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REVIEW

Takotsubo cardiomyopathy: an integrated multi-imaging approach

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Takotsubo cardiomyopathy (TTC) is a distinct clinical entity characterized by the presence of transient left ventricular wall dysfunction without significant culprit obstructive coronary artery disease. Invasive coronary angiography and ventriculography are the 'gold standard' for definitive diagnosis, with an integrated multi-modality imaging approach offering advantages in various clinical scenarios. Echocardiography is a widely available, first-line, non-invasive imaging technique appropriate both in emergency setting to confirm diagnosis, assess for various potential acute complications, and in serial follow-up to track myocardial recovery. Cardiac magnetic resonance (CMR) may be helpful to discriminate TTC from other acute cardiac syndromes with troponin elevation and ventricular dysfunction. Echocardiography, CMR, and nuclear imaging may also provide new insights into possible underlying pathophysiological mechanisms, and myocardial ^{123}I-metaiodobenzyl-guanidine imaging may have a role for retrospective diagnosis in the subacute phase of late-presenting cases. The potential diagnostic role of coronary computed tomography angiography in the emergency room requires a further study.

Keywords takotsubo cardiomyopathy • pathophysiology • cardiac imaging

Introduction

Takotsubo cardiomyopathy (TTC) is an unique cardiac syndrome characterized by the presence of transient left ventricular wall dysfunction without significant culprit obstructive coronary artery disease (CAD).[1–3] Although invasive coronary angiography (CA) remains still mandatory to rule out acute coronary syndrome (ACS), non-invasive multi-modality imaging, along with biomarker assays (brain natriuretic peptide/troponin ratio), are becoming increasingly useful for a comprehensive evaluation of TTC.[1]

Pathophysiology

The development of TTC appears to reflect the cardiac response to a surge in serum catecholamines as evidenced by a frequent stress provoking precipitant induction of TTC by epinephrine or dobutamine administration and occurrence of TTC in patients with pheochromocytoma. Serum epinephrine levels in TTC patients were significantly higher than in those with acute ischaemic heart failure, implying an excessive hypothalamic–pituitary–adrenal axis response to stress.[4] A number of pathophysiological hypotheses

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have been proposed to explain the classical apical dysfunction observed in TTC. These include multi-vessel coronary vasospasm, aborted myocardial infarction (MI) with plaque rupture, thrombus formation and dissipation, vasospasm of a large 'wrap-around' left anterior descending (LAD) artery anatomy, or direct catecholaminergic effects on the myocardium. Myocardial perfusion scans performed acutely suggest normal myocardial perfusion, and an intravascular ultrasound (IVUS) study demonstrated normal coronary artery wall anatomy with the absence of atherosclerotic plaque or thrombus in a cohort of TTC patients.[5] The epidemiology of TTC does not suggest atherosclerosis as the underlying cause, and triggering by dobutamine stress protocols contradicts coronary vasospasm as a primary mediator. Myocardial biopsies from patients during the acute episode show changes consistent with the molecular and cellular sequelae of exposure to high catecholamines,[6] and laboratory studies support a direct mechanism for high-dose catecholamines to induce the acute apical dysfunction.[7–9] One hypothesis proposes that epinephrine at high doses induces a direct negative inotropic effect via the myocardial β2-adrenoceptors (β2ARs), initiating β2AR coupling to the negative inotropic Gi messenger pathway by a reversible process known as stimulus trafficking.[7] A greater βAR density at the apex compared with the base is observed in the mammalian heart,[7] and the β2AR density is specifically higher in the apical myocardium.[7] Experimentally, an acute apical and midventricular dysfunction in a 'Takotsubo-like' pattern can be initiated by a rapid high-dose intravenous epinephrine bolus, but not by norepinephrine (*Figure 1*).[7] In summary, this hypothesis suggests that, at the very high catecholamine levels seen in TTC, there is a β2AR-mediated negative inotropic effect, more pronounced at the apex, and completely reversible on removal of the catecholamine stimulus (*Figure 2*).[10,11]

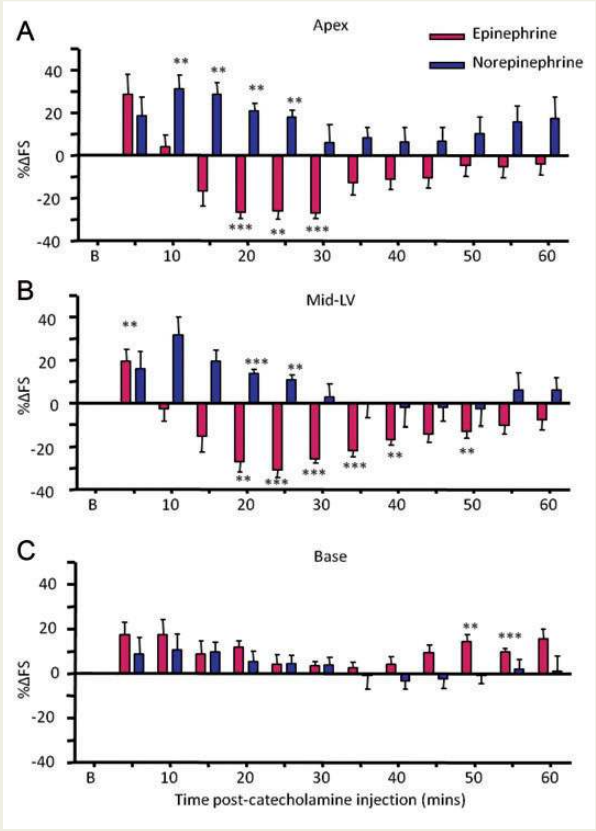

Figure 1 TTC can be reproduced in a model demonstrating an epinephrine-specific with acute, reversible apical, and midventricular dysfunction, and basal sparing, induced following high-dose intravenous epinephrine bolus, but not norepinephrine, in a rat model of TTC (reproduced from Paur *et al.*[7] with permission).

