

## VENTRICULAR FUNCTION

# Value of Gadolinium-Enhanced Magnetic Resonance Imaging in Patients with Tako-Tsubo-Like Left Ventricular Dysfunction

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### ABSTRACT

We present gadolinium-enhanced cardiac magnetic resonance imaging (CMRI) in Tako-Tsubo-like left ventricular dysfunction showing the findings in acute phase and in follow-up. Gadolinium-enhanced CMRI allows to distinguish between myocardial infarction and other myocardial alterations, e.g., myocarditis. CMRI may thus permit to non-invasively identify patients with Tako-Tsubo syndrome by ruling out myocardial infarction or myocarditis in the setting of wall motion abnormalities (WMA).

### INTRODUCTION

The Tako-Tsubo-like left ventricular dysfunction is a syndrome well reported in Japanese literature (1, 2). It is characterized by acute chest pain accompanied by reversible left ventricular apical ballooning in the absence of relevant coronary artery disease (1–4). This syndrome was primarily but not exclusively described in Japan (2). The striking predilection for Japanese patients in the literature initially suggested a unique geographic or racial distribution, with origins in Asian culture. The frequency and clinical presentation in other countries is still unclear. Beside anecdotal case reports from other parts of the world, only recently a series of 22 female, white patients was reported from North America (3–5). In the following, we focused on Gadolinium (Gd)-enhanced Magnetic Resonance Imaging (CMRI) in patients with Tako-Tsubo-like left ventricular dysfunction. The

knowledge about the clinical appearance and findings in these patients will help to identify them. CMRI allows to distinguish between myocardial infarction and other myocardial alterations, e.g., myocarditis. CMRI may thus permit to identify patients with Tako-Tsubo syndrome by showing viable myocardium in the setting of regional wall motion abnormality. In addition CMRI may help to understand the still unknown etiology of this syndrome.

### PATIENTS AND METHODS

#### *Patients*

The study population consisted of 4 patients (three female, aged 45, 52, 59 yrs; one male, age 72 yrs). All were white, three of German extraction and one (patient 2) of Turkish extraction. Three of the patients (patient 1, 3 and 4) presented with acute chest pain and subsequent admission to the hospital within two to six hours after onset of symptoms. One patient (patient 2) had recurrent chest pain over 4 days before admission.

In each patient the disease had been induced by an episode of emotional or physical stress. Patient 3 had a vehement quarrel with her partner before, and patient 2 was close to emotional breakdown due to a family conflict and travel activities.

Some concomitant disease of the patients were remarkable. Patient 1 has a history of depression. Patient 3 underwent surgical resection of adrenal gland adenoma six months prior, which had caused a Conn-syndrome. Patient 4 was in reduced physical condition because he had developed a milliar tuberculosis.

*Keywords:* Tako Tsubo Left Ventricular Dysfunction, Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging, Apical ballooning, Viability.

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**Table 1.** Demographics and patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age	45	52	59	72
ECG	ST Elevation V1–6	T-wave inversion V2–6	T-wave inversion I, II, aVF, V3–6	T-wave inversion V2–6
Trop. I level (<0.06 ng/mL)	0.4	0.125	0.23	0.36
CK/CK MB (<140/<24 U/L)	85	48	151/20	266/148
Coronary angiogram	no CAD	50% LAD stenosis	no CAD	Coronary artery sclerosis

Trop. I level = Troponin I level; CK = Creatinine kinase; CAD = Coronary artery disease.

