and pattern are very informative regarding the underlying cause. TTS patients who are LGE-positive show patchy and mild transmural LGE, corresponding to the region of WMA and also to myocardial edema (Figure 3) [8,9,13,14].

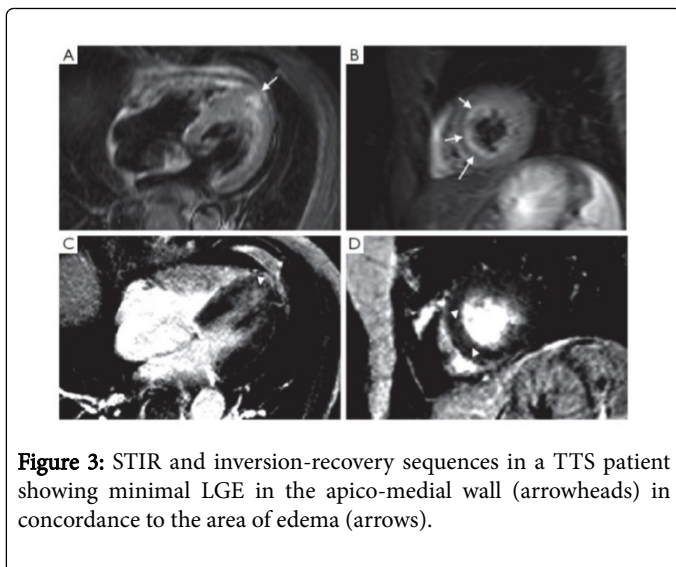


Figure 3: STIR and inversion-recovery sequences in a TTS patient showing minimal LGE in the apico-medial wall (arrowheads) in concordance to the area of edema (arrows).

Rolf et al. described that the LGE signal intensity found in TTS patients within 24 h of admission was lower than in cases of AMI or myocarditis, with concomitant lesser extension [5,15]. There is no evidence of LGE when using a threshold of 5 SD, which is usually the cut-off for fibrosis detection in myocarditis and AMI [5,9,16]. Due to a significantly higher increase of extracellular matrix in LGE-positive TTS patients, they assumed that LGE in TTS is due to transient fibrosis, but increased interstitial water also play a significant role [10,15,17]. The subtle changes in TTS are then myocardial edema-related LGE and not due to true necrosis [17].

Despite the presence of LGE may indicate a more severe form of TTS [8,18], its prognostic value is yet to be elucidated, since it is reversible and not associated with long-term reduction of LV function. Although LGE is widely considered to be a marker of increased frequency of cardiogenic shock and slower recovery of WMA, there are no large-scale studies so far to address its impact in TTS patients [7,8,15,18].

New CMR Techniques

T1 mapping, which includes native T1 and extracellular volume fraction (ECV) measurements, has emerged as a quantitative technique for detecting acute myocardial edema and extracellular matrix abnormalities in several myocardial diseases, revealing higher diagnostic performance comparing with standard CMR markers. Opposing to post-contrast T1 values, which tend to depend on many factors, ECV is calculated from pre- and postcontrast T1 relaxation times of myocardium and blood-pool and corrected for hematocrit, being a more robust and reliable parameter. However, it is not recommended in patients with estimated glomerular filtration rate <45 mL/min/1.73 m², due to the risk of nephrogenic systemic fibrosis associated with gadolinium exposure [1,2].

In accordance with native T1 and T2 relaxation times, ECV fraction is significantly higher in segments with WMA compared with the normokinetic myocardium, decreasing gradually from the apical to basal regions (Figure 4). Parallely, native T1 and T2 values as well as ECV are significantly elevated in normokinetic segments, unlike conventional CMR parameters. Groups of Dabir and Aikawa demonstrated that mapping can reveal significant involvement even in

remote myocardium (LV basal regions) in TTS patients, suggesting that some degree of myocardial edema occurs diffusely. The number of segments with increased native T1 is significantly correlated with decreased global LV systolic functions and prolonged LV wall motion recovery [1,2].

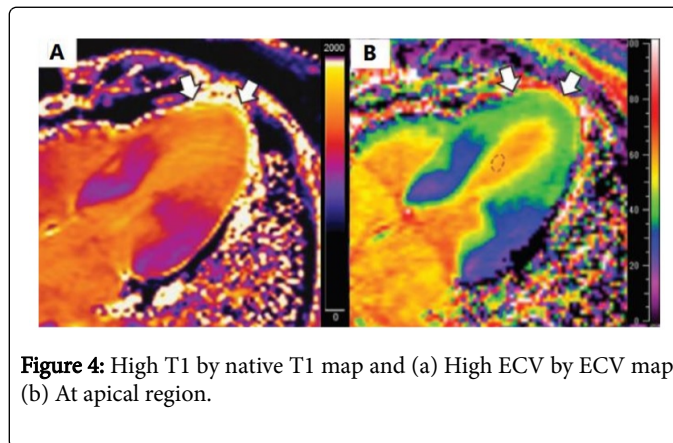


Figure 4: High T1 by native T1 map and (a) High ECV by ECV map (b) At apical region.