Epidemiology

There is a marked female predominance in TTC affecting in 90% of cases postmenopausal women from 60 to 75 years. Men are in a similar age range and represent only 4–15% of the patient population. Overall, <10% of the patients with TTC are <50 years of age, and rarely children of both sexes have been described.[12–14] The exact incidence of TTC is unknown. Among patients undergoing CA because of suspected ACS, between 1 and 3% eventually are diagnosed as having TTC.[1]

Clinical presentation

In the majority of patients (70–80%), the onset of TTC is preceded by a triggering event, with a similar distribution of severe emotional and physical stress in 30 and 40% of the patients, respectively.[12–14] The time interval from symptom onset to hospital admission ranges up to 10 ± 16 h and appears to be longer than in patients with acute myocardial infarction (AMI).[13] The most common presenting symptom in TTC is angina-like chest pain in 60–70% of the patients. Dyspnoea as the primary complaint is reported in 10–20%. An initial presentation with syncope (3–4%), nausea, cardiogenic shock, or ventricular fibrillation have also been observed.[3]

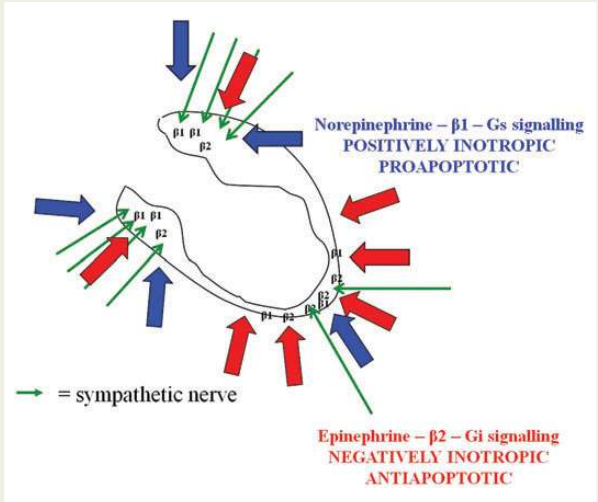

Figure 2 Schematic representation of the regional differences in response to high catecholamine doses explaining TTC (adapted from Lyon *et al.*).[10]

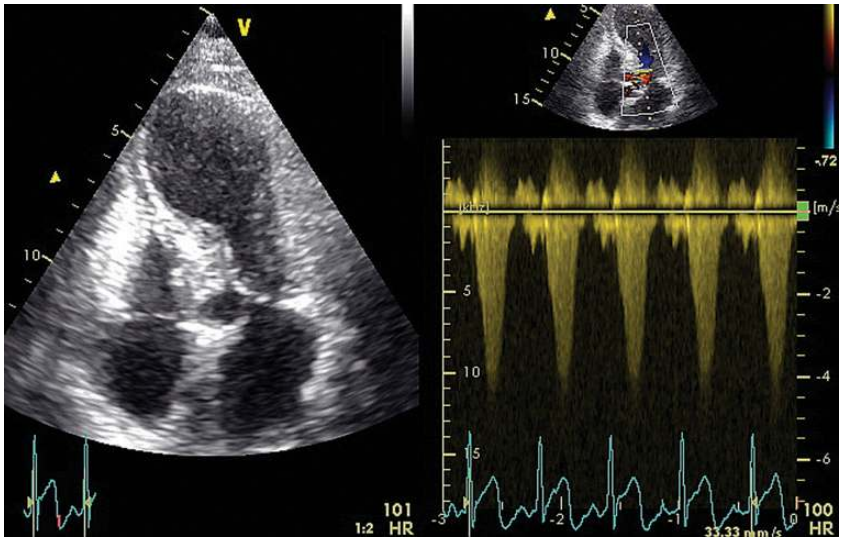

Figure 3 Example of typical TTC at the acute phase, with left ventricular obstruction due to systolic anterior motion (SAM) of the mitral valve. In the left, the four-apical chamber view, frozen at end-systole showing the SAM. Note the relative basal septal hypertrophy. In the right, the corresponding intraventricular gradient by continuous-wave Doppler.

Diagnostic methods and imaging techniques

Cardiac biomarkers and laboratory findings

An important hallmark of TTC is the relatively small increase in creatinine kinase and troponin in proportion to the extension of organ dysfunction (i.e. widespread segmental akinesia/hypokinesia).[3] Plasma catecholamines (epinephrine, norepinephrine, and dopamine), neuropeptide-Y, and serotonin concentrations are typically increased in TTC.[4] Indeed, compared with patients with AMI in Killip Class III at admission, TTC patients have two to three times higher levels of catecholamines.[4] However, other studies did not replicate this finding, possibly reflecting differences in sample timing and assays applied.[15] Serum levels of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) are increased in TTC and are a valuable marker for the assessment of myocardial deterioration and recovery. In this regard, a low serum NT-proBNP at admission is a reliable indicator of a favourable prognosis. Some authors suggest that TTC may be differentiated from ACS based on a unique cardiac biomarker profile characterized by a steep increase of NT-proBNP over the first few days in the presence of only slightly elevated markers of myocardial necrosis (↑ NT-pro BNP/troponin ratio).[16]

Electrocardiography

Electrocardiography (ECG) abnormalities are present in the majority of TTC patients at the time of diagnosis.[3] However, no pathognomonic ECG pattern has been specifically linked to TTC to date. The ECG abnormalities include ST-segment elevation, ST-segment depression, pathologic Q-wave, and T-wave inversion, which make

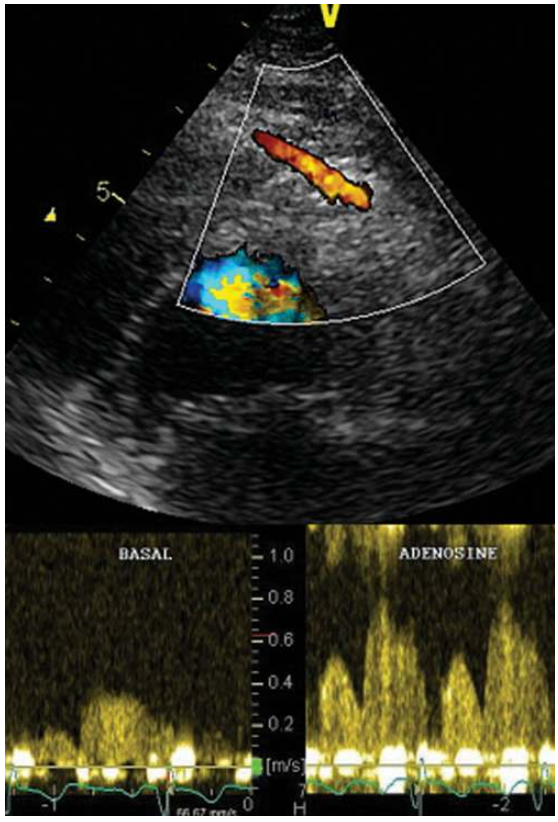

Figure 4 Example of LAD flow visualization by transthoracic colour Doppler echocardiography in the top, and example of non-invasive CFR in the bottom. Baseline LAD flow in the bottom left (biphasic with a diastolic predominance), and the hyperaemic LAD flow in the bottom right. CFR = 2.3.

