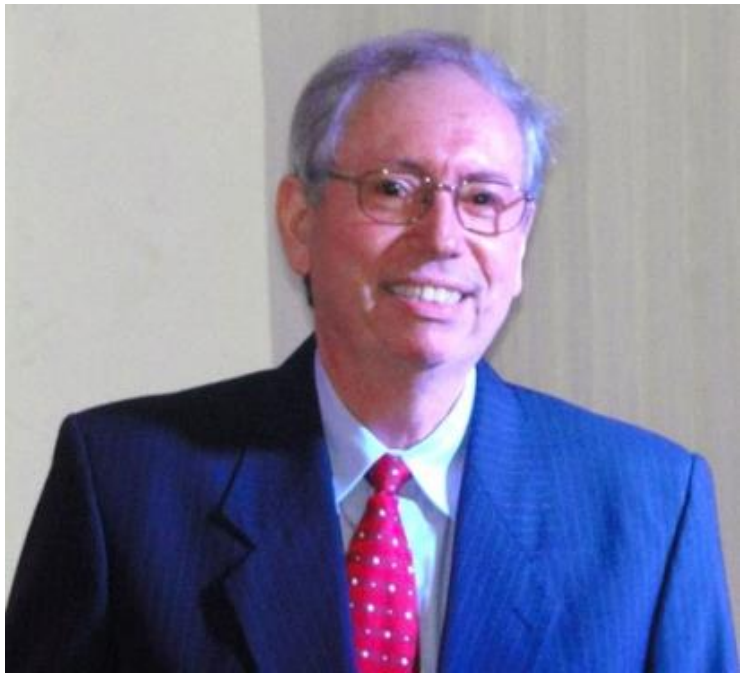
Acute cardiac event with slurring J-wave or “Lamda-like” J-wave on ECG and Left ventricle systolic dysfunction

But there is no possible knowledge which arrives not from a pre-existent knowledge
William Harvey (1578-1657)

Andrés Ricardo **Pérez-Riera, M.D. Ph.D.**
Design of Studies and Scientific Writing Laboratory in the ABC School of Medicine, Santo André, São Paulo, Brazil
https://ekgvcg.wordpress.com



Raimundo **Barbosa-Barros**, MD
Chief of the Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes. Fortaleza – CE- Brazil

English: Case report

64-year-old, female patient, Caucasian, housewife. She described having been admitted in another hospital after being operated to treat her for rectal cancer. Suddenly she presented symptoms of dyspnea and after performing an ECG (ECG-1) she was transferred to the Messejana hospital. She was admitted with increased heart rate, regular cardiac rhythm, threefold split. No murmur.
Lung auscultation: Bibasilar lung crepitant rales. ECG-1
Chest X-rays, PA, compatible with bilateral pulmonary congestion and cardiomegaly +++
Troponin T: 0.764 ng/mL (reference value 0,030 ng/mL); Creatine Kinase-MB CK-MB mass: 3.78 mkat/L (Calcium: 99mgdL,)
After performing ECG-2, the patient was referred to the hemodynamic lab where she underwent ventricular angiography.
The ventriculogram revealed severe mitral valve insufficiency (absent at admission) + severe contractile dysfunction.
Questions

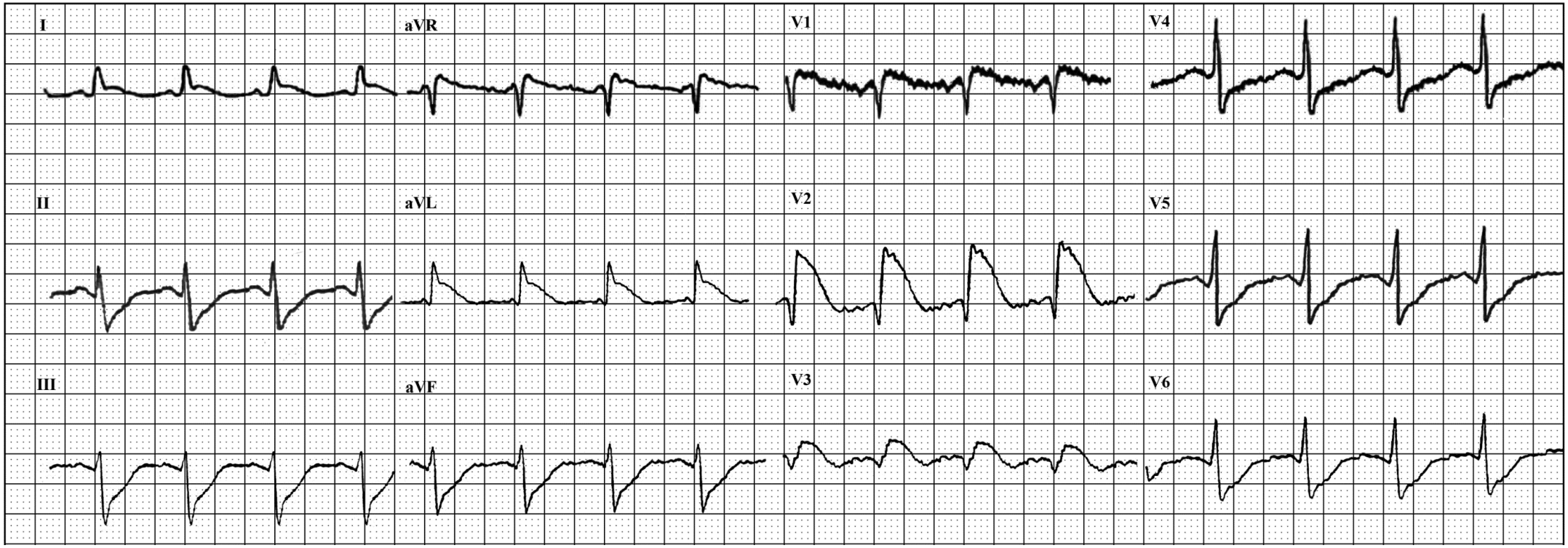
1. *What is the diagnosis of ECG-1?*
2. *What is the diagnosis of ECG-2 ?*
3. *What is the most likely clinical diagnosis? Base your hypothesis.*

