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Students scientific community

Broken heart syndrome

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Broken heart syndrome is a recently identified cardiac disease, which is far from being completely known.

In medical literature, you can find many synonyms for this condition: Takotsubo syndrome (cardiomyopathy), stress cardiomyopathy, ampulla-like cardiomyopathy, apex swelling syndrome, apex ballooning syndrome, transient left ventricular dysfunction syndrome, happy heart syndrome etc. Over the past years, more than 70 names have been introduced how to call this cardiac condition!

The term cardiomyopathy is not currently used. **The European Society of Cardiology recommends using the term Takotsubo Syndrome (TTS).**

Takotsubo syndrome is an acute and usually reversible heart failure syndrome characterized by left ventricle (LV) systolic dysfunction (I 51.81).

Patients with TTS may present with typical acute coronary syndrome (ACS) symptoms including chest discomfort or dyspnea, ST segment deviations on electrocardiogram, and cardiac biomarker abnormalities.

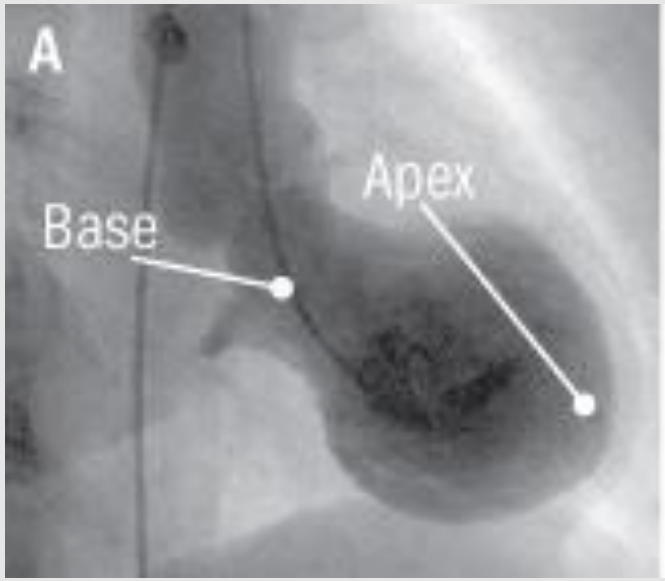
Clinical Information from ICD-10 CM (2021):
A rare disorder characterized by transient left ventricular wall systolic dysfunction, resulting in apical ballooning appearance, chest pain, and ST segment elevation.

The first cases of TTS were described in Japan (Hiroshima City Hospital) in 1983, in 1990 were published an article by doctor Sato H. and others. Subsequently, other cases were diagnosed in Japanese patients, leading to the hypothesis that this cardiac disease was typical of Asian populations. More recently, however, a French research group published a case series of TTS in a Caucasian population.

TTS gained international attention in the early 2000s, when the first diagnostic criteria were published.

*Sato H, Tateishi H, Uchida T, et al. Tako-Tsubo–like left ventricular dysfunction due to multivessel coronary spasm. Kodama K, Haze K, Hori M, editors. Clinical aspect of myocardial injury : from ischemia to heart failure (in Japanese). Tokyo: Kagakuhyoronsha Publishing Co; 1990. p. 56-64

From the Japanese word *takotsubo* 蛸壺 – "octopus trap", because the left ventricle of the heart takes on a shape resembling it. Catching octopuses with such jars is an old Japanese craft.



An estimated 4% of patients who are admitted with signs and symptoms of an acute coronary syndrome are diagnosed as TTS. The true incidence of TTS is likely to be higher due to underreporting and misdiagnosis.

TTS shows a strong predilection for females (9:1 female-to-male ratio), and more than 80% of patients involve females over the age of 50 years. The mean age of women at TTS diagnosis is around 67 years and 63 years for men.

TTS now represents a global disorder affecting both sexes, all age groups, various ethnic groups and races.

After the definition of TTS, the first cohorts enrolling around hundred patients. Subsequently, TTS registries were instituted in several countries. In Spain, Germany, France, and Italy created national registries. In Japan, several cohorts and registries were created suggesting the need to collaborate in the creation of an international registry, such as the **International Takotsubo (InterTAK) Registry**, which was designed as an international, multicenter, prospective and retrospective, observational study of patients with TTS.

Currently, more than 35 international cardiovascular centers in 15 countries contribute to this single registry, including centers in Argentina, Australia, Austria, Finland, France, Germany, Italy, New Zealand, Poland, Portugal, Switzerland, the United Kingdom, the United States and others. Data collected by this registry have enabled new diagnostic criteria and a diagnostic algorithm to be drawn up.

https://www.takotsubo-registry.com/

pubmed.ncbi.nlm.nih.gov/?term=takotsubo+syndrome

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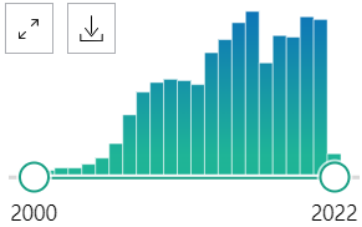
5,741 results Page 1 of 575

RESULTS BY YEAR



TEXT AVAILABILITY

- Abstract
- Free full text
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ARTICLE ATTRIBUTE

- Associated data

1 **Takotsubo syndrome**: aetiology, presentation and treatment.
Kato K, Lyon AR, Ghadri JR, Templin C.
Cite
Heart. 2017 Sep;103(18):1461-1469. doi: 10.1136/heartjnl-2016-309783.
Share
PMID: 28839096 Free article. Review. No abstract available.

2 Update of **takotsubo syndrome** in the era of COVID-19.
Okura H.
Cite
J Cardiol. 2021 Apr;77(4):361-369. doi: 10.1016/j.jjcc.2020.10.004. Epub 2020 Oct 14.
Share
PMID: 33148469 Free PMC article. Review.
Takotsubo cardiomyopathy or **takotsubo syndrome** (TTS) has become a well-known disease not only in Japan but also in the rest of the world. Early reports suggested that TTS is a self-limiting disease with better prognosis than acute coronary **syndrome** ...

3 Epidemiology, pathogenesis, and management of **takotsubo syndrome**.
Y-Hassan S, Tornvall P.

Classification

Primary Takotsubo syndrome

In primary Takotsubo syndrome, the acute cardiac symptoms are the primary reason for seeking care, usually from emergency medical services, acute cardiac services, or the primary care physician. Such patients may or may not have clearly identifiable stressful triggers (often emotional). Potential co-existing medical conditions may be the predisposing risk factors but are not the primary cause of the catecholamine rise. These cases can be considered primary Takotsubo syndrome, and their clinical management depends on the specific complications.

https://doi.org/10.1002/ejhf.424

Secondary Takotsubo syndrome

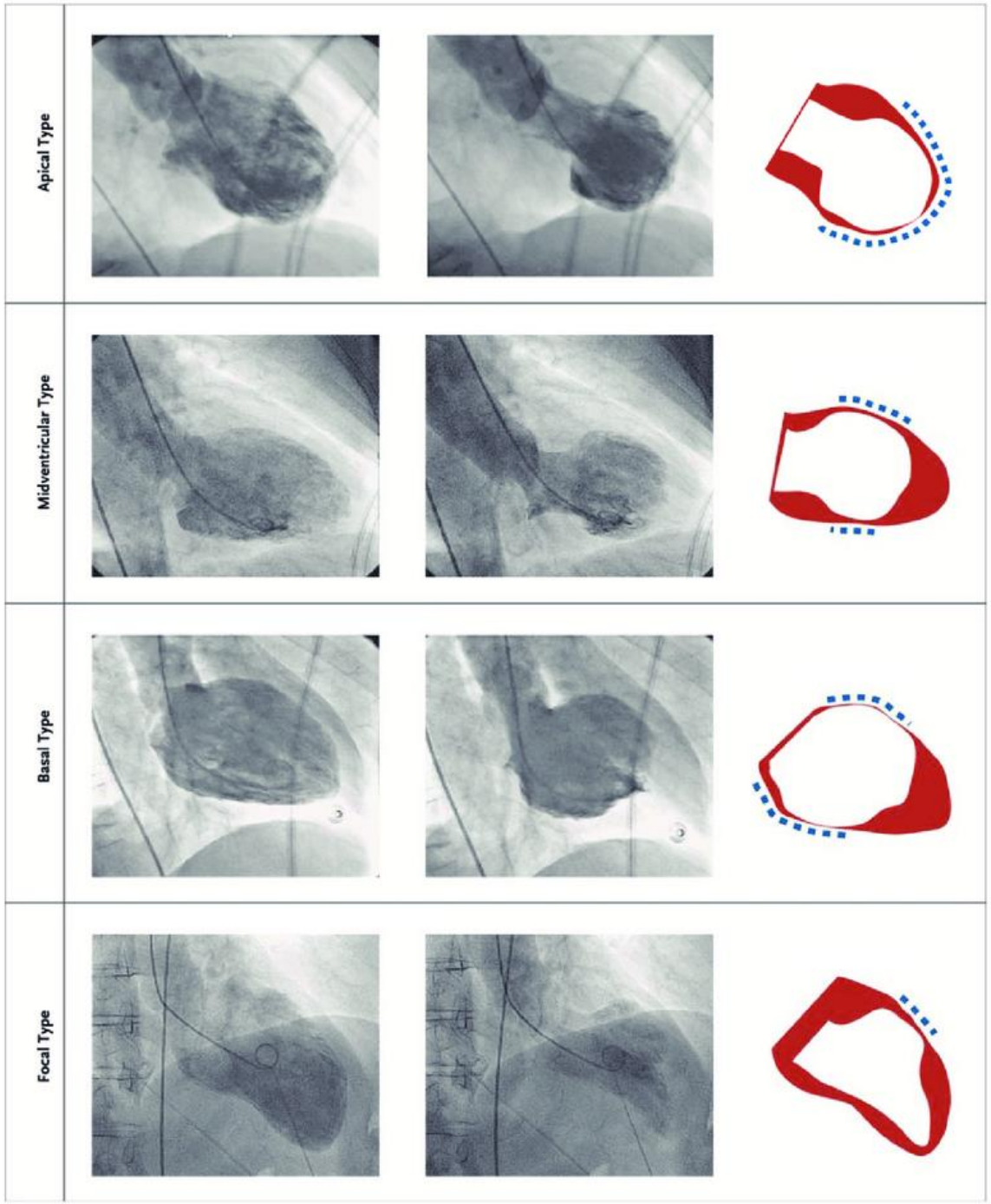
A substantial proportion of cases occur in patients already hospitalized for another medical, surgical, anaesthetic, obstetric, or psychiatric condition. In these patients, sudden activation of the sympathetic nervous system or a rise in catecholamines precipitates an acute Takotsubo syndrome as a complication of the primary condition or its treatment. We propose that such cases be diagnosed as secondary Takotsubo syndrome. Their management should focus not only on the Takotsubo syndrome and its cardiac complications but also on the condition that triggered the syndrome.