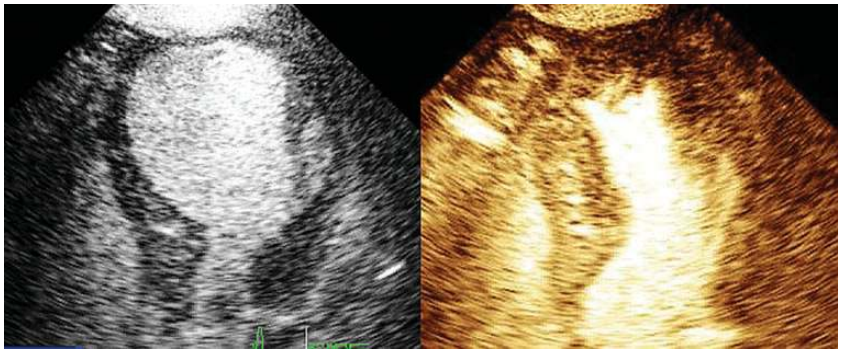

Figure 5 Example of typical TTC in the four-apical chamber view frozen at end-systole. In the left, at the acute phase: extensive, circumferential akinesia of the mid-apical left ventricular (LV) wall giving the classical Takotsubo (octopus pot) appearance. In the right, at follow-up, total recovery of wall motion abnormalities.

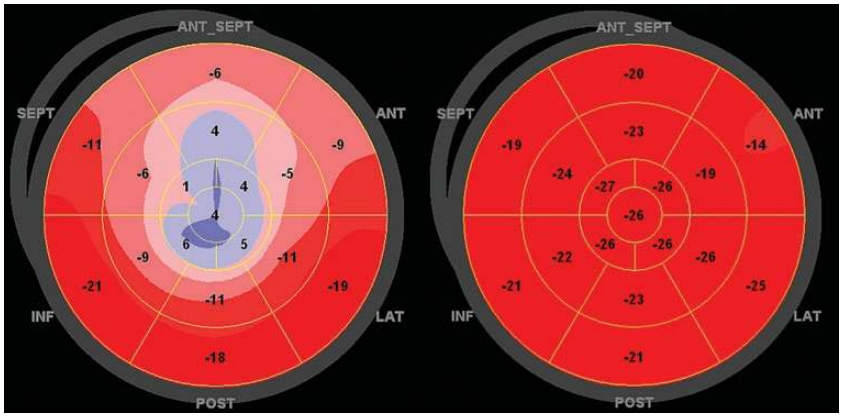

Figure 6 Example of a bull-eye illustrating the longitudinal strain of the LV in a patient with typical TTC. In the left, the acute phase, and in the right after recovery at follow-up.

difficult to differentiate between TTC and ACS. Some TTC patients may present with normal ECG. In patients who present early, ST elevation is present in ~80%.[17] Differentiation between TTC and AMI based only on ECG is therefore problematic, although there are some subtle differences. In patients with suspected acute anterior ST-elevation MI (STEMI), the absence of ST depression or the presence of ST elevation in the inferior leads may suggest the diagnosis of TTC. One frequent ECG phenomenon is transient prolongation of QTc that resolves to normal during the recovery phase.[18] The QTc prolongation is often pronounced (>500 ms), which is seldom seen in a true STEMI due to coronary occlusion and, therefore, increases suspicion of TTC where present.

Coronary angiography and left ventriculography

Although a variety of clinical examination tools are available, cardiac catheterization is still necessary for definitive differentiation between TTC and ACS due to complicated CAD. It is mandated as an emergency procedure where available in patients presenting with acute chest pain and ST elevation, and it should be preferably performed within 48 h from symptoms onset in all other cases. The most frequent finding by CA is normal coronary arteries.[19] However, many patients may present with bystander coronary disease, where stenoses may or may not be haemodynamically significant, but (by definition) are insufficient to explain the degree and pattern of acute left ventricular (LV) dysfunction. Poor distal run-off with increased TIMI frame count is frequently described reflecting microvascular dysfunction.[20] Invasive evaluation of TTC patients should include left ventriculography (if not contraindicated) to confirm the LV wall motion abnormality pattern and to promptly exclude associated mitral regurgitation (MR) that carries important prognostic information.[21] This is usually where the diagnosis of TTC is confirmed. It also allows direct measurement of the pressure gradient across the LV outflow tract (LVOT). Coronary stenoses do not seem to play a crucial role in the pathogenesis of TTC. By definition, myocardial dysfunction

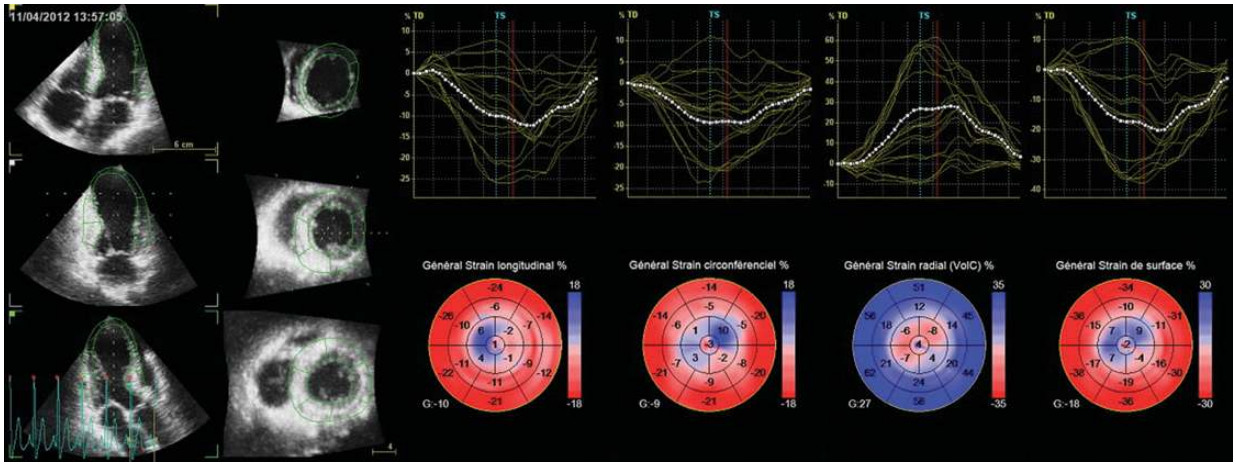

Figure 7 Example of 3D strain pattern in a typical TTC patient during the acute phase. The strain curves and bull-eyes of the respective longitudinal, circumferential, radial, and area strain demonstrating a transmural impairment of apical myocardial strain.