Português: Relato de caso

64 anos, sexo feminino, branca, dona-de-casa. Refere que estava internada em outro hospital após ser operada para tratamento de câncer de reto. Subitamente apresentou quadro de dispneia e após a realização do ECG (ECG-1) foi transferida para o hospital de Messejana. Deu entrada com FC elevada. RCR 3 tempos. Sem1 sopro. Estertores crepitantes pulmonares bi basais.
Rx tórax PA compatível com congestão pulmonar bilateral e cardiomegalia +++
Troponina: 0,764 (valor de referencia é de até 0,030 ng/ml), CK MB massa: 3,78 (Calcio: 99mgdL)
Após a realização do ECG-2 foi encaminhada para hemodinâmica onde se realizou cine-ventrículo-coronariografia. O ventriculograma revelou insuficiência mitral severa (ausente na admissão) + disfunção contrátil.
Perguntas:

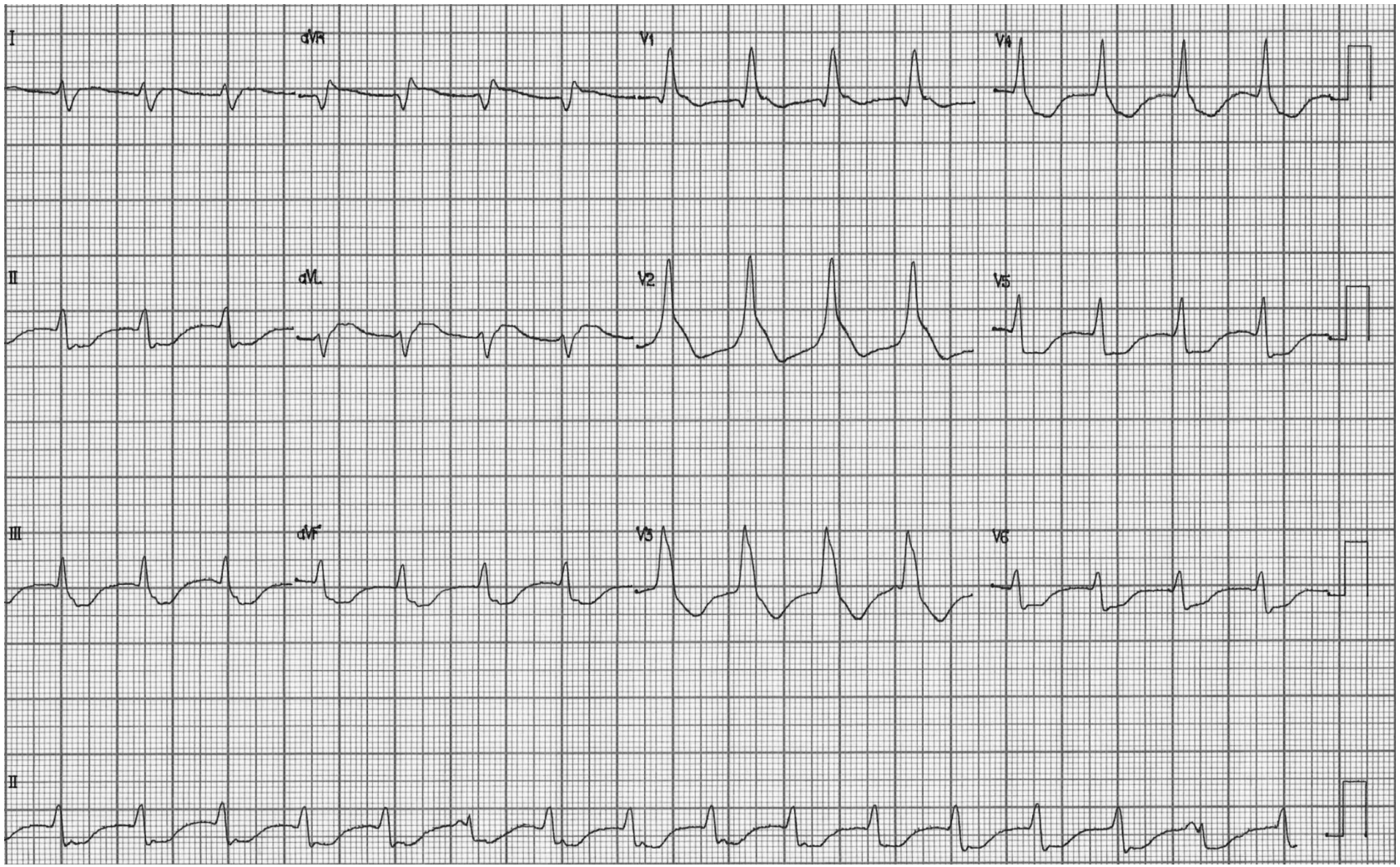
1. ***Qual o diagnóstico do ECG-1 ?***
2. ***Qual o diagnóstico do ECG-2 ?***
3. ***Qual o mais provável diagnóstico clínico? Fundamente sua hipótese.***