https://doi.org/10.1002/ejhf.424

Endocrine
e.g. Phaeochromocytoma, thyrotoxicosis (endogenous and iatrogenic), SIADH, Addisonian crisis, multiple endocrine neoplasia 2A syndrome, hyperglycaemic hyperosmolar state, hyponatraemia, severe hypothyroidism, Addison's disease, adrenocorticotropin hormone deficiency, autoimmune polyendocrine syndrome II
Neurological and neurosurgical
Acute neurosurgical emergencies (e.g. subarachnoid haemorrhage, acute head injury, acute spinal injury)
Acute neuromuscular crises, especially if involving acute ventilatory failure (e.g. acute myasthenia gravis, acute Guillain–Barré syndrome)
Epileptic seizures, limbic encephalitis, ischaemic stroke, posterior reversible encephalopathy syndrome
Respiratory
Acute exacerbation of asthma or COPD (especially with excessive use of inhaled beta2-agonists)
Acute pulmonary embolism
Acute pneumothorax
Obstetric, e.g. miscarriage, labour, emergency Caesarean section
Psychiatric
Acute anxiety attack/panic disorder
Attempted suicide
Drug-withdrawal syndromes
Electroconvulsive therapy
Gastrointestinal, e.g. acute cholecystitis, biliary colic, acute pancreatitis, severe vomiting, severe diarrhoea, pseudomembranous colitis, peritonitis
Infection
Severe sepsis
Babesiosis
Cardiological
Dobutamine stress echocardiography
Radiofrequency arrhythmia ablation
Pacemaker implantation
Electrical DC cardioversion for atrial fibrillation
Post-cardiac arrest including ventricular fibrillation
Haematological
Blood transfusions
Thrombotic thrombocytopenic purpura
Surgical
Many cases have been reported during induction of general anaesthesia or during non-cardiac surgery or interventional procedures under local or general anaesthesia (e.g. cholecystectomy, hysterectomy, rhinoplasty, Caesarean section, radiofrequency liver ablation, radiotherapy, colonoscopy, difficult urinary catheterization, carotid endarterectomy)
Medication and illicit drugs
Epinephrine injection
Nortriptyline overdose, venlafaxine overdose, albuterol, flecanide, metoprolol withdrawal, 5-fluorouracil, duloxetine
Cocaine abuse

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

https://www.researchgate.net/publication/283640459_Current_state_of_knowledge_on_Takotsubo_syndrome_A_Position_Statement_from_the_Taskforce_on_Takotsubo_Syndrome_of_the_Heart_Failure_Association_of_the_European_Society_of_Cardiology



Although several anatomical TTS variants have been described four major types can be differentiated based on the distribution of regional wall motion abnormalities. The most common TTS type and widely recognized form is the (i) apical ballooning type also known as the typical TTS form, which occurs in the majority of cases. Over the past years, atypical TTS types have been increasingly recognized. These include the (ii) midventricular, (iii)basal, and (iv) focal wall motion patterns. Recently, it has been demonstrated that patients suffering from atypical TTS have a different clinical phenotype

https://www.researchgate.net/publication/325499245_International_Expert_Consensus_Document_on_Takotsubo_Syndrome_Part_I_Clinical_Characteristics_Diagnostic_Criteria_and_Pathophysiology

Despite extensive research, the cause and pathogenesis of TTS remain incompletely understood. It is suggested that this syndrome may be associated with an increase in the level of stress hormones. Elena Gadri from the University Hospital of Zurich, studied the brain activity of 15 patients diagnosed with broken heart syndrome. The tomography data showed significant differences in the brain activity of these patients from that was observed in the control group, who were healthy. **There was a much smaller connection between the areas of the brain responsible for controlling emotions and the body's unconscious (automatic) responses (such as the heartbeat).**

Researchers cannot claim that the reduction in connections between different parts of the brain was a consequence of the development of the syndrome, or that the syndrome developed due to the reduction in connections.

Two molecules – called **microRNA-16 and microRNA-26a – that are linked to depression, anxiety and increased stress levels had previously been detected in the blood of Takotsubo patients**. Researchers assessed the impact of exposing cells from human hearts (taken from organs that were unsuitable for transplants) and rat hearts to the two molecules.

Afterwards, both sets of heart cells were more sensitive to adrenaline, they wrote in the journal Cardiovascular Research. In patients with Takotsubo, the bottom of the heart stops beating, and the top of the heart beats more. Was found the exact same thing happens when increased the exposure of the molecules.

Overall, the findings appeared to link long-term stress and the dramatic takotsubo response to a sudden shock.

Different emotional or psychological stressors have been identified to precede the onset of TTS. **The anatomic structures that mediate the stress response are found in both the central and autonomic nervous systems.** Acute stressors induce brain activation, increasing bioavailability of cortisol and catecholamine. Both circulating epinephrine and norepinephrine released from adrenal medullary chromaffin cells and norepinephrine released locally from sympathetic nerve terminals are significantly increased in the acute phase of TTS. **This catecholamine surge leads, through multiple mechanisms, that is, direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm**, and increased cardiac workload, to myocardial damage, which has a functional counterpart of transient apical left ventricular ballooning.

The relative preponderance among postmenopausal women suggests that estrogen deprivation may play a facilitating role, probably mediated by endothelial dysfunction.

Sympathetically mediated epicardial spasm has been proposed as a potential cause in TTS. It may be associated with endothelial dysfunction and other conditions of abnormal vasomotor function such as migraine or Raynaud's phenomenon. Similarly, endothelium-dependent dilation is reduced after emotional stress and prevented by endothelin antagonists. At presentation, patients with TTS have marked impairment in brachial artery flow-mediated dilation compared to those with infarction or healthy controls, which gradually improves over several weeks. In the early recovery period, predisposition to coronary vasospasm using intracoronary acetylcholine was demonstrated in some, but not all cases.

Furthermore, it has been suggested that the pattern of LV dysfunction in patients with TTS may require involvement of specific coronary side branches. Similarly, myocardial bridging in the LAD has been considered.

Myocardial hibernation is a persistent inhibition of contractility of the viable myocardium of the left ventricle, resulting from its hypoperfusion. The most important manifestation of hibernation is the preservation of the viability of the myocardial tissue. This phenomenon is based on three main mechanisms: 1) myocardial metabolic adaptation, manifested by enhanced glucose uptake; 2) activation of the cardiomyocyte death gene program; 3) programmed cell death, i.e. autophagy and apoptosis of cardiomyocytes.

Symptoms and Signs: Chest pain and dyspnea are the most common presenting symptoms. The chest pain often has the characteristics of angina. Cardiac arrest, syncope and arrhythmias have also been described. In patients who are already critically ill with other medical conditions, a clue to the diagnosis may be clinical worsening, or may be incidentally discovered after noting ECG changes or biomarker elevations. The symptoms and signs are similar to those seen in other acute cardiac conditions characterized by acute myocardial ischemia or heart failure, such as ACS and myocarditis, and hence do not help in the differential diagnoses.

There are no single universal criteria for diagnosing TTS. The most authoritative are the diagnostic criteria proposed by the American Mayo Clinic and the European Society of Cardiology.

American Mayo Clinic Criteria for diagnosing TTS (2014):

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of:
    a. Pheochromocytoma
    b. Myocarditis

https://www.researchgate.net/publication/264867924_Diagnosis_of_Takotsubo_Cardiomyopathy_-_Mayo_Clinic_Criteria

Heart Failure Association of the European Society of Cardiology for diagnosing TTS (2015):

1. Transient regional wall motion abnormalities of LV or RV myocardium which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography (ECG) abnormalities (ST-segment elevation, ST depression, LBBB, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Signicantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e. disparity between the troponin level and the amount of dysfunctional myocardium present).
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).