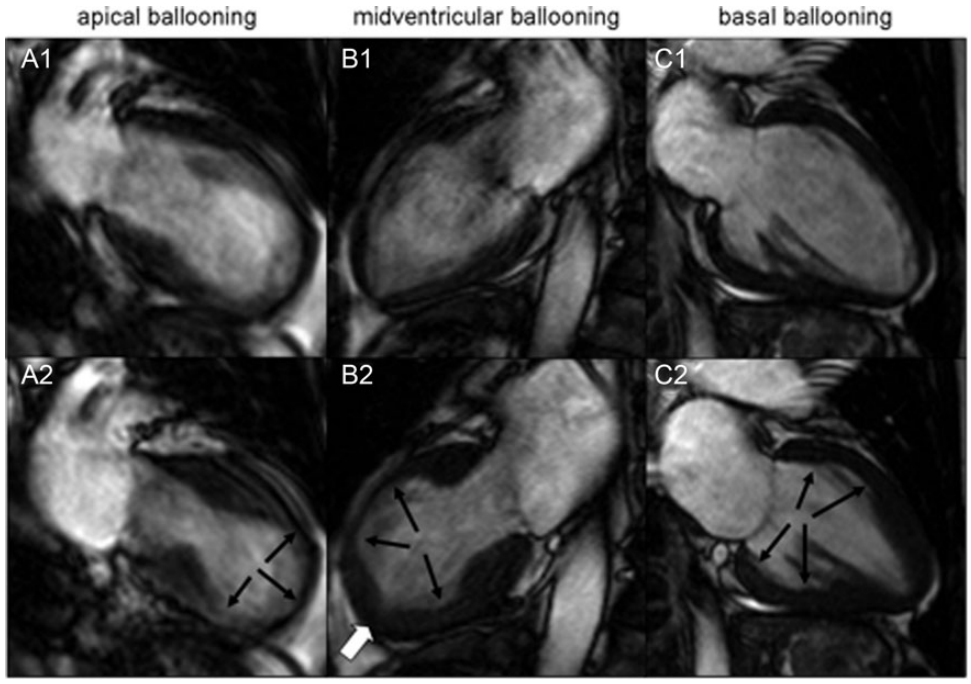

Figure 8 Representative examples of each pattern of regional dysfunction in TTC and related syndromes: 'classical' apical dysfunction in end-diastole (*A*1) and end-systole (*A*2), 'mid left ventricular variant' with midventricular dysfunction in end-diastole (*B*1) and end-systole (*B*2), 'inverted TTC' with circumferential basal dysfunction in end-diastole (*C*1) and end-systole (*C*2). Black arrows in A2, B2, and C2 indicate the wall regions with akinesia; white arrow in B2 indicates the normokinetic apex of the left ventricle. Modified and reprinted with permission from Athanasiadis *et al.*[36]

exceeds the area supplied by the vascular bed of a single major coronary artery in which stenosis is located, or is definitively not supplied by the stenotic artery.[1–2]

Echocardiography

Owing to its widespread availability even in emergency settings, echocardiography plays a key role in diagnostic assessment of TTC and contributes to the increased detection and reported incidence in contemporary clinical practice.[22] During the acute phase, transthoracic echocardiography (TTE) examination may detect a large area of dysfunctional myocardium usually extended beyond the territory of distribution of a single coronary artery. Furthermore, wall motion analysis reveals a typical pattern of LV myocardial contractility characterized by symmetrical regional abnormalities extending

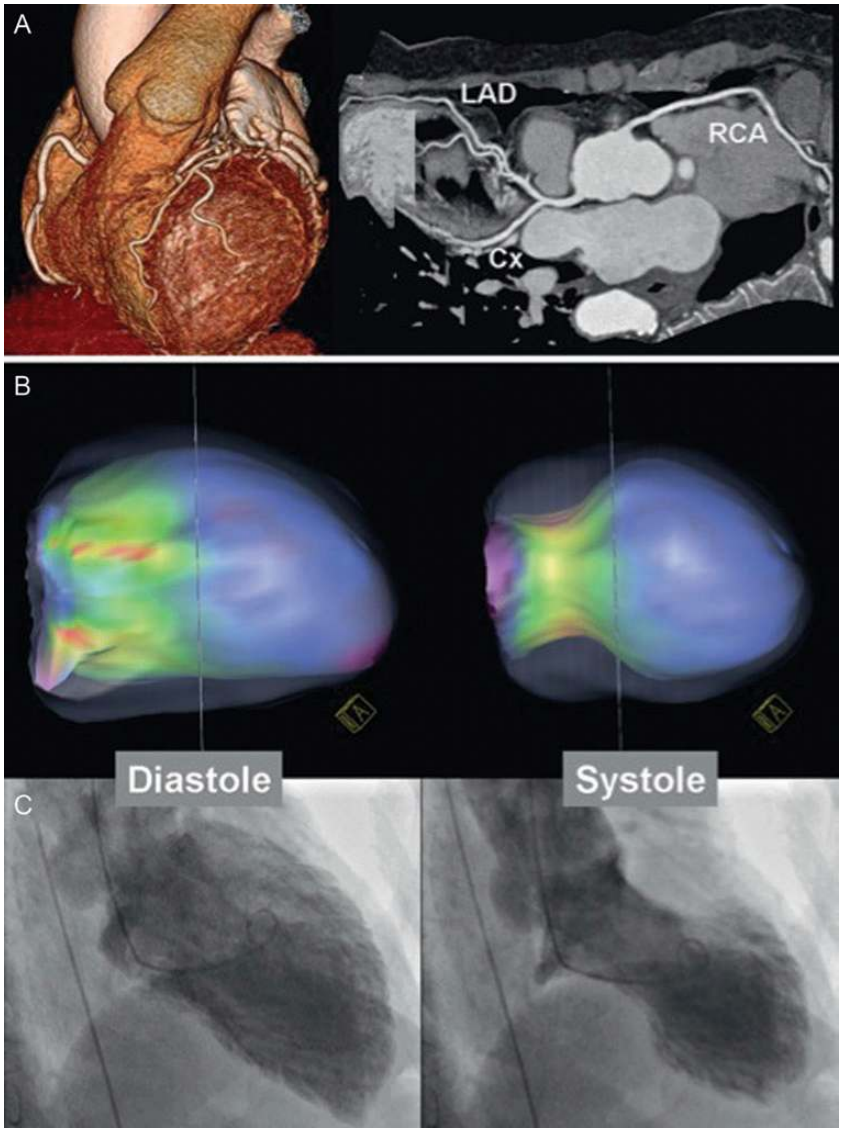

Figure 9 Diagnosis of TTC in an elderly subject (age 70s) that presented with acute chest pain after dead of spouse. (*A*) CCTA revealed normal coronary arteries. (*B*) Functional analysis showed LV apical hypokinesis with systolic ballooning prompting a diagnosis of TTC. (*C*) Left heart catheterization confirmed TTC diagnosis showing normal coronary arteries and persistent LV apical hypokinesis with systolic ballooning. Adapted from Nance *et al.*[38] with copyright permission.