When myocardial injury is subtler, fibrosis may go undetected on conventional LGE threshold methods. T1 mapping sequences have the potential to improve the sensitivity of CMR tissue characterization, especially when diffuse and subtle fibrosis is the possible mechanism, like in TTS [5].

Recently, CMR feature tracking was introduced as a novel method for quantitative evaluation of cardiovascular function, similar to speckle tracking echocardiography [7,19]. In addition to reliable and reproducible assessments of biventricular systolic myocardial function, it allows complex quantification of myocardial mechanics such as myocardial twist and dyssynchrony. Circumferential and longitudinal strain differentiates between ballooning types, and global longitudinal strain might represent a potential parameter for long-term risk stratification in TTS. Strain values in TTS are significantly lower than in healthy subjects or patients with non-ST segment elevation MI, but similar compared with ST- segment elevation MI patients [6,19].

Transient dyssynchrony is increased in the acute phase of TTS, most pronounced in apical ballooning, and resolves with recovery of overall systolic function. Patients with high amounts of dyssynchrony have also reduced rotational performance. TTS patients show overall impairment of diastolic recoil whilst systolic twist remains preserved [6].

Myocardial Perfusion

First-pass perfusion (FPP) CMR typically shows no resting myocardial perfusion defects in patients with TTS [20]. However, in some cases, FPP CMR studies may appear normal at basal segments, but demonstrate subendocardial perfusion defects especially in the apex [5,21]. Although perfusion CMR is a well-established exam for the assessment of epicardial and microvascular ischaemia, there is little evidence of its utility in TTS [7].

Complications

Evidence of heart failure, including pleural effusion, pericardial effusion, and pulmonary edema, are often seen on CMR sequences. Intracavitary thrombus develops in approximately 5% of TTS patients, and may pass undetected by echocardiography [5,8,12,14]. Early

gadolinium enhancement sequence, ideally performed within 2 min after contrast agent infusion, is optimal for identification of adherent endocardial thrombus on mid-apical segments with severe hypokinesis or akinesis. It appears as a low signal intensity (no gadolinium uptake), contrasting with the intermediate signal of myocardium and blood pool (Figure 5) [5,7,8].

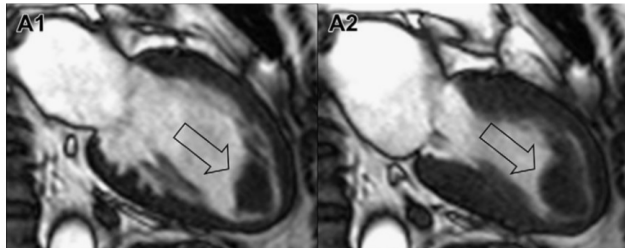


Figure 5: Vertical long axis views. Arrows indicate a large thrombus in the apex of the LV, which is seen in end (A1) Diastole and (A2) End systole.

In a small proportion of TTS patients, both basal hyperkinesis and mid-apical akinesis can produce a dynamic obstruction in the LV outflow tract, which could be associated with systolic anterior motion of the mitral leaflets and/or functional mitral valve regurgitation. This is a reversible phenomenon and will recover when the cardiomyopathy resolves [5,9].

Recent CMR studies have shown that Right Ventricular (RV) systolic dysfunction is relatively common in TTS, occurring in up to 40% of patients. It is associated with a longer hospitalization and a more severe clinical course, particularly presenting with heart failure development and pleural effusion. Consequently, biventricular ballooning may portend a worse prognosis, when compared with isolated LV involvement. Isolated RV involvement is exceptionally rare [8,9,16,18].

When to Perform CMR in TTS Patients?

In a patient admitted with a clinical picture suggestive of TTS, if ST-segment elevation is present, emergent coronary angiogram is mandatory. If absence of significant coronary lesions or non ST-segment elevation, it should be considered to perform CMR within 72 hours of admission, in order to support the diagnostic hypothesis of TTS, due to the inherent therapeutic and prognostic implications [13].

A complete clinical follow-up including CMR and/or echocardiography should be available 3-6 months after presentation. Since the underlying pathophysiology of TTS is believed to be a form of myocardial stunning, systolic function recovery is important to confirm the diagnosis. Interestingly, both electrocardiographic and WMA persist longer in patients who demonstrate initial low-intensity LGE, which should completely disappear at follow-up [5,9].