### MR imaging technique

After obtaining informed consent, patients were imaged using a 1.5 Tesla MRI scanner (Siemens, Sonata, Erlangen, Germany), patient position supine, using breath hold steady state free precession (SSFP or TrueFISP) cine-sequences (TE 1.58 ms, TR 41.08 ms, flip angle 60°, slice thickness 6 mm) and single turbo-spin echo sequences (TSE) T1-weighted (TE 6.7 ms, TR 700 ms, flip angle 180°, slice thickness 6 mm) and T2-weighted (TE 83 ms, TR 600 ms, flip angle 180°, slice thickness 7 mm). Prospective ECG triggering was used. Left ventricular function, volumes, and ejection fraction (EF) were calculated using ARGUS-software by summation of discs (Siemens Medical Systems, Erlangen, Germany). Evaluation of wall motion abnormalities was done using the AHA 16 segment model. Contrast agent (dosage: 0.1 mmol Gd-DTPA/kg/ bodyweight, Magnevist®, Schering, Germany) was injected at 4 mL/s and followed by saline flush (20 mL NaCl 0.9%, 4 mL/s). In one patient (patient 4), a resting-perfusion study was performed in acute state and on follow-up using a breath hold segmented k-space turbo gradient echo technique (TE 2.1 ms, TR 590 ms, slice thickness 8 mm, flip angle 25°). In all patients 3D-Turbo-Flash inversion recovery sequences (TE 1.24 ms, TR 440 ms, TI adjusted to null myocardium, TD 350 ms, slice thickness 5 mm, slices per slab 14, matrix 128 × 256) covering the entire left ventricle in two long axis and multiple short axis orientations were acquired during the following 15 min after Gd-DTPA administration.

Cardiac MRI was performed in the acute phase of the disease (patient 1: 4 hours after admission; patient 2: 44 hours after admission; patient 3: 3 hours after admission; patient 4: 14 hours after admission) and on follow-up (patient 1: 4 day later; patient 2: 9 days later; patient 3: 62 days later; patient 4: 11 days later).

## RESULTS

### Clinical presentation

On ECG patient 1 showed ST elevations in lead V1–6. Patient 2 and 4 presented with T-wave inversion in V2-6 and patient 3 with T-wave-inversions in II, III, aVF and V3–6. On admission Troponin I was moderately elevated (between 0.12 and 0.4 mg/mL—normal range <0.08 ng/mL) in all patients. Three patients showed no elevation of creatinine kinase levels; in patient 4 creatinine kinase/MB was 266/148 U/L (<70/12 U/L). In two patients (patient 3 and 4) NT-pro-BNP levels had

been measured showing increased levels (4168 pg/mL and 2954 pg/mL—normal range 1.00-153.00 pg/mL).

All patients underwent emergency coronary angiography on admission. In patient 1 and 3 a coronary artery disease was ruled out. In patient 2 a stenosis in the mid LAD of 50% was found, patient 4 had a dilatative form of coronary artery sclerosis without coronary artery stenosis. In all patients ventriculography and echocardiography showed a balloon-like apical wall motion abnormality with impaired left ventricular function (Table 1). In addition, a biopsy of the right ventricle was performed in patient 4 showing no evidence of myocarditis and, in particular, no signs of inflammation or necrosis.