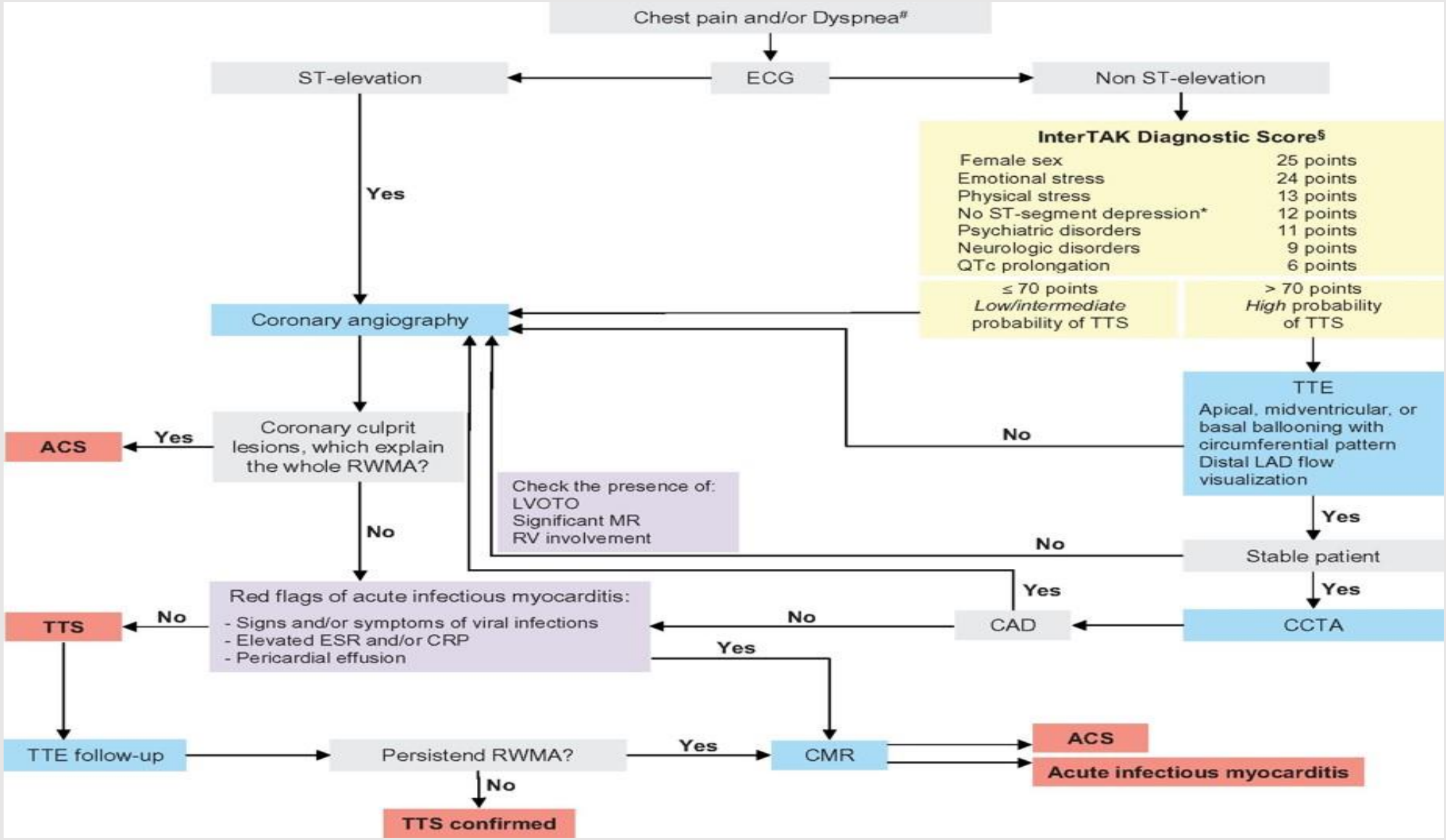
https://www.researchgate.net/publication/283640459_Current_state_of_knowledge_on_Takotsubo_syndrome_A_Position_Statement_from_the_Taskforce_on_Takotsubo_Syndrome_of_the_Heart_Failure_Association_of_the_European_Society_of_Cardiology

European Society of Cardiology for diagnosing TTS (2018)

Stress trigger followed by transient regional wall motion abnormalities of the LV or RV myocardium (these regional wall motion abnormalities usually extend beyond a single epicardial bloodstream).

1. Absence of atherosclerotic lesions of the coronary arteries.
2. During the acute phase, new and reversible ECG changes are present.
3. Elevated levels of natriuretic peptide. Elevated troponin levels.
4. On follow-up, the diagnosis indicates recovery of ventricular systolic function.

Diagnostic algorithm of Takotsubo syndrome



https://doi.org/10.1093/eurheartj/ehy077 *European Heart Journal*, Volume 39, Issue 22, 07 June 2018, Pages 2047–2062,

TAKOTSUBO INTERNATIONAL REGISTRY

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InterTAK Diagnostic Score

The InterTAK Diagnostic Score predicts the probability of the diagnosis of a Takotsubo cardiomyopathy event and differentiates patients from Acute coronary syndrome. The InterTAK Diagnostic Score is based on data from the International Takotsubo Registry and includes 7 clinical variabels that can be easily applied without using invasive imaging tools. The maximal score yields 100 points.

- ☐ **Female Sex** (25 points)
- ☐ **Emotional Stress** (24 points)
- ☐ **Physical Stress** (13 points)
- ☐ **No ST-Segment Depression** (12 points)
- ☐ **Acute, Former or Chronic Psychiatric Disorder** (11 points)
- ☐ **Acute, Former or Chronic Neurological Disorder** (9 points)
- ☐ **Prolonged QTc Time** (Female > 460ms; Male > 440ms) (6 points)

Total InterTAK Diagnostic Score: ☐

Probability of Takotsubo: ☐ %

https://www.takotsubo-registry.com/takotsubo-score.html

Depending on the disease prevalence this means that patients with 30 score points have a predicted probability of <1%, while patients with 50 points have a probability of 18%, and patients with a score value >70 points have a probability of ~90% of suffering from TTS

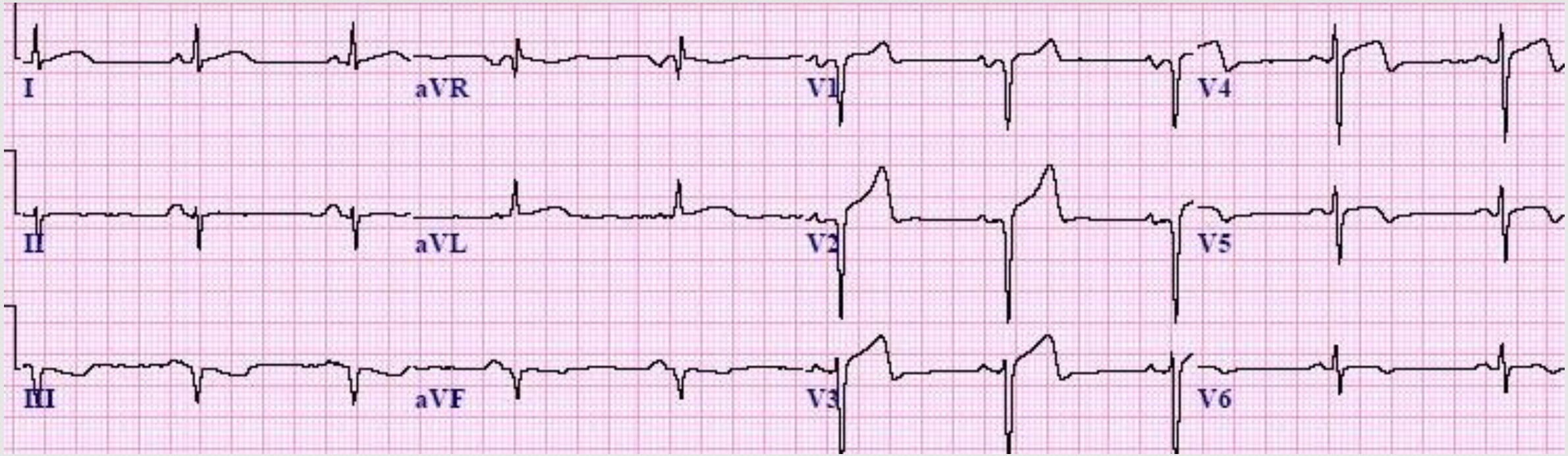
Electrocardiogram

The initial ECG is abnormal in most patients with TTS usually demonstrating **ischaemic ST-segment elevation, T-wave inversion**, or both. In the InterTAK Registry, ST-segment elevation was present in 44%, ST-segment depression in 8%, T-wave inversion in 41%, and left bundle branch block in 5%. As in acute coronary syndrome (ACS), the ECG in TTS demonstrates temporal **evolution typically with resolution of initial ST-segment elevation** (if present), followed by **progressive T-wave inversion and QT interval prolongation** over several days, with subsequent gradual resolution of T-wave inversion and QT interval prolongation over days to weeks. The initial and subsequent ECG findings are influenced by several variables, including the geographic pattern of left ventricular ballooning, presence or absence of right ventricular ballooning, time from symptom onset to presentation, presence of myocardial oedema, and recovery rate of myocardial cellular function.