ECG1 at admission



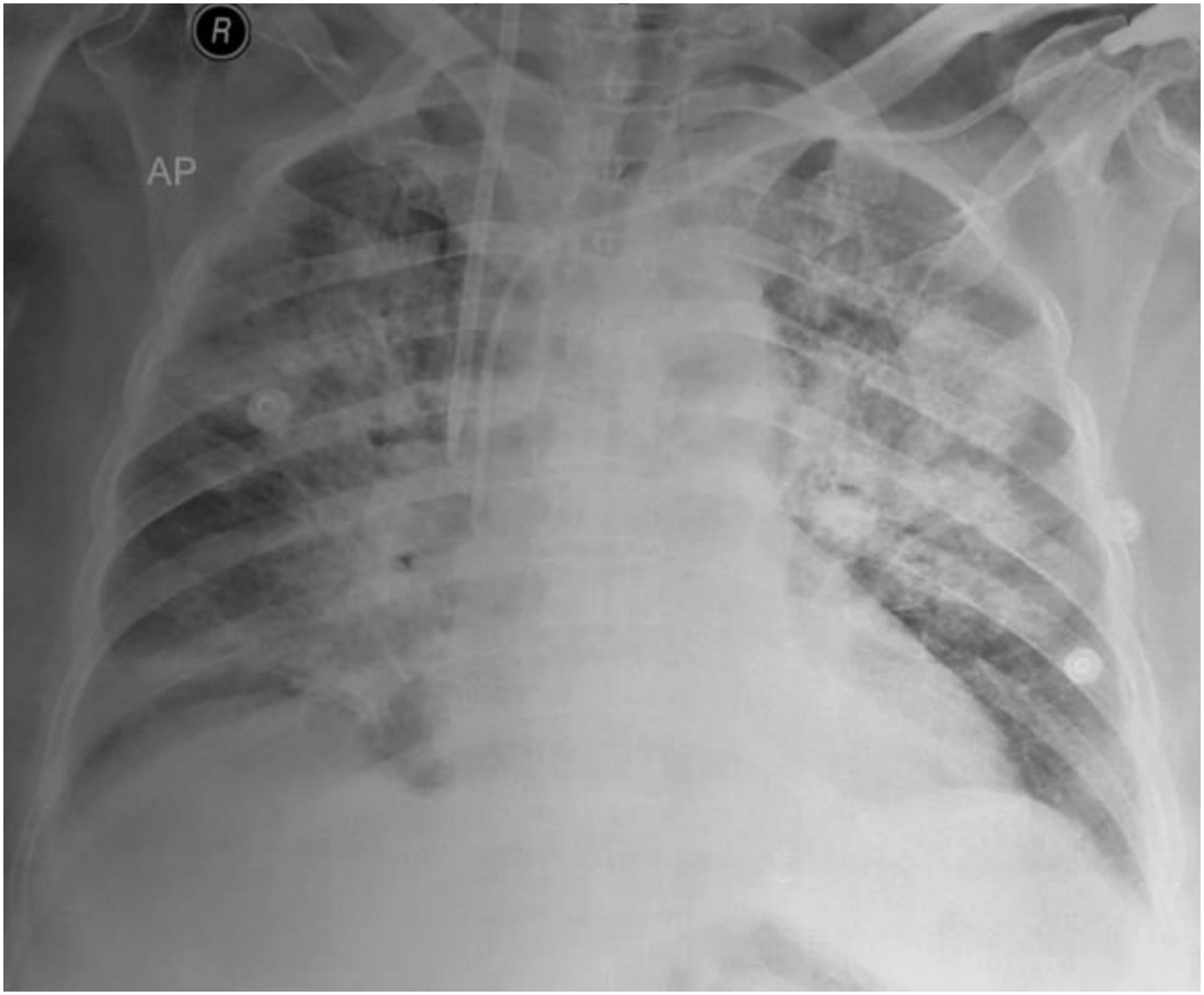
ECG-1 diagnosis:

ECG-2 performed before angiography - Antes da coronariografia



ECG-2 diagnosis:

Chest x-ray - Anteroposterior (AP)



Colleagues opinions

Spanish: Queridos amigos Andrés y Raimundo:

Trataré de ser muy concreto.

El relato de la Historia Clínica revela el antecedente de cirugía (¿ muy reciente ?) de cáncer rectal, y una muy importante hipocalcemia. (0.99). No hay relato de dolor de pecho. El ventriculograma NO habla de alteraciones segmentarias de la contractilidad; entiendo que es una hipo quinesia global y aguda del V.I.

Uniendo esos 4 datos, pienso que la causa de su cuadro tan brusco de edema agudo de pulmón por severo déficit de la contractilidad miocárdica, puede ser explicado si es que la paciente ha recibido importantes transfusiones de sangre fría, con 2 consecuencias:

El citrato de cada unidad de sangre actúa como quelante del calcio. Además, podría sospechar que la sangre fría de cada sachet ha originado hipotermia, que, junto con la hipocalcemia, puede explicar los cambios ECG y la brusca caída del inotropismo miocárdico.

Quizás no hubiese indicado estudio hemodinámico. Hubiese preferido un buen ecocardiograma, en principio.

El antecedente quirúrgico, más los cambios ECG, más el dato de hipocalcemia severa, más una severa hipocontractilidad global, creo que dan la pista del diagnóstico.

Ahora bien: si la paciente NO recibió transfusiones masivas de sangre, retiro todo lo dicho.... "violín en bolsa"...y espero la resolución de este interesante caso.

Abrazos,

Mario

Dr. Mario Heñin
Resistencia, Chaco
Argentina

Dear friends, Andrés and Raimundo:

I will try to be very concrete

The clinical history reveals the history of surgery of rectal cancer (very recent?) and a very important hypocalcemia (0.99). There is no report about chest pain. The ventriculogram does not show segmental alterations of contractility; I understand that it is a global and acute hypokinesis of LV.

Considering these 4 data, I think that the cause of her abrupt picture of acute pulmonary edema due to a severe deficit of myocardial contractility can be explained if the patient has received important cold blood transfusions with 2 consequences:

The citrate of each unit of blood acts as a calcium chelator. In addition, you may suspect that the cold blood from each sachet has caused hypothermia, which, together with hypocalcemia, may explain the ECG changes and the sudden drop in myocardial inotropism.

He might not have indicated hemodynamic study. I would have preferred a good echocardiogram, at the beginning.

The surgical history, plus ECG changes, plus the data of severe hypocalcemia, plus a severe global hypocontractility, I think they give the diagnosis.

Now, if the patient did NOT receive massive blood transfusions, I take back everything I said .... "violin in a bag" ... and I await the resolution of this interesting case.

Hugs,

Dr. Mario Heñin
Resistencia, Chaco
Argentina

Dear Mario, Nikus and colleagues: Unfortunately, there was a typographical error. The calcium value is not 0.99. In fact it is 9.9mg / dL
Consequently there are normal levels of serum calcium.
We apologize for the lack of attention.
Andrés & Raimundo

Spanish
Buenas noches Maestros Andrés y Raimundo:
Creo se trata de una paciente con un sindrome coronário agudo con elevación del segmento ST (ACS-STSE) con insuficiencia cardiaca aguda por la clínica, laboratorio, RxTx, ECG y ECGs.
ECG #1: ritmo sinusal 100 bpm, con elevación del segmento ST aVL > D1 (lambda-Like, onda J) y en aVR ≥V1. elevación del segmento ST con qR de V1 a V3; depresión del ST en DII > DIII, (el vector de necrosis apunta a -30°), aVF y de V4 a V6 y onda S empastada
En ECG #2: bloqueo atrioventricular completo con ritmo de la unión con frecuencia cardiaca de 100 bpm, con depresión del segmento ST en cara inferior qR en V1, R de V2 a V4 que disminuye de voltaje en derivaciones izquierdas. BCRD y fuerzas an teriores prominentes (bloqueo del fasciculo septal vs. Infarto lateral).
Solicitaría derivaciones posteriores y derechas.
Podría tratarse de oclusión de tronco de de la coronaria izquierda ó enfermedad multivaso con compromiso de la circunfleja (Cx) y rotura de músculo papilar posteroinferior con Iinsuficiencia mitral severa referida, y compromiso de irrigación del nódulo AV. y quizás compromiso de la coronaria derecha caso la Cx no fuera la responsable del bloqueo atrioventricular completo (85% de los casos irrigado por la CD y 15% por Cx).
Afectuosamente