equally into the anterior, inferior, and lateral walls. This 'circumferential pattern' can be considered a hallmark of TTC.[23] Moreover, echocardiography depicts LV morphology allowing the recognition not only the classic LV apical dysfunction, but also variant forms, such as midventricular dysfunction and apical sparing.[22] It also plays an important role in the early detection of severe potential complications such as right ventricular (RV) involvement (biventricular dysfunction), LVOT obstruction (*Figure 3*), thrombus formation, MR, and ventricular rupture.[21–25] Additionally, it can be used at follow-up to confirm recovery of LV function. Finally, non-conventional echocardiographic techniques (tissue Doppler, strain imaging, real-time three-dimensional [3D] echocardiography), coronary flow velocity reserve, and myocardial contrast echocardiography may provide new insights in the assessment of LV and RV myocardial function and coronary microcirculation physiopathology (*Figures 4–7*).[22,26] The symmetric pattern of wall motion abnormalities (WMA) characteristic of typical TTC is sometimes difficult to assess by transthoracic echo. In such cases, the use of a contrast agent for LV opacification could magnify this pattern as illustrated in *Figure 5*. This peculiar pattern of WMA could also be evaluated by myocardial deformation imaging using the speckle tracking method, which demonstrates a transient circular impairment of not only longitudinal LV function as illustrated in *Figure 6*, but also circumferential and radial LV function (see *Figure 7*), as well as LV twist mechanics deficiency.[27–29]

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) provides unique opportunity for further evaluation and characterization of patients with TTC. CMR allows complete cardiac anatomical information, may help to distinguish TTC from other acute cardiac syndromes, and provides additional insights into the pathophysiological mechanisms of the disease. CMR allows precise quantification of ventricular volumes and function. The large and unrestricted field of view of CMR permits full visualization of the ventricles in the main long axes, which may not be possible in all subjects with non-contrast, two-dimensional echocardiography. Thus, one can accurately visualize regional wall motion abnormalities to identify the three typical different LV wall motion abnormality patterns (apical, midventricular, and isolated basal dysfunction) (*Figure 8*).[30] The frequencies of these wall motion abnormality patterns vary across reported cohorts, and it is not clear whether this depends on specific population studies or represents the result of differences in the sensitivity and access to various imaging modalities. In the German Takotsubo Registry, which included 324 patients, the distribution was 64% apical dysfunction and 36% midventricular dysfunction. No patient with basal dysfunction was included in this German registry.[31] Many recent studies have in common that the number of patients with midventricular dysfunction is increased compared with the initial description of TTC.[32] TTC is not necessarily limited to the left, but may also involve the RV in up to one-third of patients.[30] In daily clinical practice, evaluation of the RV is performed by echocardiography despite limitations such as difficult acoustic windows and difficulties in viewing all parts of the RV in many patients. In such patients, CMR provides complete views of the RV and may demonstrate apical akinesia.[22,33] TTC may also exist as isolated RV TTC.[34] Serial CMR examinations may therefore be indicated in patients with unexplained sudden RV failure if echocardiography is not able to fully depict RV anatomy. CMR is, therefore, helpful as a second-line technique in patients with suspected TTC but suboptimal images by echocardiography, and in the ability to exclude MI on late gadolinium enhancement (LGE). Patients with large areas of LV akinesia may develop thrombi in the LV apex. Acute phase-contrast CMR may be helpful given the superior CMR capabilities of thrombus detection and apical imaging.[25] A unique capability of CMR is tissue characterization of acute myocardial changes occurring in TTC patients. The characteristic finding on short T_1 inversion recovery CMR images in TTC patients is oedema of the hypokinetic LV myocardium, showing high signal intensity with a diffuse or transmural distribution. The oedema is restricted to the parts of the ventricle, showing the wall motion abnormality and—similar to wall motion abnormalities—this is not restricted to a single coronary artery territory. These features aid distinguishing TTC from AMI, in which oedema is usually located transmurally but always coherent with a vascular distribution. In patients with acute myocarditis, short T_1 inversion recovery sequences similarly show a high signal intensity in the ventricular wall, but the signal is more heterogeneously distributed and is frequently restricted to the middle or subepicardial layers of the ventricular wall, and often seen in the inferolateral LV segments.[35] Thus, CMR maybe useful in the often difficult differential diagnosis in patients with suspected TTC. The pathophysiological mechanism(s) underlying the development of myocardial oedema in TTC remains unclear. Typically, LGE is absent in TTC both acutely and at follow-up, and this LGE absence is an important criterion to distinguish between AMI and TTC.[36,37] It remains, however, controversial, whether minor amounts of LGE may be present in some patients with TTC and which type of LGE may be observed in patients with TTC.[30,38] The frequency at which LGE may be observed in TTC patients largely depends on the threshold of signal intensity above normal used for defining areas of LGE. At the usual 5 SD cut-off above normal, LGE is usually absent in TTC patients during the acute phase, and where reported acutely it is usually absent at follow-up. Rarely small, restricted transmural apical LGE persists at follow-up.[39] A small study based on 15 patients with TTC who had LV biopsies suggested that LGE may be transient and related to patchy myocardial fibrosis.[40]

