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; FFP: 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 nonischaemic 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).
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, T2-STIR image quality is easily degraded with respiratory motion, tachyarrhythmia or slow-flow artifacts [2,7,10].

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].
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].

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].

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.](image)

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 [4,24,25]. 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].

Conclusion
ST-segment elevation, and has the potential to avoid invasive 1.

has an incremental value for the 2.

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 7.

imaging modality of choice in the diagnosis and follow-up of TTS. It 4.

morphology, with tissue characterization, CMR is emerging as the 5.

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Wall Motion Abnormalities

Apical ballooning in classic form; circumferential 2.

Myocardial edema

Matches WMA; circumferential; resolves faster 3.

Late enhancement gadolinium enhancement

If present, matches WMA, it is patchy and of low-intensity; rapidly reversible 1.

RV involvement

Up to 40%; worse prognosis 6.

Microvascular obstruction

No 8.

Resolution at 3 months

Yes 9.

No

Myocarditis

Usually diffuse/global 10.

Subepicardial; non- circumferential 11.

Mostly in the mid-wall to subepicardial layer, not extending to subendocardium; high-intensity 12.

Vascular distribution; subendocardial or transmural pattern; high- intensity 13.

Vascular distribution

Residual alterations can be seen

Yes

No

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

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

Wall Motion Abnormalities (WMA)

Takotsubo syndrome

Apical ballooning in classic form; circumferential

Myocarditis

Usually diffuse/global

Acute Myocardial Infarction

Follows a coronary artery perfusion territory

Myocardial edema

Matches WMA; circumferential; resolves faster

Subepicardial; non- circumferential

Vascular distribution

Late enhancement 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

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Câmara Municipal de Loulé.

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