Dr Juan Carlos Manzzardo
Mendoza Argentina

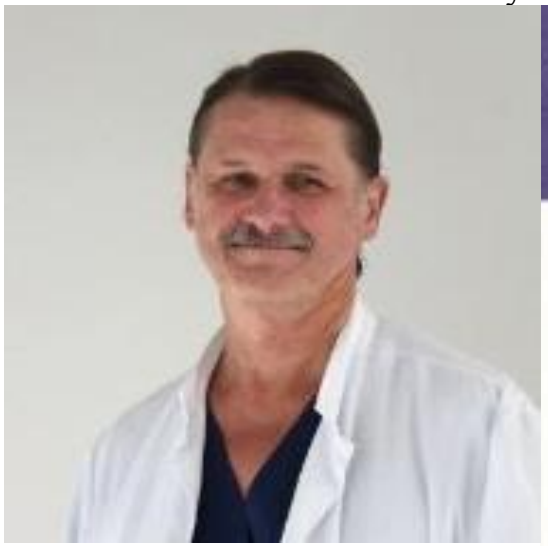
English

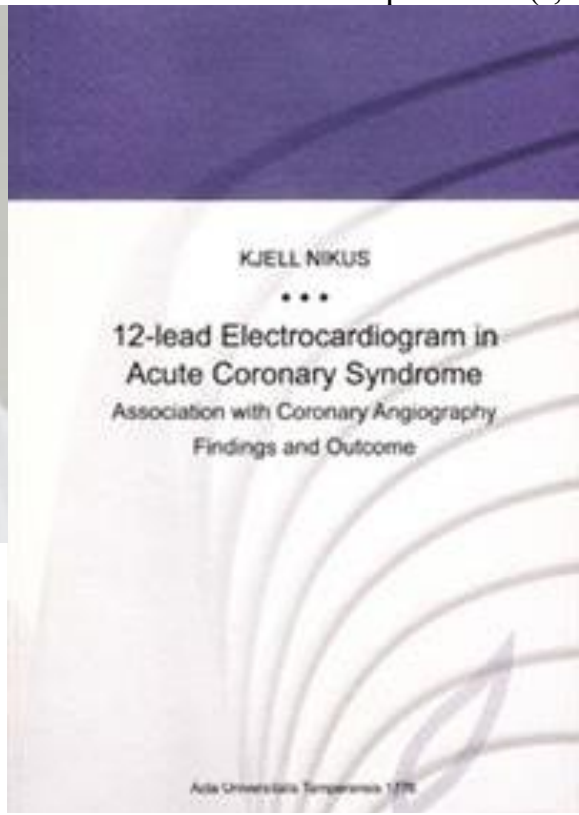
Good evening Teachers Andrés and Raimundo:
I believe it is a patient with an acute coronary syndrome with ST-Segment Elevation (ACS-STSE) with acute heart failure by the clinic, laboratory, Chest RX, and ECGs.
ECG # 1: sinus rhythm, HR: 100 bpm, ST-segment elevation aVL> I (lambda-like, J wave) and in aVR ≥V1.
ST segment elevation with qR from V1 to V3; ST depression in II> II, (the injury vector points to -30 °), aVF and from V4 to V6 and wide final S wave.
ECG # 2: complete atrioventricular block with heart rate junction rate of 100 bpm, with ST segment depression in inferior leads; qR in V1, R of V2 to V4 that decreases voltage in left leads. RBBB and prominent anterior QRS forces (LSFB vs. lateral infarction).
I would request right and posterior leads.
It could be occlusion of the left main coronary artery or multivessel disease equivalent with left circumflex (L.Cx) involvement and rupture of the posteroinferior papillary muscle of the mitral valve and secondary severe mitral regurgitation and compromise of irrigation of the AV node and perhaps compromise of the RCA if the LCx was not responsible for the complete atrioventricular block (85% irrigated by RCA and 15% by L.Cx).

Affectionately

Juan Carlos Manzzardo MD
Mendoza Argentina

Dear friends. A very rare and interesting case, once again!
An elegant explanation was proposed by Dr. Mario Heñin and he could be right. We published a case with hypocalcemia-induced ST elevations simulating acute STEMI **(Ilveskoski E et al Am J Emerg Med 2012**).
ECG 1 shows severe transmural ischemia (Grade 3 ischemia; tombstoning) with anterior ST elevations, probably with RBBB+LAFB. Also ST elevations in I, aVL and aVR. It could be acute left main or proximal LAD occlusion. I am not sure if takotsubo can induce such severe ST changes. The text does not say if it was global or regional contractile dysfunction in ventriculography, but because of the mitral regurgitation, it was probably not the typical takotsubo pattern. Such ECG changes can also be present in coronary spasm, but the severe clinical picture does not indicate spasm.
ECG 2 shows a clear shift in the QRS axis, but I think it is because of idioventricular rhythm, which seems to indicate that there was a coronary occlusion. It was recorded before the angiography. Then it was probably not left main occlusion. Pulmonary embolism does not seem probable (I, aVL ST elevation).
Maybe it was hypocalcemia-induced severe coronary spasm???
Best regards