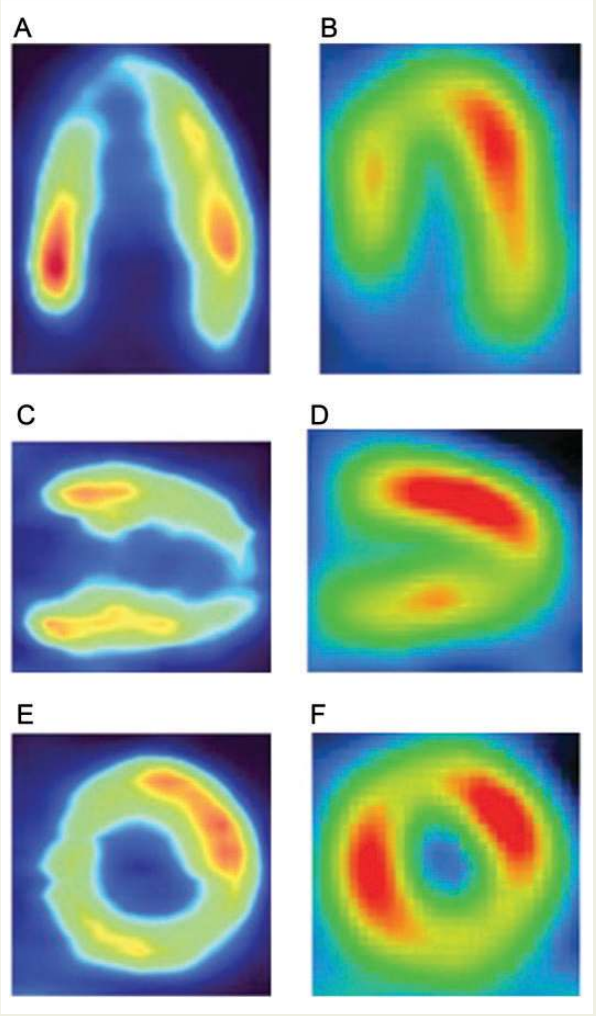

Figure 10 A pathophysiological study of TTC with 18F-FDG-PET. Comparison between PET (*A*, *C*, and *E*) and SPECT (*B*, *D*, and *F*) images: metabolic image revealed severely reduced 18F-FDG uptake in the apical and midventricular segments compared with perfusion abnormalities. (A and B) Horizontal long-axis; (C and D) vertical long-axis; (E and F) short-axis. Adapted from Yoshida *et al.*[40] with copyright permission.

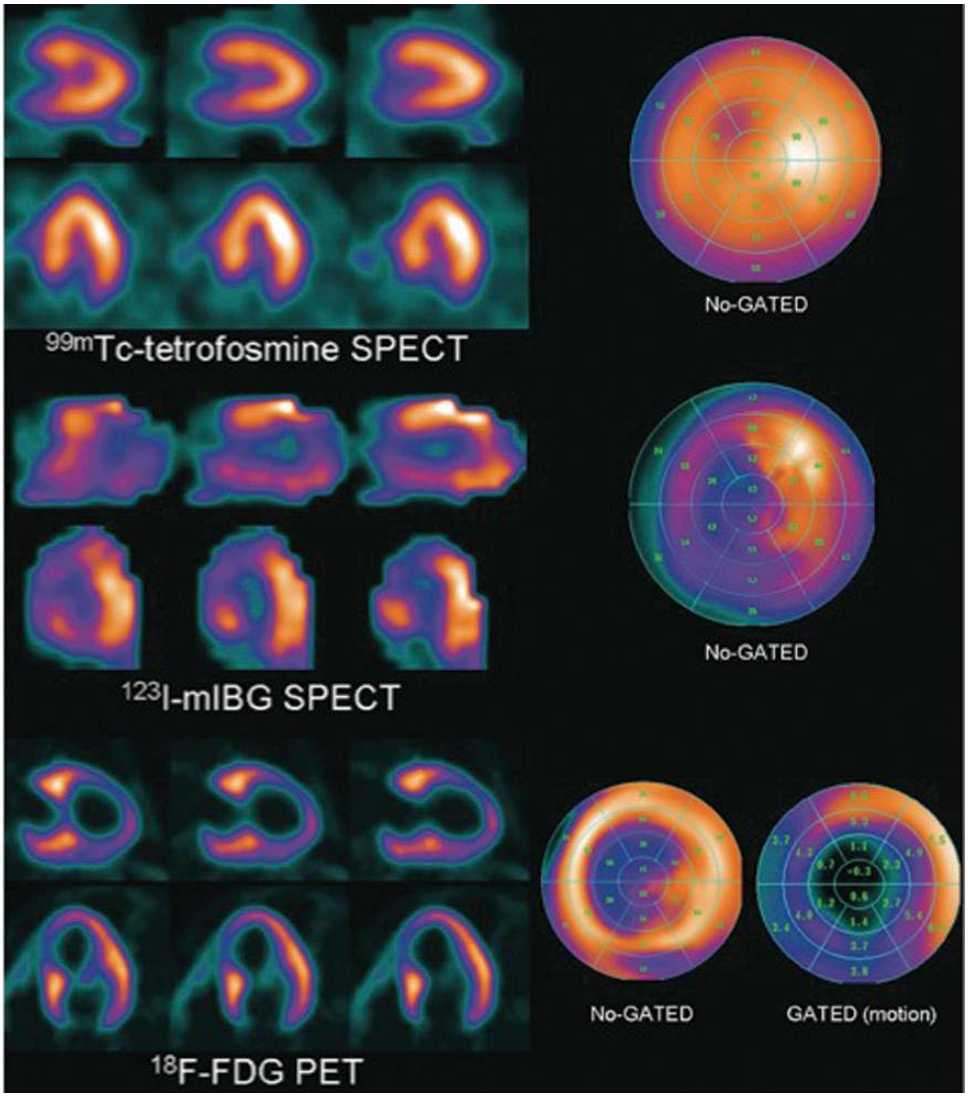

Figure 11 Vertical long-axis, horizontal long-axis, and polar map images of cardiac ^{99m}Tc-tetrofosmine SPECT, ^{123}I-mIBG SPECT, and 18F-FDG PET performed during the subacute phase in Patient 1. 18F-FDG and ^{123}I-mIBG uptake were severely reduced in the apical and midseptal segments of the left ventricle, whereas myocardial perfusion was normal. Myocardial 18F-FDG-PET gated acquisitions showed marked contractile dysfunction in the apical and midseptal regions, corresponding to the segments with ^{123}I-mIBG and 18F-FDG uptake abnormalities. [Adapted from Cimarelli *et al.* Nuclear medicine imaging of takotsubocardiompyopathy: typical form and midventricular ballooning syndrome. J Nucl Cardiol 2008;15:137–41 with copyright permission.]

Coronary computed tomography angiography

There are only a few case reports using coronary computed tomography angiography (CCTA) in the acute setting of TTC (*Figure 9*).[41,42] In patients with acute chest pain, this technique can rule out high-grade coronary stenoses[43] and also exclude pulmonary embolism and acute aortic disease.[44,45] Acquiring information throughout the cardiac cycle (spiral or helical acquisition mode) also shows the typical systolic dysfunction but at the price of a higher radiation exposure. However, delaying access to immediate invasive CA, where available, to perform CCTA is not currently recommended. In patients who are stable and at low risk according to the TIMI and GRACE risk scores, CCTA may be an alternative to CA for rule out high-grade coronary stenoses. LV function should then be assessed by transthoracic Doppler echocardiography (TDE) or MR imaging (*Figure 13*).