### CMRI investigation

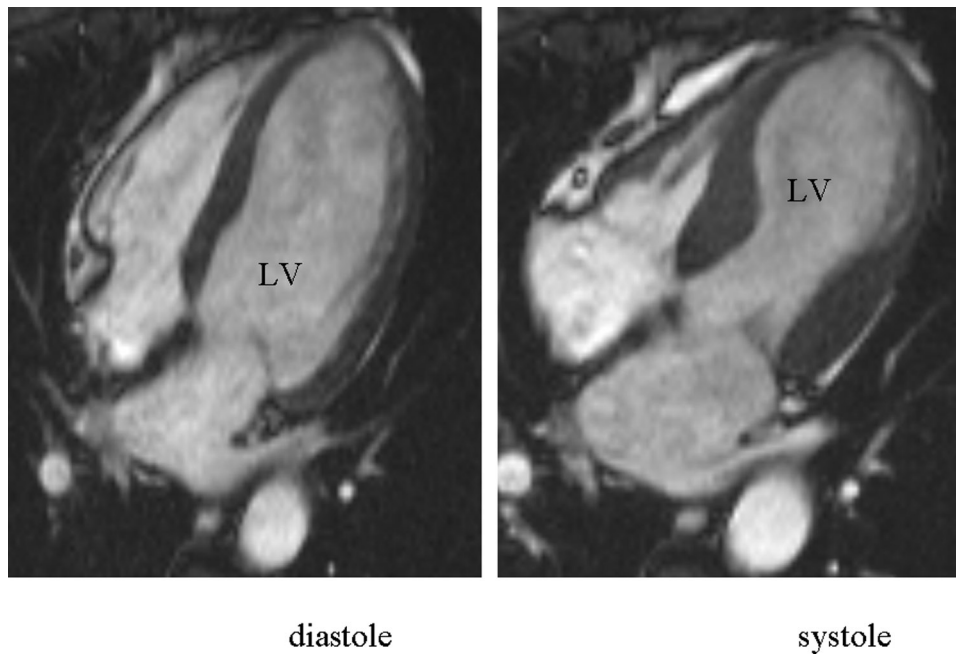
The first cardiac MRI was performed in the acute phase of the disease. In the TrueFISP cine sequences all patient presented with an akinesis of the apical and midventricular wall segments without systolic wall thickening, whereas the basal segments showed hyper-contraction (Figs. 1 and 2). The ejection fraction (EF) was impaired (patient 1: 35%, patient 2: 36%, patient 3: 34%, patient 4: 25%). On T1-weighted images without fat saturation and on T2-weighted images with fat saturation no signal abnormality was found. After intravenous administration of GD-DTPA 3D-Turbo-Flash inversion recovery sequences showed no signs of pathological signal enhancement (Table 2).

On follow-up investigation all patients presented with normalized regional and global left ventricular function on TrueFisp cine sequences (Figs. 3 and 4). Ejection fraction has been improved to values between 60–67% (patient 1: 62%, patient 2: 60%, patient 3: 67%, patient 4 : 62%). Three patients recovered

**Table 2.** MRI-findings in acute phase

	Patient 1	Patient 2	Patient 3	Patient 4
Time of first MRI (hours after coronary angiography)	4	44	3	14
EF in %	35	36	34	25
WMA	apical ballooning; akinesis of apical and midventricular wall segments			
T1 and T2 TSE	no signal abnormalities			
Late enhancement	no late			

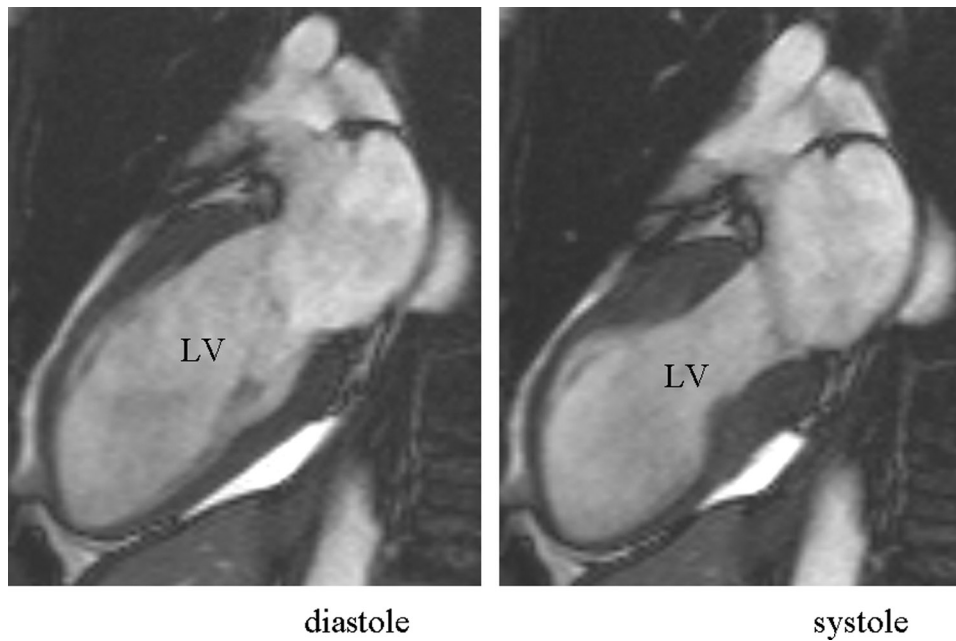
MRI = Magnetic resonance imaging; EF = Ejection fraction; WMA = Wall motion abnormality; T1 and T 2 TSE = T1 and T2 turbo spin echo sequences.