ST-segment elevation

As with STEMI myocardial infarction, the location and extent of ST-segment elevation in TTS corresponds to the anatomic location of myocardial injury. **Usually involves precordial, lateral, and apical ECG leads, closely resembling that of anterior STEMI due to left anterior descending coronary occlusion.** **ST-segment elevation in TTS is centred on precordial leads V2–V5 and limb leads II and aVR**, whereas in anterior STEMI the ST-segment elevation centres on precordial leads V1–V4 and limb leads I and aVL. Most focus on ST-segment elevation in the precordial leads, particularly **lead V1**, as ST-segment elevation in this lead is less pronounced in TTS than in anterior STEMI. **ST-segment elevation limited to the inferior leads (II, III, aVF) is distinctly uncommon in TTS.**

Despite these differences, overlap exists.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V4
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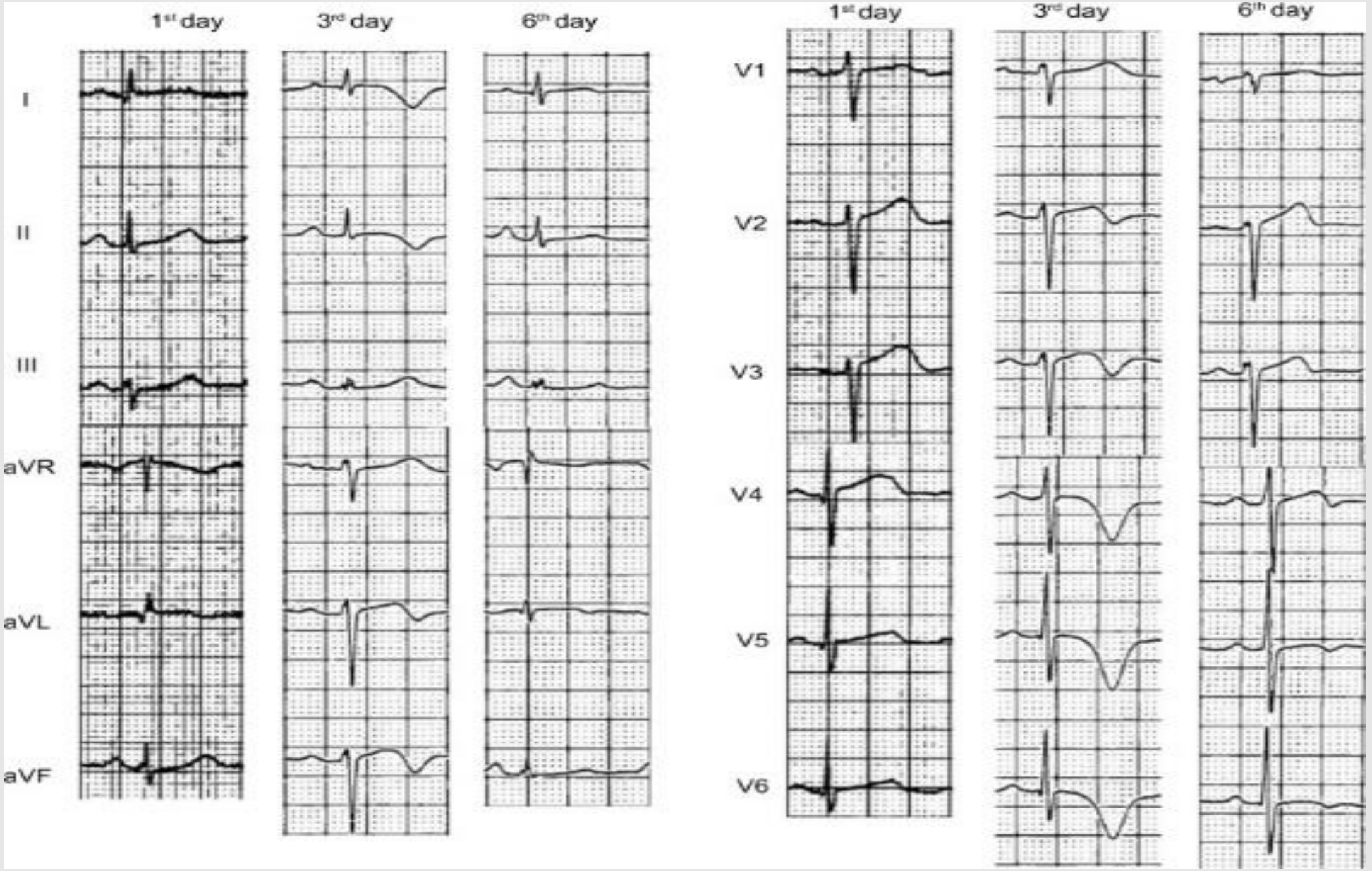
V5
III
aVF
V3
V6

T-wave inversion and QT interval prolongation

Progressive T-wave inversion and QT interval prolongation is a common ECG finding in TTS. In patients with delayed presentation, these changes can be the only detectable changes and therefore important for the diagnosis. In TTS, T-wave inversion is often more prominent and more broadly distributed than in ACS. Furthermore, T-wave inversion is associated with presence of myocardial oedema, and may persist for several months even after LV contractile recovery, thus leaving an electrophysiological footprint of the TTS event. **QT interval prolongation provides a substrate for torsades de pointes ventricular tachycardia and may be a prognostic marker for sudden cardiac death**·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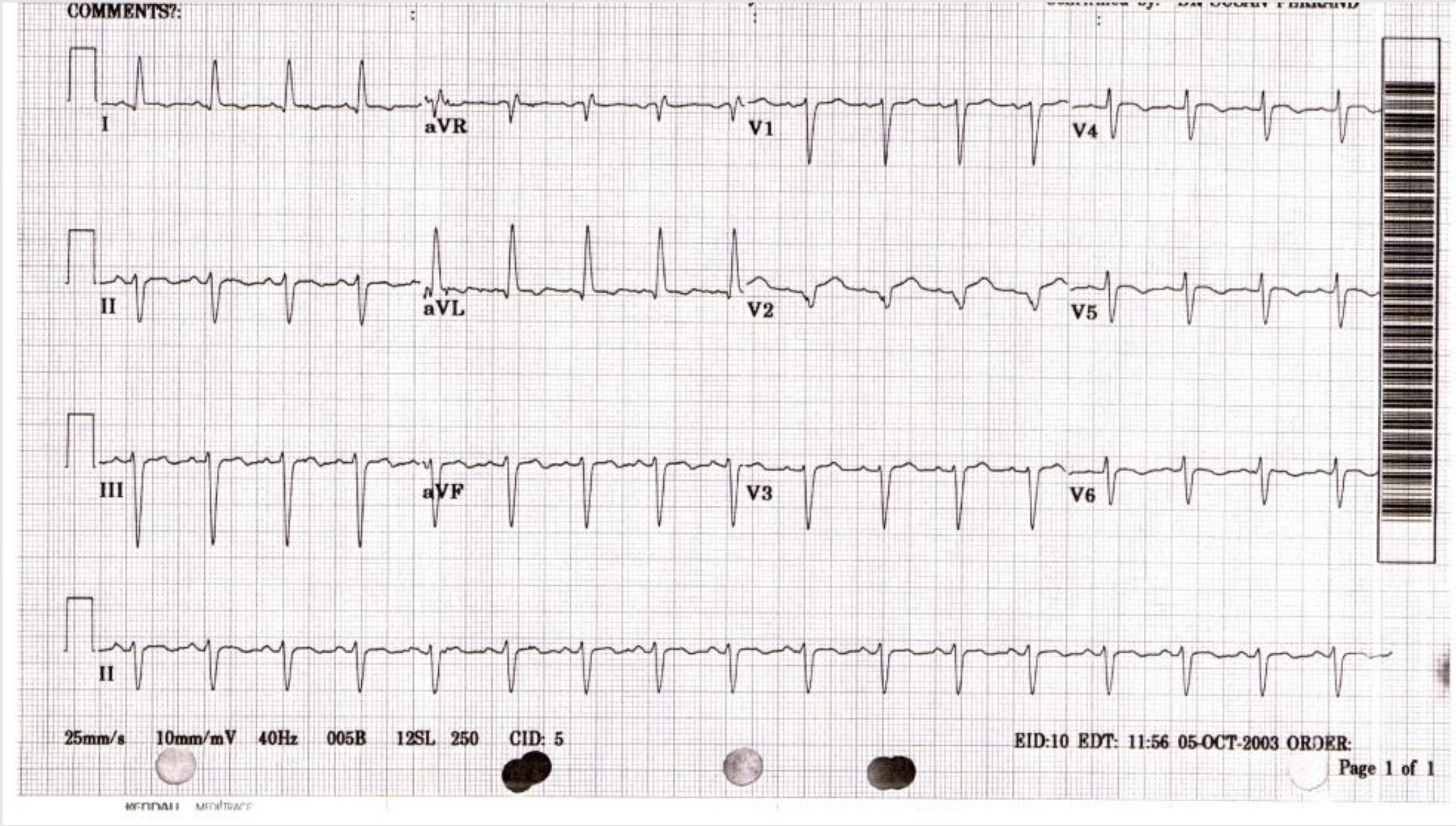
V2
V3
V4
V5
V6

Other electrocardiogram findings

Anterior Q-waves (or poor R-wave progression) without accompanying ST-segment elevation or T-wave inversion, a pattern sometimes referred to as ‘anterior infarction, age indeterminate’ occurs with some frequency in TTS. In TTS, as in anterior STEMI, Q-waves may occur in the acute phase, and regress rapidly with R-wave re-appearance, consistent with electrical stunning. Both J-wave and/or fragmented QRS complexes have been reported acutely, the former associated with death from cardiac causes and/or ventricular tachyarrhythmia. **Low QRS voltage likely representing myocardial oedema is prevalent in TTS**. **Left bundle branch block is present in around 5% of patients. ST-segment depression is uncommon**, occurring in fewer than 10% of TTS patients but in over 30% of ACS patients.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Page 1 of 1

Biomarkers

Markers of myocardial necrosis

Virtually all cases of TTS exhibit evidence of myocardial necrosis. On admission, **troponin values are usually equally elevated** compared to ACS, however, **peak values are substantially lower compared to the classical ACS**. High admission troponin levels are a predictor for a worse in-hospital outcome. Typically, there is only a **slight increase in creatine kinase**. The extent of LV regional wall motion impairment generally greatly exceeds that of associated myocardial necrosis biomarkers, likely reflecting a large mass of reversibly injured (stunned) myocardium.

B-type natriuretic peptide and N-terminal prohormone of brain natriuretic peptide

TTS is frequently associated with a substantial increase in the plasma levels of BNP and NT-proBNP reaching its peak approximately 24–48 h after symptom onset as a reflection of regional LV dysfunction. A gradual return of BNP/NT-proBNP towards normal levels occurs within the next few months after presentation.