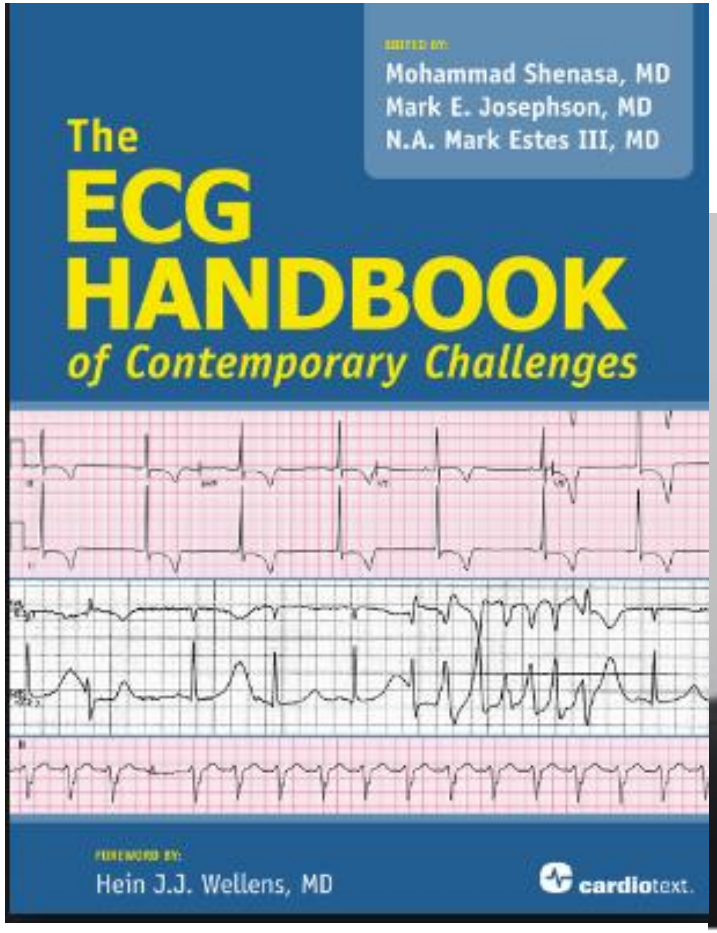
Kjell Nikus
Tampere
Finland
Dear Nikus and colleagues: Unfortunately, there was a typographical error. The calcium value is not 0.99. In fact it is 9.9mg / dL Consequently there are normal levels of serum calcium.
We apologize for the lack of attention
Andrés & Raimundo

No hay ningun problema
Nikus
Ilveskoski E, Sclarovsky S, Nikus K.Severe hypocalcemia simulating ST-elevation myocardial infarction. Am J Emerg Med. 2012 Jan;30(1):256.e3-6.

Dear Andrés and Raimundo,
It appears this patient has acute ischemic event anteroseptal Q wave and St elevation with high lateral ST elevation. Severe mitral Valve insufficiency suggest acute papillary muscle dysfunction or rupture. The tachycardia is regular RBBB LPFB morphology without obvious P-wave with a relatively narrow QRS. It may be SVT but it is more likely VT in the setting of LV dysfunction.
Please let me know the correct answer for my education.
Thank you for sharing.

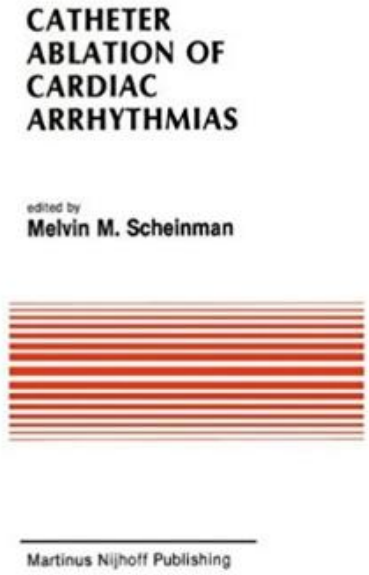
Very best,
Mohammad

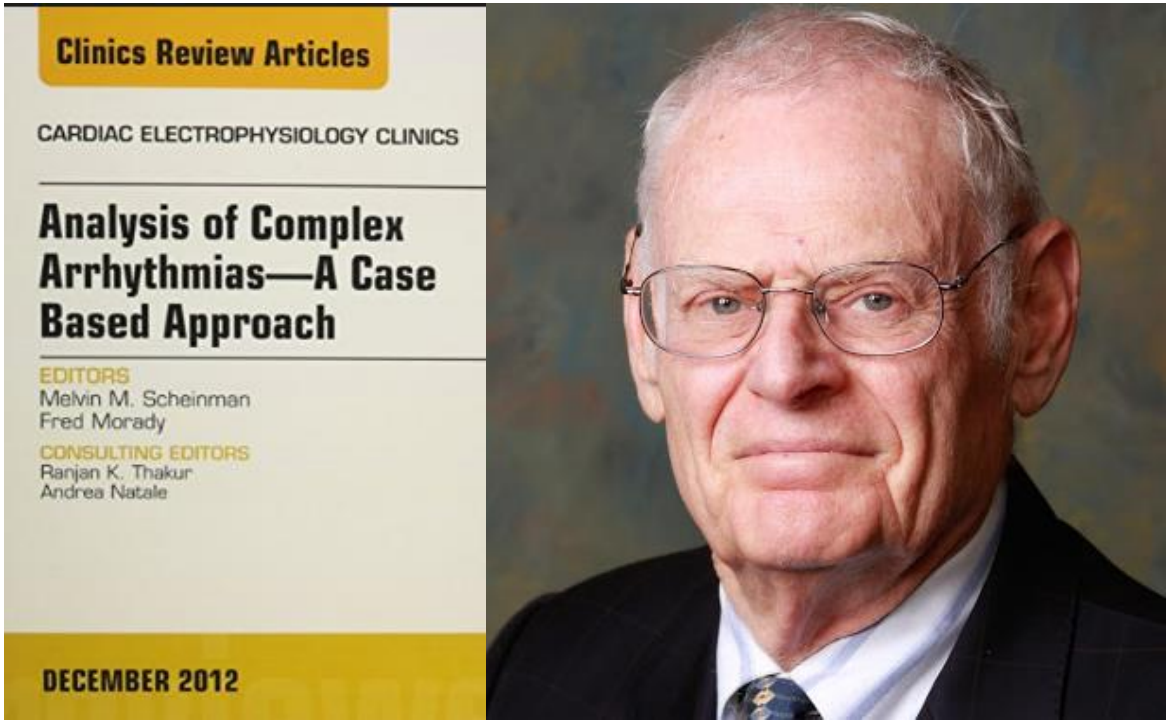
Mohammad **Shenasa** MD, FACC, FESC, FAHA, FHRS,
Heart & Rhythm Medical Group
105 N. Bascom Ave Suite 204
San Jose, CA 95128
408-930-9400 (Mobile)
408-286-2922 (Fax)
mohammad.shenasa@gmail.com



ECG#1: Looks like an acute anterolateral MI probably due to very proximal LAD occlusion with basal ischemia and reciprocal changes in the inferior wall.
ECG #2: shows RBBB with strong anterior forces possibly due to left septal block RAD may be due to LPFB or due to lateral MI
Melvin Scheinman
Dr. Melvin Scheinman is Professor of Medicine, Walter H. Shorenstein Endowed Chair in Cardiology, and one of the founding fathers of the field of cardiac electrophysiology. Dr. Melvin Scheinman is one of the founding pioneers of clinical cardiac electrophysiology. He grew up in Brooklyn, New York and took his undergraduate degree at Johns Hopkins University where he graduated first in his class. Postgraduate medical education included Albert Einstein College of Medicine, residency training at the University of North Carolina (Chapel Hill) and cardiology training at the University of California, San Francisco Medical Center. Dr. Scheinman is best known as the first person to have performed catheter ablation in humans. This was done after extensive animal studies.
Congratulations dear maestro for your spectacular trajectory!