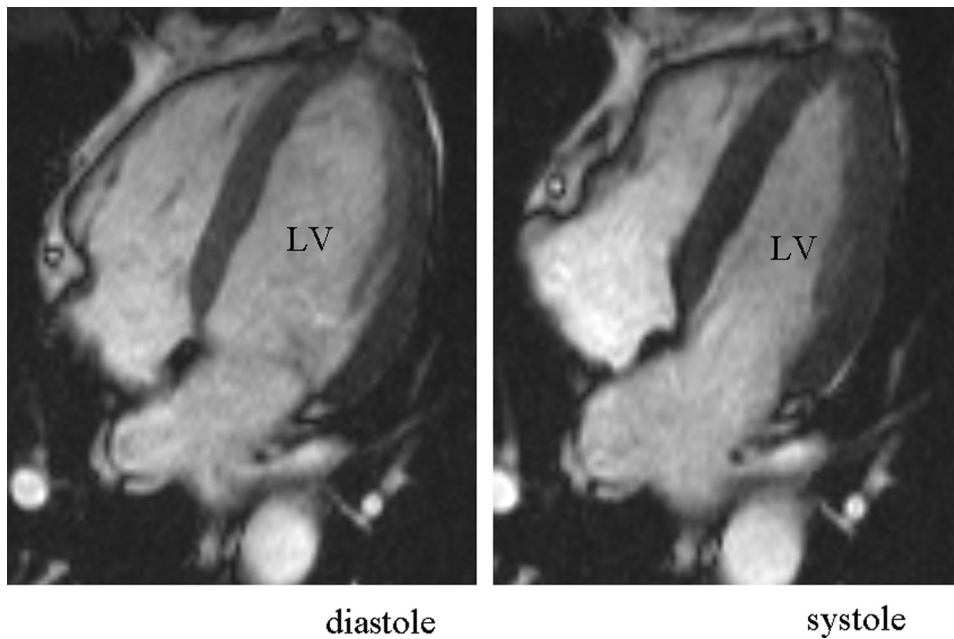
**Figure 1.** Breath hold TrueFisp cine-sequences in 4-chamber orientation of patient 3 showing diastole and systole of left ventricle a few hours after admission to the hospital. In the end-systolic phase of left ventricular contraction the apex shows a balloon-like wall motion abnormality.

within a few days (patient 1 after 4 days, patient 2 after 9 days, and patient 4 after 11 days). Patient 3 showed delayed recovery. After 10 days his left ventricular function was improved, but still impaired (EF 45%). On follow-up after 62 days left ventricular function was normalized (EF 62%). In all patients apical and

midventricular wall segments showed normalized systolic thickening. On T1- and T2-weighted images no signal abnormalities were present. After administration of Gd-DTPA pathological signal enhancement was ruled out using a 3D-Turbo-Flash inversion recovery sequence (Table 3).



**Figure 2.** Cine-sequences in 2-chamber orientation; third patient; diastole and systole at the time of admission showing the typical phenomenon of apical ballooning.