Nuclear imaging

Myocardial perfusion and sympathetic innervation can be investigated by single-photon emission tomography (SPECT) using ^{201}Thallium or ^{99m}Technetium-labelled radiopharmaceuticals and ^{123}I-metalodobenzylguanidine (mIBG). Myocardial glucose metabolism can also be

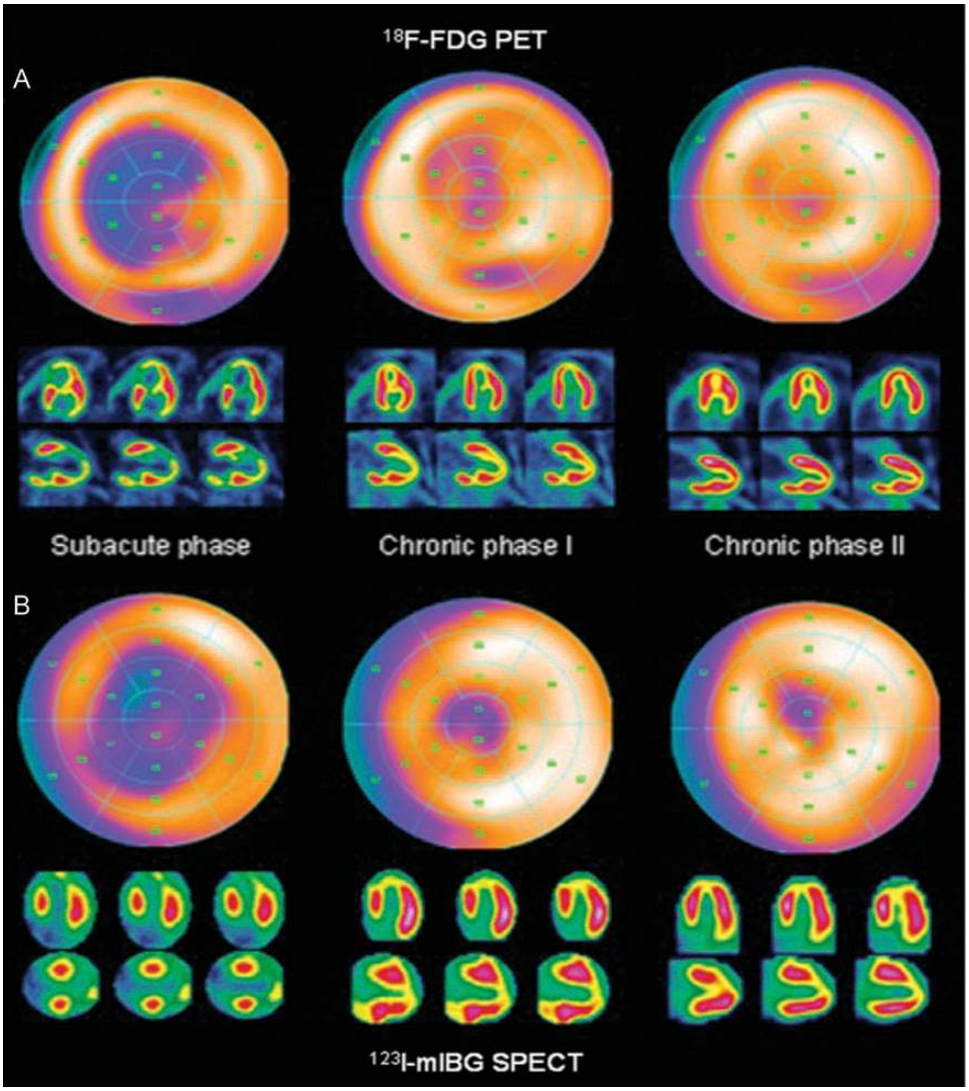

Figure 12 Left ventricle transaxial slices (short-axis, vertical long-axis, and horizontal long-axis) and 'bull's eye' presentation (17-segment models) of, respectively, cardiac 18F-FDG PET (*A*) and ^{123}I-mIBG SPECT (*B*) performed during subacute (3–21 days after the acute episode), chronic 1 (3 months later), and late chronic 2 (>6 months later) phases in, respectively, Patients 1 and 3 with TTC. Markedly reduced 18F-FDG and ^{123}I-mIBG uptake was observed in the apical region of left ventricle during the subacute phase. Follow-up examinations demonstrated a significant improvement of tracer uptake in the left ventricle apex, but myocardial glucose metabolism and sympathetic innervation were not completely normalized 6 months after the onset of symptomatology. Adapted from Cimarelli *et al.*[41] with copyright permission.

investigated by positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG). Recently, isotopic studies were conducted at different phases during the TTC time course.[46,47] In the acute and subacute phases, similar defects of mIBG and FDG uptake, despite only slighty reduced perfusion, have been demonstrated in the hypocontractile LV segments (Figures 10 and 11). Subsequently, rapid normalization of myocardial perfusion, and delayed recovery of both LV glucose metabolism and sympathetic innervation, are observed (*Figure 12*). This delayed recovery of sympathetic nerve ending function, in the context of normalized LV contractile function, may allow a potential role for mIBG imaging in suspected cases with a delayed presentation but still within a few months of the suspected triggering episode. The pathophysiological basis of TTC remains to be confirmed, with a stress-induced catecholamine overproduction and myocardial response the most likely causative mechanism (see above).[48] Coronary microvascular dysfunction superimposed upon the myocardial contractile abnormalities may also explain the transient perfusion abnormalities where present. Excessive catecholamine exposure induces toxic effects in cardiomyocytes, including abnormalities glucose metabolism disorder in preclinical models and a decrease of catecholamine pre-synaptic reuptake.[49] The parallel temporal evolution of ^{123}I-mIBG and 18F-FDG abnormalities have provided new insights into the functional myocardial changes and timecourse in TTC, but the critical question remains

Table 1 Relative strengths and weaknesses of non-invasive multi-modality imaging in TTC

	Echocardiography	CCTA	MRI	Nuclear imaging
Availability	++++	+++	++	++
Portability	++++	−	−	−
Cost	Low	Medium	High	Medium
Speed of acquisition	++++	++++	+	+
Radiation risk	−	+++[c]	−	++++
Suitability for sick or claustrophobic patients	++++	++++	+/−	+/−
Contrast agents	+/−	++++	+[a]	−
Temporal resolution	++++	++	+++	−[b]
Spatial resolution	++	++++	+++	+
Cardiac structure	+++	++	++++	−
Ventricular function quantification	+++	−	++++	+++
Regional function assessment	++++	−	++++	+
Tissue characterization	+	+	++++	+
Myocardial viability	+	+	++++	++++
First-pass perfusion	++	−	++++	++++
Coronary artery imaging	+	+++	++	−
Assessment of pressure gradients	++++	−	+	−
Clinical Application	-Widespread use in the emergency room -Assessment of reversible wall motion abnormalities -Detection of cardiac complications	-Ruling out underlying coronary disease noninvasively in the emergency room -'Triple out' strategy of major acute thoracic disease	-Differential diagnosis between TC and other cardiac disease (myocardial infarction or myocarditis) -Higher sensitivity to detect thrombi and RV involvement	-Evaluation of myocardial sympathetic activity (^{123}I-mIBG SPECT) and metabolism (18F-FDG PET)

[a]Renal insufficiency (glomerular filtration rate <30 mL/min) contraindicates the use of gadolinium contrast agents.
[b]Temporal resolution for nuclear techniques is variable and depends on the radiotracer and counts.
[c]Radiation risk is significantly higher when the cine ventricular function and first-pass perfusion are performed.

between cause and effect of these observed changes regarding their role in pathophysiology.