Andrés & Raimundo





Dear friends,
There are only 2 ECGs in the slides and a chest X ray (no ECG 3). ECG 1 shows an injury pattern in the antero-septal and lateral wall of the LV. The second ECG is an idioventricular rhythm or very slow VT originating from the LV. There is one fusion beat.

The clinical picture is consistent with an acute antero-lateral MI with mitral insufficiency secondary to involvement of the anterolateral papillary muscle.

Because of her sex, age, and previous history of surgery, I would also consider Takotsubo cardiomyopathy.

Best regards,

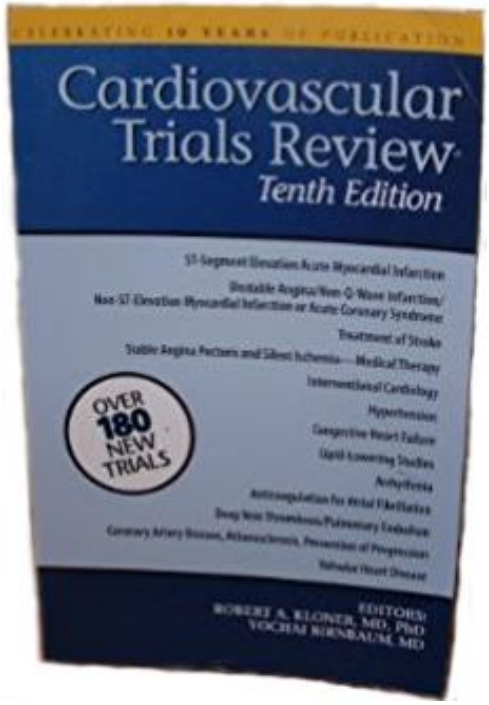
Mario D. Gonzalez
Professor of Medicine.
Director, Clinical Electrophysiology
Penn State Heart and Vascular Iinstitute.
Milton S. Hershey Medical Center
Penn State University
HHershey, Pennsylvania.

ECG 1: Sinus with short PR. ST elevation in I, aVL, V1-V3. The QRS in V1-V2 is distorted and the ST elevation is downsloping. There is upsloping ST depression in the inferior leads and V4-V6. This is compatible with severe ischemia (proximal occlusion of a short LAD). I had discussion with Dr. Galen Wagner to call it grade IV of ischemia. However, this pattern is very rare, so you cannot have statistics. I saw one patient with Takotsubo with similar ECG.

The second ECG shows AV dissociation and a junctional versus AIVR. There is an RBBB pattern with right axis. There is less ST elevation in the anterolateral leads, but ST depression inferiorly and in V3-V6 and ST elevation in aVR. This can be AIVR of reperfusion.