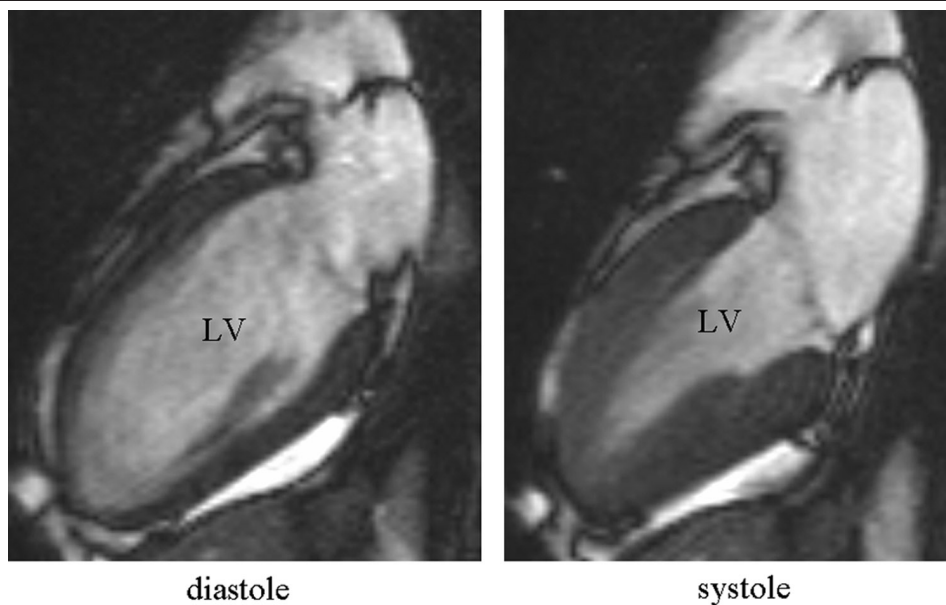
**Figure 3.** Cine-sequences of the same patient in 4 chamber orientation 62 days later showing completely recovered LV function and no wall motion abnormalities.

In patient 4 a resting-perfusion study was performed in the acute phase showing a circular, subendocardial perfusion defect in the apical and midventricular segments of left ventricle. On follow-up resting-perfusion was normalized.

## DISCUSSION

Tako-Tsubo like left ventricular dysfunction is a syndrome first reported in Japan (1, 2). The syndrome is characterized

by acute chest pain accompanied by reversible balloon-like LV wall motion abnormality of the apex with hyper-contraction of the basal segment in the absence of relevant coronary artery disease (1–5). The term “Tako-Tsubo-like LV dysfunction” was proposed in 1990 because the early end-systolic ventriculogram looks like a “Tako-Tsubo” used for trapping octopuses in Japan (2, 4–7). The syndrome is also described under the term “transient left ventricular apical ballooning” or “Tako-Tsubo-cardiomyopathy” (1, 2, 4). Most cases are induced by



**Figure 4.** Cine-sequences in 2 chamber orientation; third patient; 62 days after first investigation with normalized LV wall motion.

**Table 3.** MRI-findings: follow-up investigation

	Patient 1	Patient 2	Patient 3	Patient 4
Time of follow-up MRI (in days after 1 MRI)	4	9	62	11
EF in %	62	60	67	62
WMA	on WMA; normalized LV function			
T1 and T2 TSE	no signal abnormalities			
Late enhancement	no late			

MRI = Magnetic resonance imaging; EF = Ejection fraction; WMA = Wall motion abnormality; T1 and T2 TSE = T1 and T2 turbo spin echo sequences; LV = Left ventricle.