Diagnostic algorithm: the key role of imaging

Several peculiar clinical, laboratory, and echocardiographic findings may raise the suspicion of TTC in the emergency setting. In addition to the characteristic phenotype (LV apical hypokinesia), the detection of mid-distal LAD flow by TTE (absent in ST-elevation ACS with acute LAD occlusion) may be helpful particularly in patients presenting with anterolateral ECG ST-segment elevation and/or T-wave inversion.[26] Other features as RV involvement and LV obstruction, albeit not specific may be suggestive of TTC.[25,31] After CA, in addition to TTE and biochemistry (troponin peak), several imaging tools, although not required for each patient, may be useful to confirm the diagnosis of TTC in difficult cases. CMR helps in excluding the differential diagnoses of myocarditis or aborted MI, and defining the ventricular abnormalities in patients with poor echogenicity, while nuclear cardiac imaging for the detection of viable myocardium and the functional abnormalities. A challenging situation is the presence of an intermediate stenosis of the proximal LAD in a patient with an apical hypokinesia. The following findings strongly argue for the definite diagnosis of TTC with bystander coronary disease: left ventricular dysfunction extending beyond the LAD territory, no evidence of plaque rupture at angiography confirmed eventually by coronary imaging (IVUS, optical coherence tomography), no myocardial scar demonstrated by CMR, abnormal sympathetic nerve ending uptake on mIBG imaging, a discrepancy between the low level of troponin peak and the extent of WMA, spontaneous recovery of WMA within days or weeks (without the need for LAD angioplasty), as well as no functionally significant upstream stenosis proven by a non-invasive imaging tool (TTE, CMR, or nuclear imaging). It has been demonstrated using several tools including non-invasive

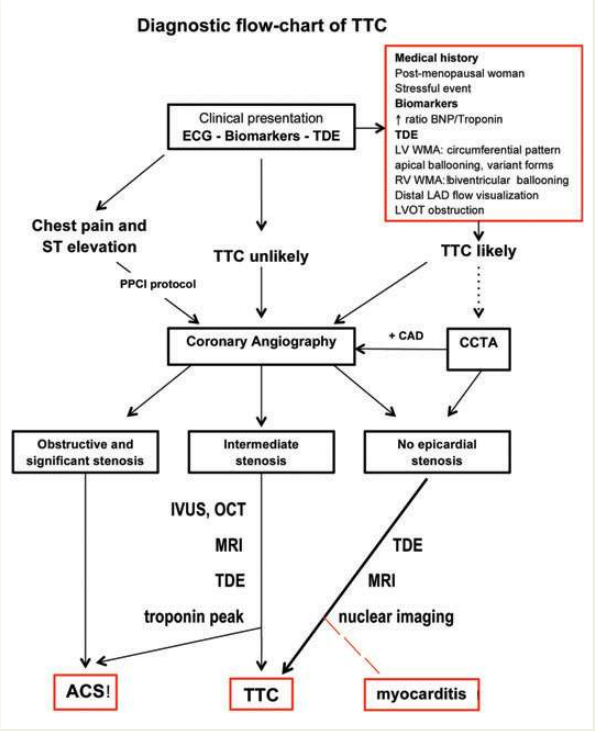

Figure 13 CA is the cornerstone for the differential diagnosis between TTC and acute myocardial infarction and is performed in emergency in most cases. Because of its high availability and effectiveness, TDE is the first-line imaging technique upstream and downstream to angiography. MRI is the second-line imaging modality downstream to angiography. In selected cases with a high suspicion of TTC, CCTA could substitute CA because of its high negative predictive value for CAD. Finally, nuclear imaging is reserved to patients with a high suspicion of TTC who had already recovered, or in second intention to assess the functional significance of coronary stenosis, or for research purpose. Diagnostic flow chart of TTC. ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LV, left ventricle; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PPCI, primary percutaneous coronary intervention; RV, right ventricle; TDE, transthoracic Doppler echocardiography; TTC, Takotsubo cardiomyopathy; WMA, wall motion abnormalities.

coronary flow reserve (CFR) that the coronary microcirculation may be transiently impaired during the acute phase in some TTC cases.[50] However, the majority of patients do not demonstrate severe reduction of CFR in the acute phase. Finally, the potential role of CT in the emergency room as 'triple out strategy' should be highlighted in the case of high suspicion of TTC without access to immediate CA (for more details see Table 1 and *Figure 13*).

Prognosis

TTC patients surviving to discharge generally have a good prognosis, with a rapid improvement of LV systolic function in a period of days to few weeks.[1,12] However, a variety of complications may occur in the acute course of the disease (up to 50% of patients have one or more complications), including pulmonary oedema, intraventricular pressure gradients, acute MR, right ventricular involvement with pleural effusion, intraventricular thrombi resulting in stroke or arterial embolism, atrial fibrillation, malignant ventricular arrhythmias, and cardiogenic shock.[3] Rarely, perforation of the LV or the interventricular septum has been described. In-hospital mortality ranges between 1 and 2% of patients, whereas long-term mortality ranges from 0 to 17% with a lower rate of cardiovascular death (range 0–7%).[1] The TTC recurrence rate has been reported from 0 to 11.4%.[1] As recovery of the LV RWMA is required to confirm the diagnosis, follow-up with clinical assessment and repeat cardiac imaging (TTE and/or CMR) should be performed at discharge, 3 and/or 6 months depending on availability and clinical status.

Conclusions

TTC is a fascinating clinical condition reflecting an interplay of complex pathophysiological mechanisms. Invasive CA remains the 'gold standard' for the definitive diagnosis of TTC, with echocardiography the first-line, non-invasive imaging modality for verifying a suspected diagnosis of TTC, detecting severe potential complications, and tracking recovery during follow-up. CMR may be considered as a second-line technique in patients with suboptimal ultrasound images. Finally, mIBG nuclear imaging and CMR may be helpful to discriminate TTC from other cardiac diseases and to provide insights into underlying pathophysiology.

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