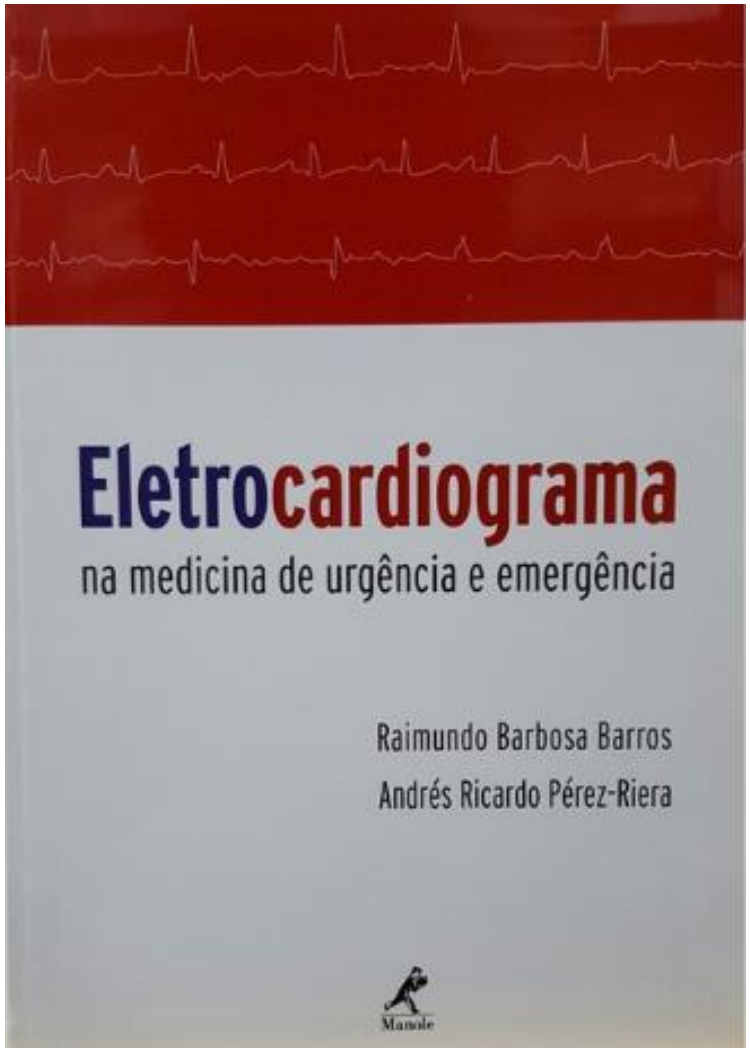
Yochai **Birnbaum,** MD, FACC, FAHA

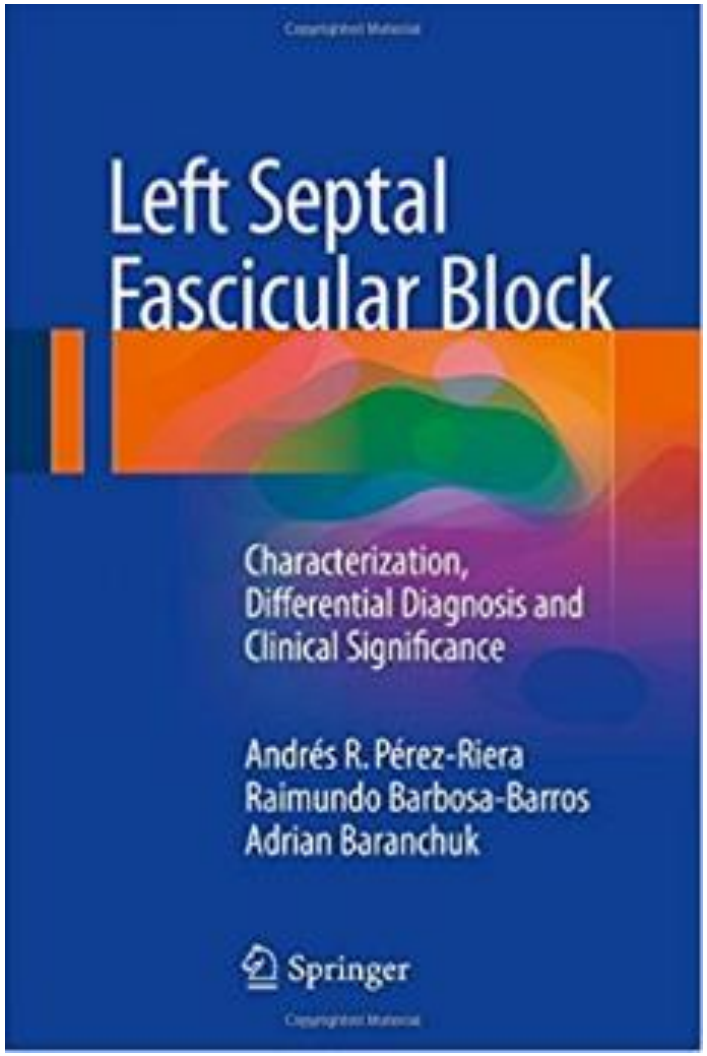
Professor of Medicine
John S. Dunn Chair in Cardiology Research and Education
The Department of Medicine, Section of Cardiology
Baylor College of Medicine
One Baylor Plaza
MS BCM620
Houston, TX 77030
Phone: 713-798-2735
Fax: 713-798-0270
Email: ybirnbau@bcm.edu



Final Comments

By Raimundo Barbosa-Barros & Andrés Ricardo Pérez-Riera





Diagnosis: Basal or reverse Takotsubo Cardiomyopathy (it is an atypical variant). What are the suspected diagnostic clues in this case?

1. **Postmenopausal Woman**
2. **Recent cancer**: Prevalence of malignant diseases is high in Takotsubo Cardiomyopathy (TCM) patients, and is a risk factor for worse outcome. Screening for malignancies should be recommended in all patients presenting with TTC. Further studies are needed to define the association on molecular levels. At time of the TCM event, a malignant disease had been diagnosed in ≈ 14.0% patients. Colorectal cancer is the predominant form of cancer, followed by bronchial carcinoma such as the present case (**Sattler 2017**).

	Typical	Atypical
Age	**older**	**Younger**
Brain natriuretic peptide levels on admission	**higher**	**lower**
ST-segment elevation	**More frequent**	**Less frequent**
Neurologic disorders	**Less frequent**	**More frequent**
LVEF	**Lower**	**higher**

Different Wall Motion abnormalities in Takosubo Cardiomyopathy in the acute phase

Of 1750 patients diagnosed with TCM between 1998 and 2014, a total of 1430 (81.7%) Ghandri et al observed two main LV morphologies:

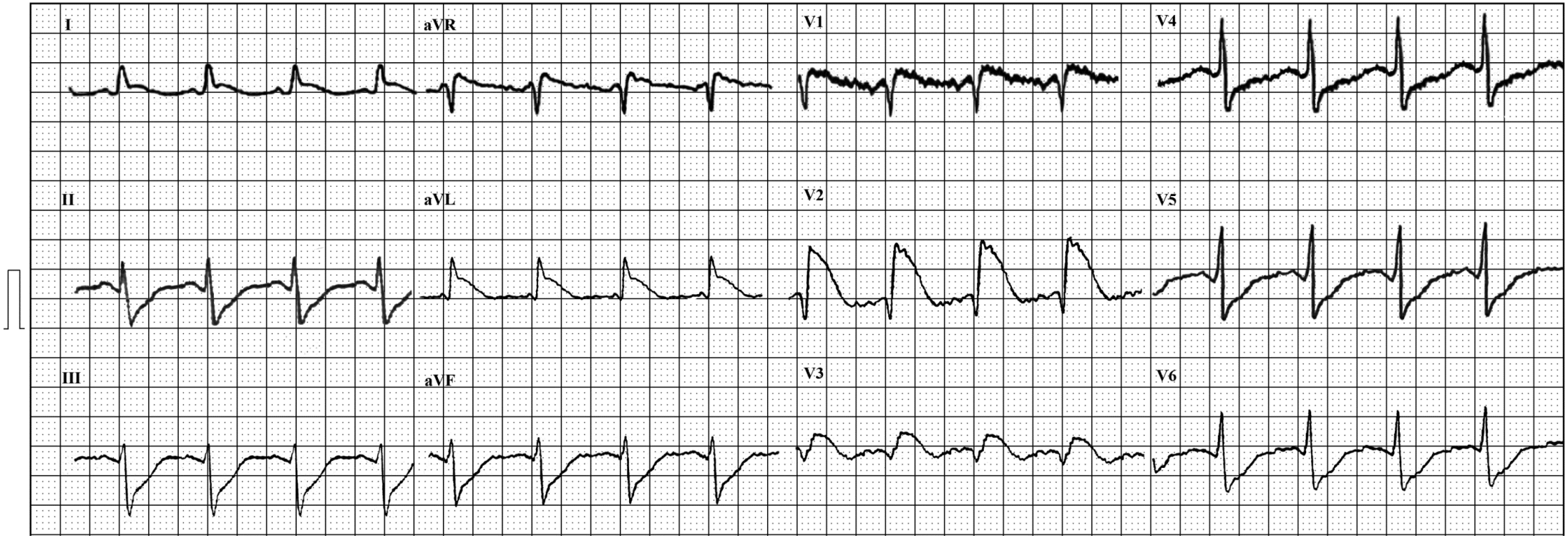
A) Typical TCM Apical akinesia and basal hyperkinesia

B) Atypical TCM with 3 sub-types:

1. Mid-ventricular/ Mid-ventricular ballooning with basal and apical hyperkinesia (**Botto 2003**). This type is more often accompanied by T wave inversion (60%) (**Weihs 2016**).
2. Basal or reverse Takotsubo (Basal akinesia and apical hyperkinesia) The present case (**Ennezat 2011**).
3. Focal TCM (**Ghandri 2016**). Localized to any one segment (**Suzuki 2015**).