The degree of NT-proBNP elevation appears directly related to: (i) the degree of sympathetic overactivation (as reflected by normetanephrine concentrations), (ii) peak C-reactive protein concentrations (suggesting that BNP release might be at least in part of inflammatory origin), and (iii) systolic LV dysfunction [as measured by wall motion score index (WMSI)].

Other potential biomarkers

Interleukin (IL)-6 levels appear less elevated while those of IL-7 are more elevated in TTS compared with AMI. However, differences between groups were small and unlikely to be of diagnostic utility.

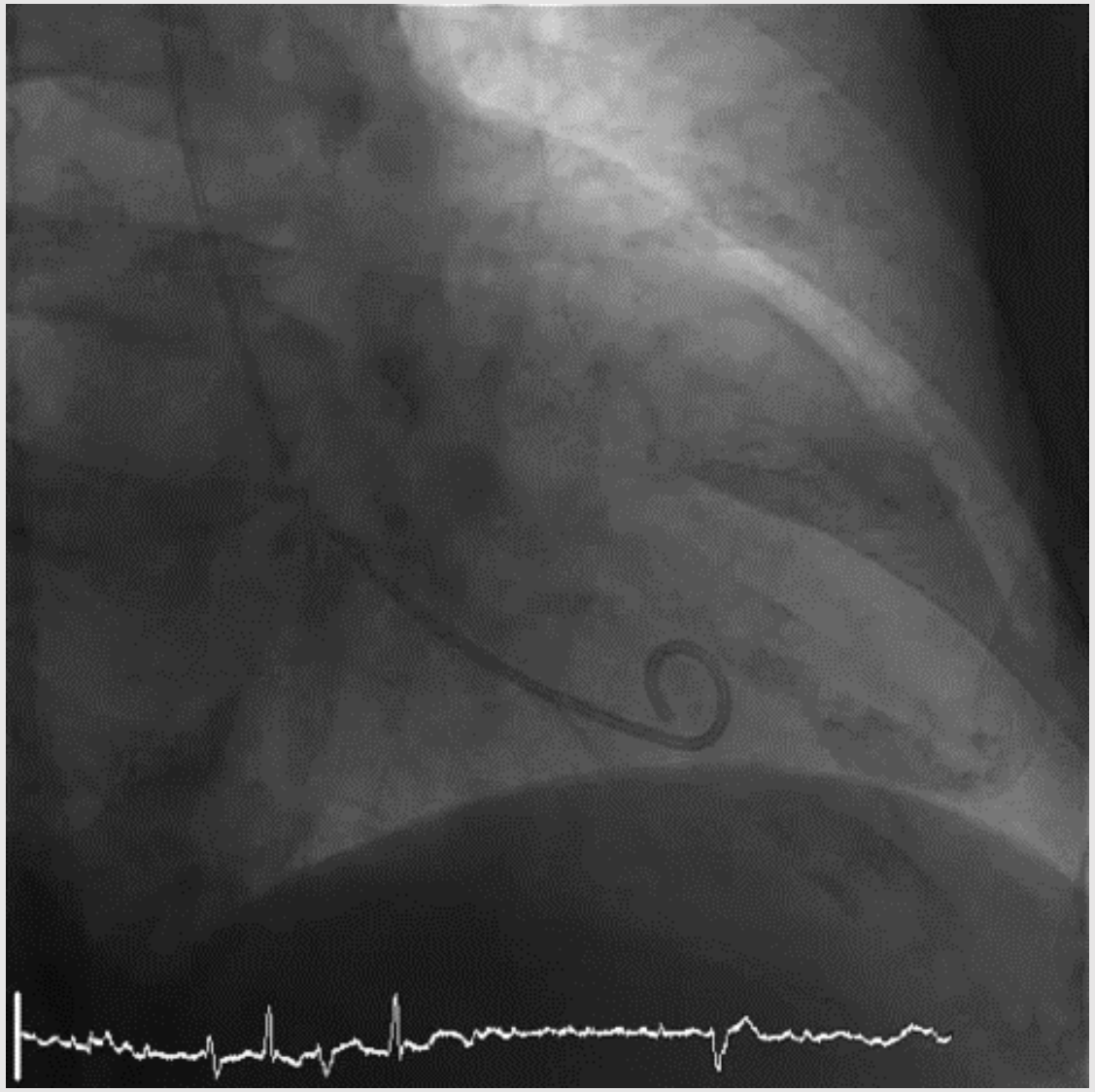
Two recently published studies focused on the potential utility of the release and circulation of certain microRNAs (miRNAs) in association with TTS onset. However, subsequent analyses of cases of TTS and evolving STEMI suggested that the elevation of miR-133a was more marked in STEMI than in TTS. Furthermore, demonstrated that a unique signature including miR-1, miR-16, miR-26a, and miR-133a represents a robust biomarker on admission and can be used to differentiate TTS from STEMI patients. Furthermore, the up-regulation of miR-16 and miR-26a is known to be associated with stress- and affective disorders.

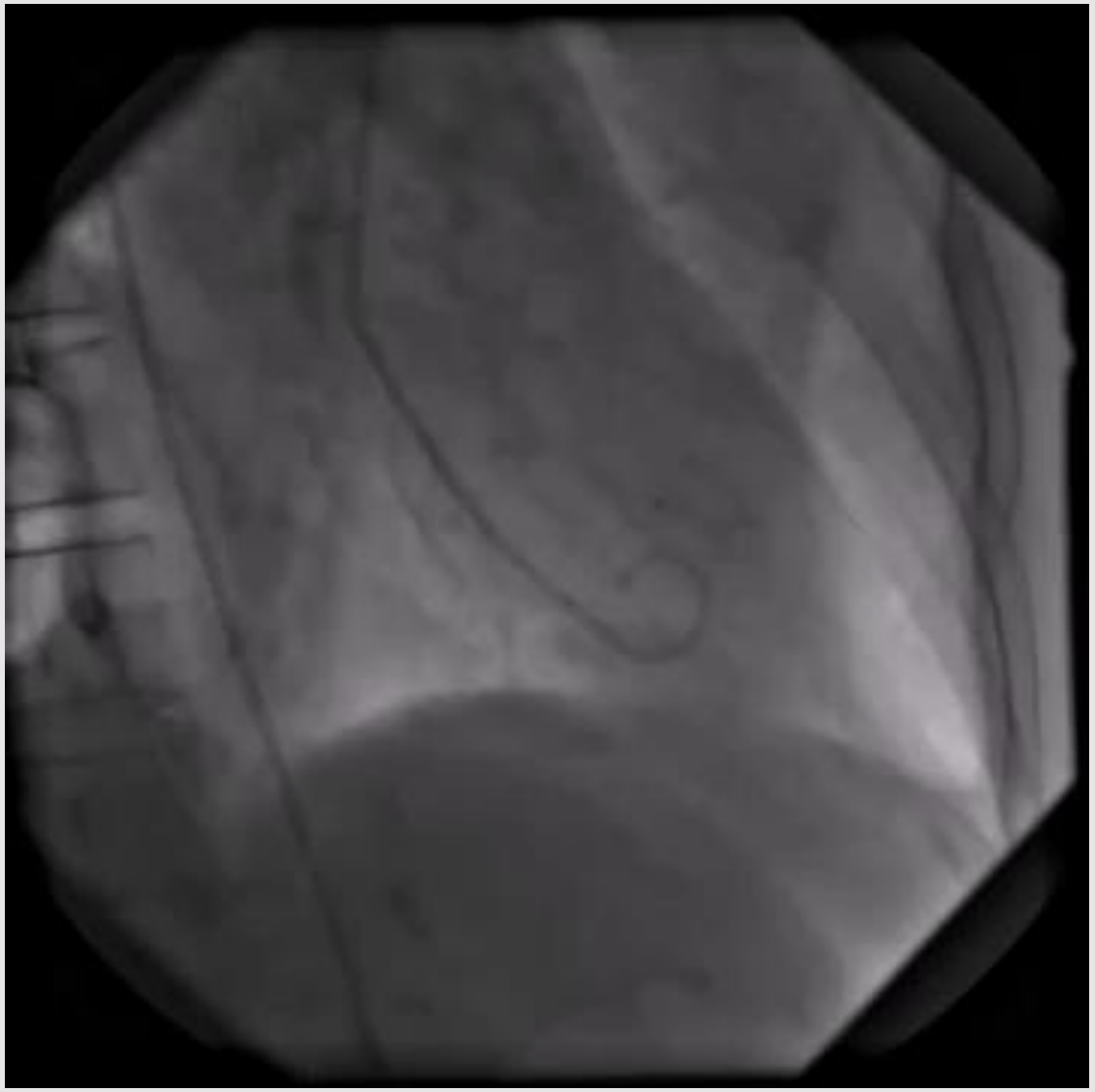
Especially in patients with biventricular involvement, it has been shown that **plasma concentrations of the stress-responsive cytokine growth differentiation factor-15 increased more rapidly after the onset of TTS**

Imaging

Coronary angiography and ventriculography

Although non-invasive imaging are useful in the workup of patients with TTS, **final differential diagnosis from ACS requires coronary angiogram**. In case of suspected TTS with coexisting and significant CAD, careful comparison of CAG and biplane ventriculography in similar views is mandatory to search for a perfusion-contraction mismatch. In this regard, it has been reported that approximately one-third of patients with the classical apical ballooning show a small zone with preserved contractility in the most distal portion of the apex, which is described as the 'apical nipple sign'. **Haemodynamic assessment for the presence of a pressure-gradient in the outflow tract as well as assessment of left ventricular end-diastolic pressure are recommended.**