physical and emotional stress (1–4, 6, 7). A striking predilection for middle-aged women is reported in Japanese literature with a 6-fold higher incidence in woman than men. This is in strong agreement with findings of an American group, where all 22 patients were female (1–5). The ST-T-segment abnormalities on electrocardiograms (ECG) are similar to acute myocardial infarction (1–4, 8). Coronary angiography shows no signs of relevant coronary artery disease (1–4, 9). The cardiac markers like Troponin and creatinine kinase are elevated (1, 3, 4, 8). The etiology of this syndrome is still unknown and various diagnostic approaches have been made to find an explanation. In a Japanese study no correlation to increased values of viral antibody titres was found (1). Myocardial biopsy showed interstitial fibrosis without significant inflammatory infiltrate or necrosis (1). The typical acute phase balloon-like LV wall motion abnormalities disappeared at a median of 18 days after onset completely (1). An other Japanese study group used rest 201 Thallium and 123 I-BMIPP dual isotope myocardial Single Photon Emission Computed Tomography (SPECT) and showed a transient perfusion-metabolism mismatch in the apex persisting over several months (2). This perfusion-metabolism mismatch is thought to be typical for myocardial stunning (2). Ako et al detected impaired coronary microcirculation using an intracoronary Doppler flow-wire technique (7, 10). A myocardial stunning-like phenomenon, unrelated to atherosclerotic coronary disease but with microvascular abnormalities is suspected. Adrenergic stress with overflow of catecholamine causing coronary artery spasm and disturbance of microcirculation may also be involved (1, 4, 9). Kono et al suggested direct toxic effects of norepinephrine as cause for the impaired myocardial function (1, 10, 11). A transient left ventricular hypo-contraction was induced by emotional stress in rats (4, 12). This was proposed to be a possible animal model of Tako-Tsubo-left ventricular dysfunction. A pathophysiological explanation for the unusual gender and age distribution is unknown.

The patients enrolled in this study showed characteristic signs of Tako-Tsubo syndrome. Distribution of gender and age was also typical. In three patients (patient 1, 2 and 4) LV function normalized within a few days after the onset of symptoms in agreement with the data of Japanese studies with a median of 18 days. Patient 3 had a delayed recovery after 62 days. Remarkably, she reported recurrent episodes of chest pain with relief

after administration of nitrates. She was exposed to ongoing emotional stress due to a family conflict. Besides the reported cases in Japan and North America, these four cases belong to the few cases published in Europe. In our study CMRI on admission and on follow-up turned out to be the crucial diagnostic modality. Like ventriculography or transthoracic echocardiography, CMRI allows to detect the typical balloon-like WMA of the left ventricle but with high reproducibility and precise measurement of wall thickening and ejection fraction. In addition, the unique technique of contrast enhanced CMRI allows to detect myocardial damage such as myocardial infarction or myocardial alternations due to infiltrative or inflammatory processes (e.g., myocarditis). Among the patients in this study, myocardial infarction or myocarditis could be ruled out by CMRI although the typical severe WMA was present on first examination with normalization on follow-up. CMRI proved to be the most valuable diagnostic tool for the identification of the Tako-Tsubo syndrome and to non-invasively differentiate this syndrome from other cardiac settings like myocardial infarction or myocarditis. CMRI findings substantially complete the clinical diagnosis in Tako-Tsubo cardiomyopathy.

Regarding potential pathophysiological mechanisms CMRI investigations of myocardial perfusion with and without Adenosin-stress perfusion may contribute to detect alternations of microcirculation. This is emphasized by the observation of a circular, subendocardial defect during resting-perfusion imaging in the acute phase of patient 3.

## LIMITATIONS

Due to the fact that this syndrome is relatively unknown and thus the lack of recognition, the number of study patients is very small. All four patients had been diagnosed of having a Tako-Tsubo-like left ventricular dysfunction after being investigated by CMRI. There was no systematic screening of all patients admitted to our clinic with acute chest pain for the presence of Tako-Tsubo syndrome. A resting-perfusion study was performed in only one patient.

## CONCLUSION

The Tako-Tsubo syndrome represents a still relatively unknown differential diagnosis of acute chest pain. Recognition and understanding of this syndrome will help to differentiate it from other acute myocardial alterations. CMRI proved to be an important diagnostic tool in diagnosing Tako-Tsubo-like left ventricular dysfunction by showing viable myocardium in the setting of severe wall motion abnormalities. A baseline and follow-up investigation should be performed to detect the transient character of the WMA.

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