Differential Diagnosis: Myocarditis

The commonest entity in patients presenting with suspected ACS and unobstructed coronary arteries is myocarditis, whose prevalence

ranges from 15% to 75%. Subepicardial edema is a typical finding of acute myocarditis on CMR and T2W triple inversion recovery sequences frequently show higher signal intensity on mid-wall or subepicardial myocardial layer [4,5,10]. However, the occurrence of multifocal and heterogeneous patterns could complicate the differential diagnosis. It tends to be basal, lateral and non-circumferential and to not reflect the coronary perfusion areas [5,9,22]. In contrast to TTS, the T2 signal remains visible for a longer time period [8].

Lake Louise diagnostic criterion establish that CMR findings are consistent with the diagnosis of myocarditis if two of three sequences demonstrate myocardial edema, hyperemia, and fibrosis. ECV quantification together with LGE imaging significantly improved the diagnostic accuracy of CMR compared with the Lake Louise criteria [10]. The presence of LGE in an area that does not correspond to any particular coronary artery distribution and is located mostly in the mid-wall to subepicardial layer strongly correlates with myocarditis. Delayed contrast-enhancement imaging visualizes areas of uptake with a patchy and multifocal pattern, which could be transmural but not extending to the subendocardium, opposing to AMI [5,22,23]. Although edema and LGE may be focal in acute myocarditis, WMA are typically diffuse [9].

Differential Diagnosis: AMI with Normal Coronary Arteries

About one-third of patients with suspected TTS have an apical AMI, using CMR for the final diagnosis [24]. Several mechanisms have been proposed to explain this phenomenon, namely rupture of a vulnerable plaque (causing transitory occlusion that resolves spontaneously), distal vessels or small-caliber side branches disease, distal embolization, coronary vasospasm, or coronary dissection [10].

CMR can provide information about the chronology of the MI, since acute ischaemic myocardial injury leads to myocardial edema. T2 hyperintensity of segments affected by MI is maintained for more than 2 or 3 months after symptom onset. The location of the edema correlates with WMA and has a vascular distribution, similar to the necrosis [4,5,8-10].

In AMI with angiographically normal coronary arteries, CMR shows a perfusion defect in inversion-recovery gradient-echo or T1-weighted steady state free precession sequences [4]. LGE has a subendocardial or transmural pattern, reflecting the vascular distribution of the affected myocardial territory [13,24,25]. LGE signal intensity is high (>5 SD above the mean signal intensity of remote myocardium), and the transmural extent of the area of enhancement indicates the nonviable territory [14,23].

Microvascular Obstruction (MVO), characterized by hypoenhanced core within MI scar (hyperenhancement) on rest FPP or LGE imaging, can occasionally be demonstrated. The presence and extent of MVO after AMI is associated with adverse LV remodelling and poor clinical outcome, reflecting less functional recovery [10].

	Takotsubo syndrome	Myocarditis	Acute Myocardial Infarction
Wall Motion Abnormalities (WMA)	Apical ballooning in classic form; circumferential	Usually diffuse/global	Follows a coronary artery perfusion territory
Myocardial edema	Matches WMA; circumferential; resolves faster	Subepicardial; non- circumferential	Vascular distribution
Late gadolinium enhancement	If present, matches WMA, it is patchy and of low-intensity; rapidly reversible	Mostly in the mid-wall to subepicardial layer, not extending to subendocardium; high-intensity	Vascular distribution; subendocardial or transmural pattern; high- intensity
RV involvement	Up to 40%; worse prognosis	Rare	May be seen, particularly if right coronary artery is affected
Microvascular obstruction	No	No	Maybe
Resolution at 3 months	Yes	Residual alterations can be seen	No

Table 1: Distinct CMR features between Takotsubo syndrome, myocarditis and acute myocardial infarction.

Limitations of CMR

CMR has some limitations that should be acknowledged. Assessment of myocardial edema relies on comparison of the signal intensity with areas of normal muscle. Since there are many other parameters influencing signal intensity in the individual patient, a consistent absolute threshold value cannot be applied. Also, artifacts related to motion, volume averaging, and inability to null areas of static blood can result in areas of increased T2W signal [21]. As already mentioned, imaging quality and interpretation is influenced by tachyarrhythmia and respiratory movements [2,10]. In addition, CMR is a less available imaging modality in many centers, adding to its higher cost, comparing with echocardiography.

Conclusion

The combination of the characteristic apical ballooning, mid-apical myocardial edema and, contrary to initial reports, the possible occurrence of low-intensity LGE points toward the diagnosis of TTS. Due to its accurate assessment of myocardial function and morphology, with tissue characterization, CMR is emerging as the imaging modality of choice in the diagnosis and follow-up of TTS. It has an incremental value for the differential diagnosis and therapeutic decision making in patients with suspected TTS that present without ST-segment elevation, and has the potential to avoid invasive procedures, like coronariography.

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Câmara Municipal de Loulé.

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