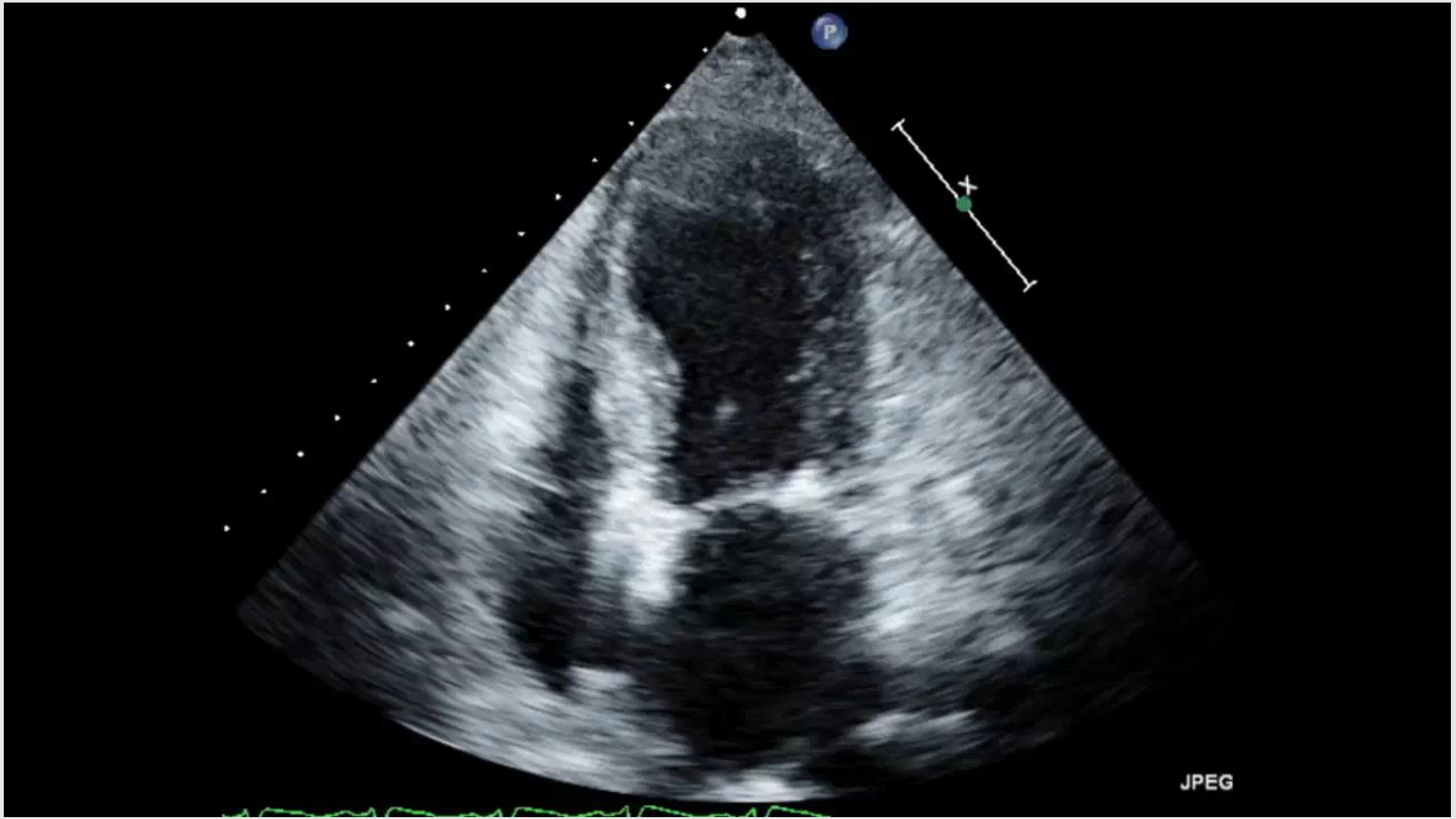
Echocardiography

Echocardiography is the most used imaging tool to assess changes in LV function such as symmetric regional wall motion abnormalities (RWMAs).Different variants can be identified with echocardiography which include:

1. **Apical ballooning, hypo-, a-, or dyskinesia of mid-apical myocardial segments is typical**, sometimes associated with hypokinetic mid-segments. The anterior or entire interventricular septum, inferior or midventricular anterolateral wall may also be involved. **LV twisting on 2D speckle-tracking imaging is reduced or reversed to clockwise apical rotation and the rate of untwisting (a sensitive index of regional diastolic dysfunction) is reduced in the acute phase.**

2. Midventricular TTS featured by hypo-, a-, or dyskinesia of midventricular segments, most often resembling a cuff.
3. Basal forms where only basal segments are involved. This phenotype is rare and appears commonly in patients with subarachnoid haemorrhage, epinephrine-induced TTS or phaeochromocytoma.
4. Focal TTS mostly involving an anterolateral segment has been described. Differentiating this unusual TTS type from ACS or myocarditis requires CMR.

Right ventricular involvement is characterized by RV dilatation with hypo- to akinesia of the free wall and apex in its isolated form.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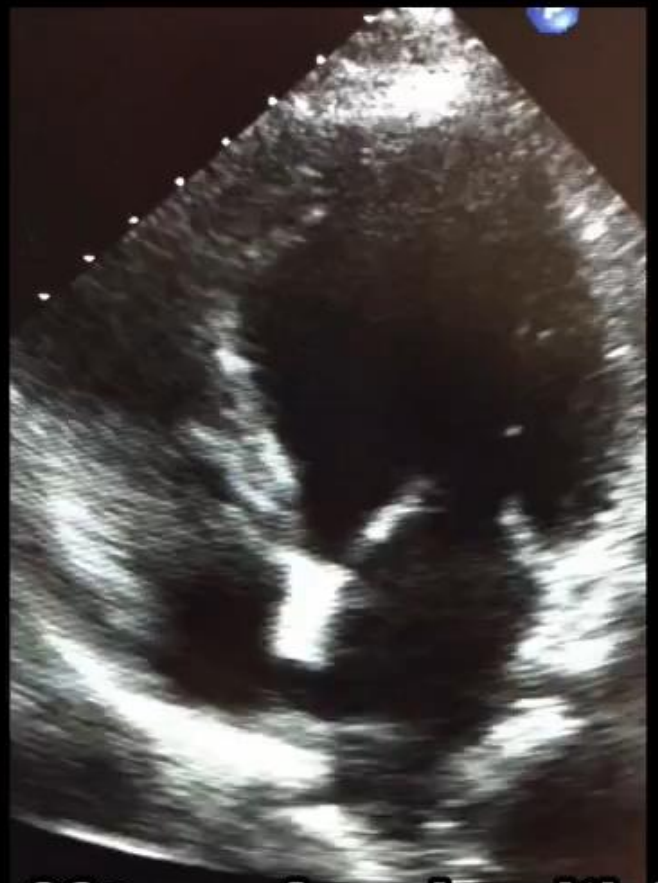
In TTS, LV wall motion abnormalities extend beyond the distribution of a single coronary artery territory, therefore systolic dysfunction appears ‘circular’ at speckle-tracking echocardiography. **Doppler estimation of coronary artery flow ameliorates the diagnostic accuracy of wall motion abnormalities,** whereas adenosine may lead to dramatic improvements of global and regional LV function.

Importantly, echocardiography allows detection of all acute TTS complications. In LV apical ballooning, basal segments are hyperkinetic and may cause dynamic LVOTO, mainly in patients with pre-existing septal bulge which further reduces stroke volume and is associated with mitral regurgitation (MR) due to systolic anterior motion of the mitral leaflet. Severe MR may also result from leaflet tethering by displacement or dysfunction of papillary muscles. Mitral regurgitation is estimated to be present in 14–25% of TTS patients.

Typically, LV contractility recovers completely in 4 - 8 weeks. Some segments of the LV recover earlier than others, displaying increased apical rotation, LV twisting and untwisting and recovered global longitudinal strain. Resolution of LVOTO and MR occurs in parallel with myocardial functional recovery. During TTS recurrence, the LV ballooning pattern may resemble the initial event or alternatively, manifest as other variants.



90+ y.o. female with Takotsubo Cardiomyopathy

BEFORE: Ballooning of Apex with low EF

6 MONTHS AFTER: Normal LV with Normal EF

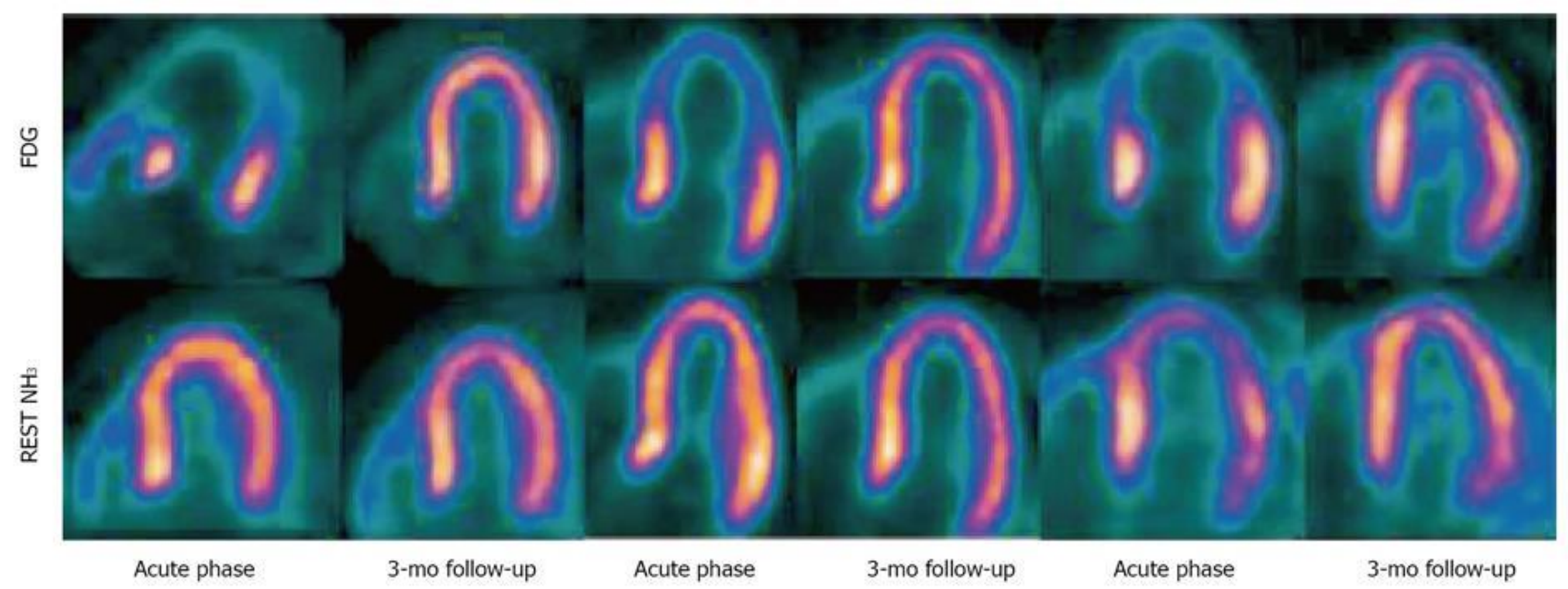
Other imaging methods

- Cardiac computed tomography angiography
- Cardiac magnetic resonance imaging
- Cardiac nuclear imaging:

Perfusion imaging

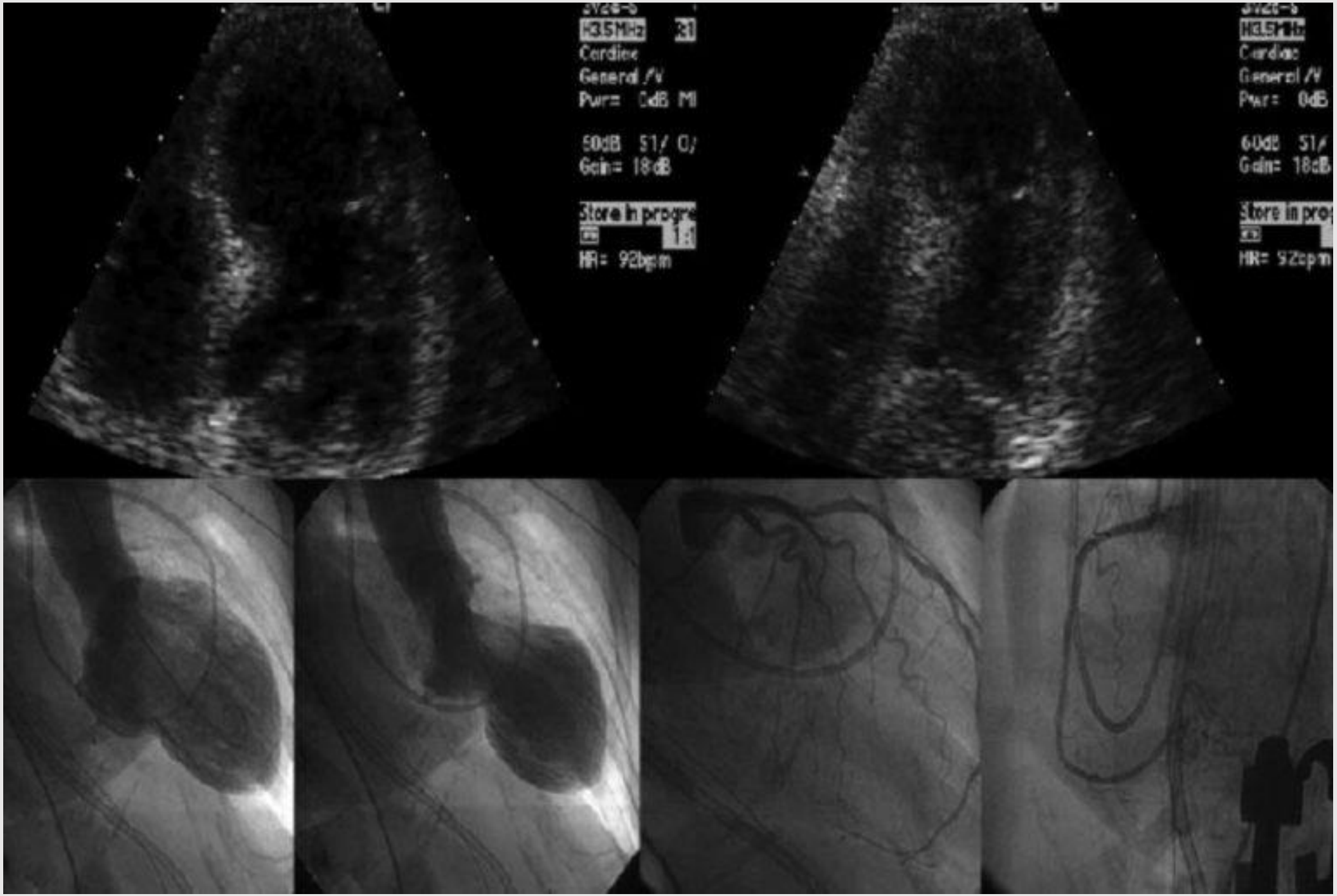
Metabolic imaging

Sympathetic nervous imaging

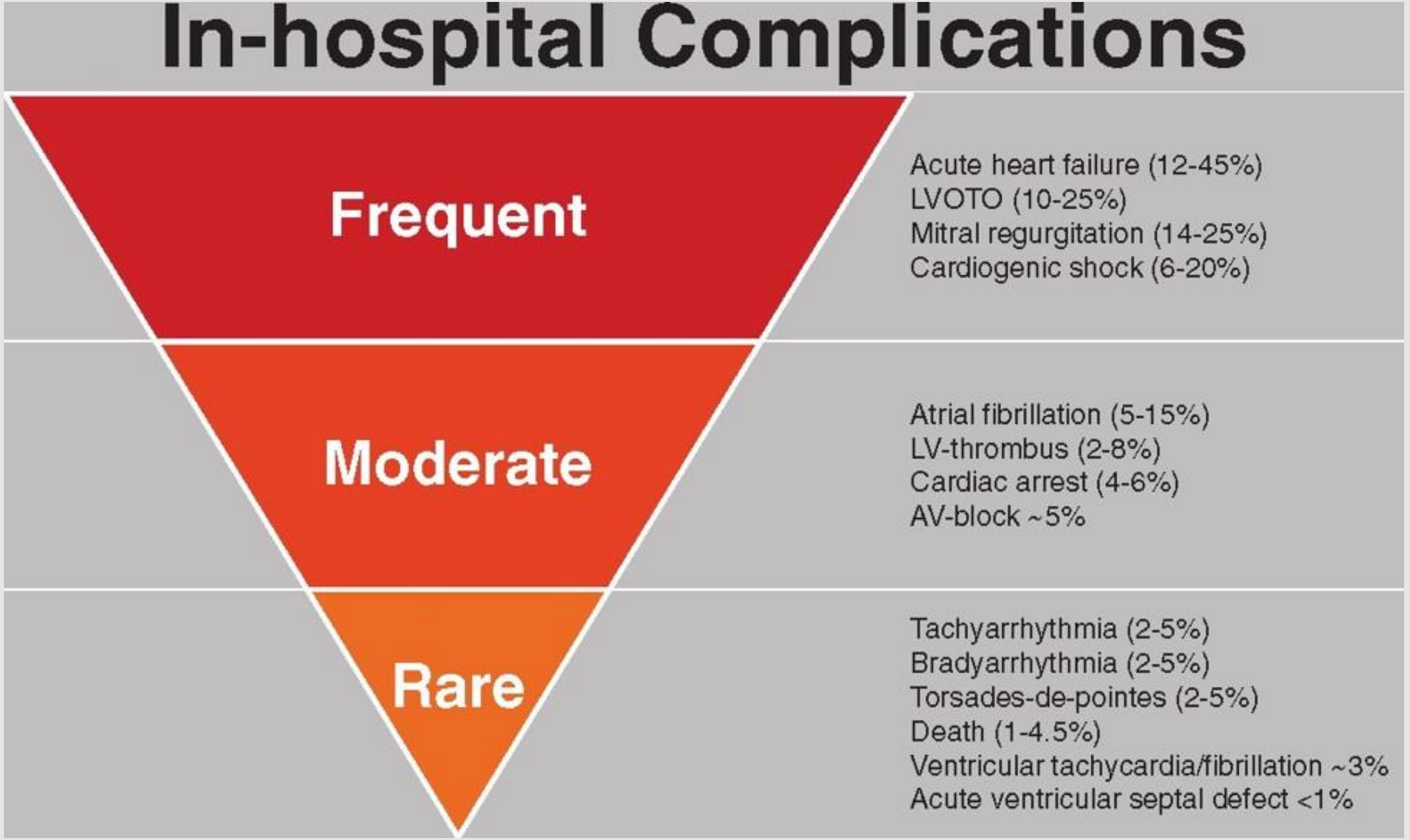


Images representing three different consecutive female patients with diagnosis of Takotsubo cardiomyopathy in which in the acute phase a clear inverse flow/metabolism mismatch emerged (reduction of fluorodeoxyglucose uptake and preserved blood flow obtained with ammonia). The mismatch was reversible and disappeared at 3-mo follow-up. FDG: Fluorodeoxyglucose;

Testa M, Feola M. Usefulness of myocardial positron emission tomography/nuclear imaging in Takotsubo cardiomyopathy. *World J Radiol* 2014; 6(7): 502-506 [PMID: 25071891 DOI: 10.4329/wjr.v6.i7.502]


H3.5MHz
Cardiac
General /V
Pwr= 0dB MI
50dB
Gain= 18dB
Store in progra
HR= 92bpm

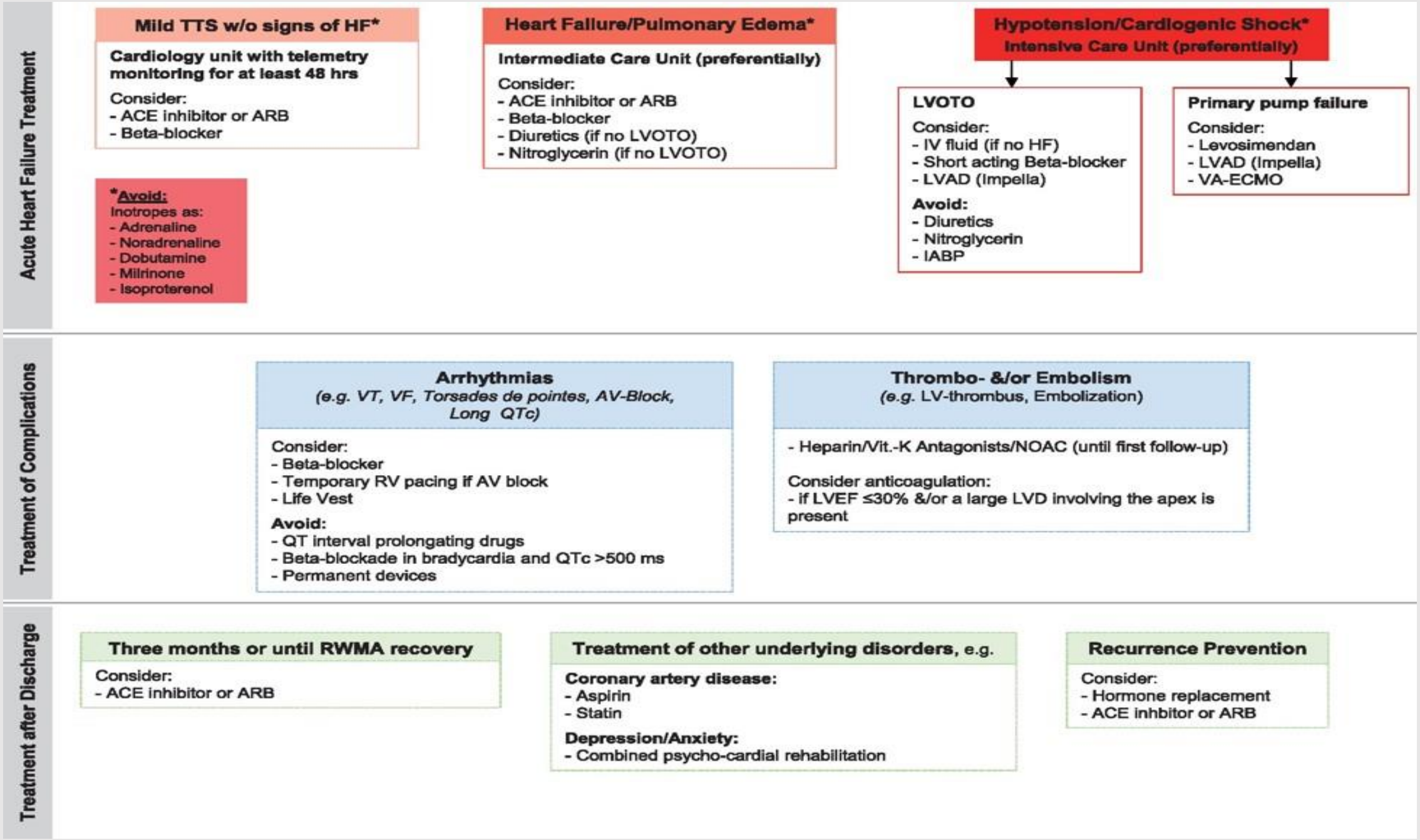
Category	Takotsubo syndrome	Acute myocarditis
Gender and age	90% female. Majority >50 years and post-menopausal.	No sex prevalence. More frequent in the young.
Preceding events	Stressor trigger identifiable in ~70% of cases.	Symptoms and signs of infection often present (fever, chills, headache, muscle aches, general malaise, cough, nausea, vomiting, diarrhoea).
Cardiac symptoms	Chest pain, dyspnoea, palpitations.	Chest pain, dyspnoea, peripheral oedema, fatigue, and palpitations.
Clinical signs	Pericardial rub rare.	Pericardial rub may be present.
ECG at admission	ST changes such as ST-segment elevation or non ST-segment elevation. Deep T wave inversion. QT prolongation. Rarely normal.	ST-segment elevation or depression, negative T-wave, bundle branch block, atrioventricular block, low voltage, and/or ventricular arrhythmias. Normal in several cases.
Cardiac enzymes	Low/moderate troponin rise. Discrepancy between the large amount of dysfunctional myocardium and peak troponin level.	Frequently significant troponin rise, proportional to the hypokinetic area. Normal in several cases.
Other biomarkers	C-reactive protein (CRP) mildly elevated unless infective trigger. BNP	Erythrocyte sedimentation rate and CRP elevated. BNP basically elevated.



Eur Heart J, Volume 39, Issue 22, 07 June 2018, Pages 2047–2062, https://doi.org/10.1093/eurheartj/ehy077

Therapeutic management

Guidelines regarding TTS management are lacking as no prospective randomized clinical trials have been performed in this patient population. Therapeutic strategies are therefore based on clinical experience and expert consensus (evidence level C).



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Pre-hospital treatment

As TTS is clinically difficult to distinguish from ACS, upon first presentation **patients should be transferred to a cardiology unit with imaging capabilities and a cardiac catheterization laboratory and receive guideline based treatment of ACS, in particular aspirin, heparin, and if required morphine and oxygen**. Patients with cardiogenic shock or post cardiac arrest require intensive care. Electrocardiogram monitoring is essential as a prolonged QT-interval may trigger malignant ventricular arrhythmias (torsades de pointes) and AV-block may occur.

Acute treatment

Takotsubo syndrome patients with cardiogenic shock, in particular those with apical ballooning **should be promptly evaluated for the presence of Left ventricular outflow tract obstruction**, which occurs in about 20% of cases.

In TTS patients treated with catecholamine drugs a 20% mortality has been reported; although this may represent a selection bias due to the initial presentation of the patients. Recently, it has been suggested that **the Ca2+-sensitizer Levosimendan could be used safely and effectively in TTS as an alternative inotrope to catecholamine agents**. Furthermore, **beta-blockers may improve LVOTO, but are contraindicated in acute and severe heart failure with low LVEF**, hypotension, and in those with bradycardia. Although evidence is unproven, TTS **patients with LVOTO may benefit from the If channel inhibitor Ivabradine.**

Beta-blockers seem to be reasonable until full recovery of LVEF, but trials supporting this hypothesis are lacking. In an animal model, intravenous metoprolol improved epinephrine-induced apical ballooning. **However, due to the potential risk of pause-dependent torsades de pointes, beta-blockers should be used cautiously, especially in patients with bradycardia and QTc >500 ms**.

Angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) may potentially facilitate LV recovery. **Diuretics are indicated in patients with pulmonary oedema.** In addition, nitroglycerin is useful to reduce LV and RV filling pressures and afterload in the case of acute heart failure; however, the administration of nitroglycerin in the presence of LVOTO has been found to worsen the pressure gradient and therefore should be avoided in this scenario.

Severe LV dysfunction with extended apical ballooning entails the risk of an LV thrombus and subsequent systemic embolism. Although evidence is lacking, **anticoagulation with intravenous/subcutaneous heparin would appear to be appropriate in such patients and post-discharge oral anticoagulation or antiplatelet therapy may be considered on an individual, per-patient basis**.

As LV dysfunction and ECG abnormalities are reversible, an implantable cardioverter-defibrillator for primary or secondary prevention is of uncertain value in TTS patients experiencing malignant ventricular arrhythmias.

In case of excessive prolongation of the QT interval or life-threatening ventricular arrhythmias a wearable defibrillator (life vest) could be considered. A temporary transvenous pacemaker is appropriate for those with haemodynamically significant bradycardia.

The use of ACEi or ARB was associated with improved survival at 1-year follow-up even after propensity matching. In contrast, there was no evidence of any survival benefit for the use of beta-blockers. Moreover, one-third of patients experienced a TTS recurrence during beta-blockade suggesting that other receptors such as alpha-receptors, that are more prevalent in the coronary microcirculation, might be involved.

If concomitant coronary atherosclerosis is present, aspirin and statins are appropriate. As TTS mainly occurs in postmenopausal women oestrogen supplementation in those with recurrence is questionable. Psychiatric disorders (e.g. depression, anxiety) are common in TTS patients, and those might benefit from a combined psycho-cardiologic rehabilitation. Whether anti-depressants or other psychiatric drugs might provide clinical benefit in such patients is controversial.

Prospective approaches

The link between the brain and heart seems to play a key role in TTS. Additionally, studies on circulating miRNAs suggest there could be a genetic aspect to the pathophysiology of TTS, and the predominance of female patients suggests that TTS could be related to sex hormones and the endocrine system. Takotsubo syndrome is more than a cardiac disease, and it requires a new and interdisciplinary approach to increase awareness among not only cardiologists, but physicians at large.

THANK YOU FOR ATTENTION!!