After 1 year, patients with both types showed a similar prognosis at long-term follow-up. However, variants of this syndrome with Different Wall Motion Patterns in TCM.

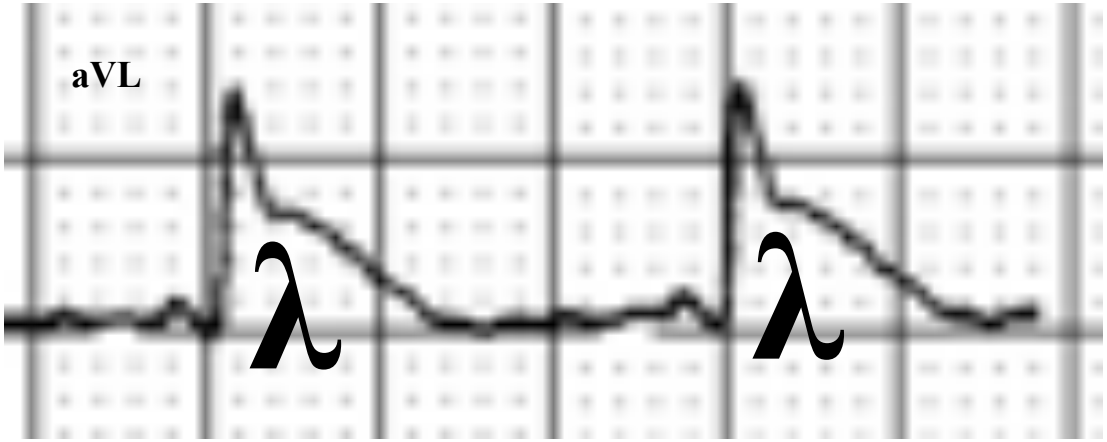
ECG-1 at admission

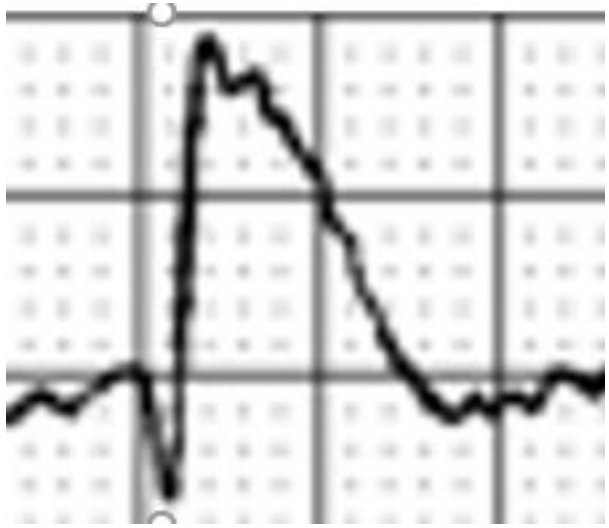


ECG-1 diagnosis: Sinus rhythm, heart rate 100bpm, J point and ST-segment elevation with Q wave formation in right precordial (V1-3) and aVR, aVL and also some subtle in I. Significant ST-segment depression (reciprocal changes or mirror image) in inferior leads II, III, aVF and from V4-6. Observation: In cases of STSEAMI The magnitude of the reciprocal changes in the inferior leads is determined by the magnitude of the ST-SE in I and aVL (as these leads are electrically opposite to III and aVF), hence may be minimal or absent in anterior STEMIs that do not involve the high lateral leads.

Conclusion: LAD occlusion proximal to first diagonal branch (D1)?: ST elevation / Q-wave formation in aVL ST depression ≥ 1 mm in II, III or aVF (reciprocal to STE in aVL) present in this case, or another diagnosis? Electrocardiographic differential diagnosis between TCM and distal occlusion of LAD is not easy (**Carrillo 2010**). Nowadays, TCM is considered a cause of so called J-wave syndrome. We think that slurring J-wave is the same as λ-wave or "Gussak wave" (**Gussak 2004**).

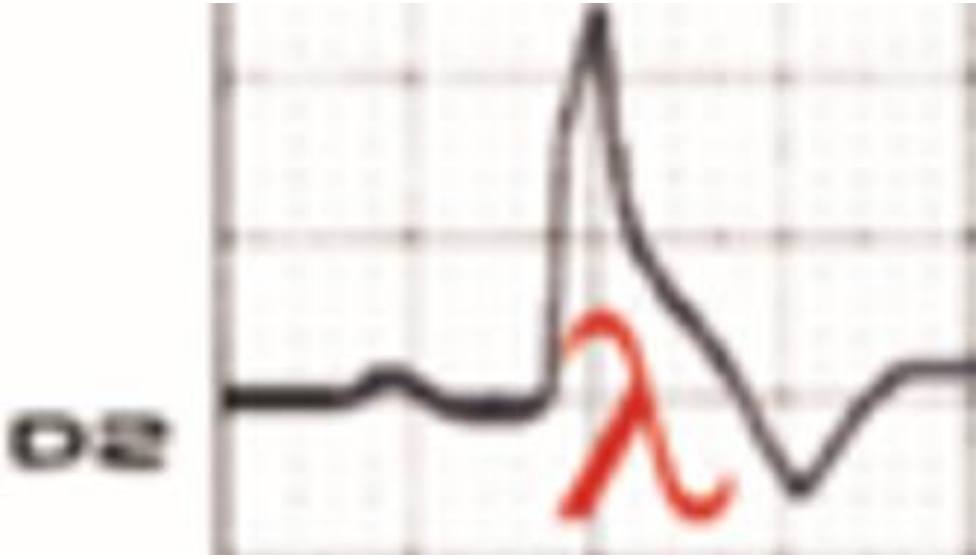
Acute event with slurring J-wave or “Lambda-like” J-wave on ECG and systolic dysfunction

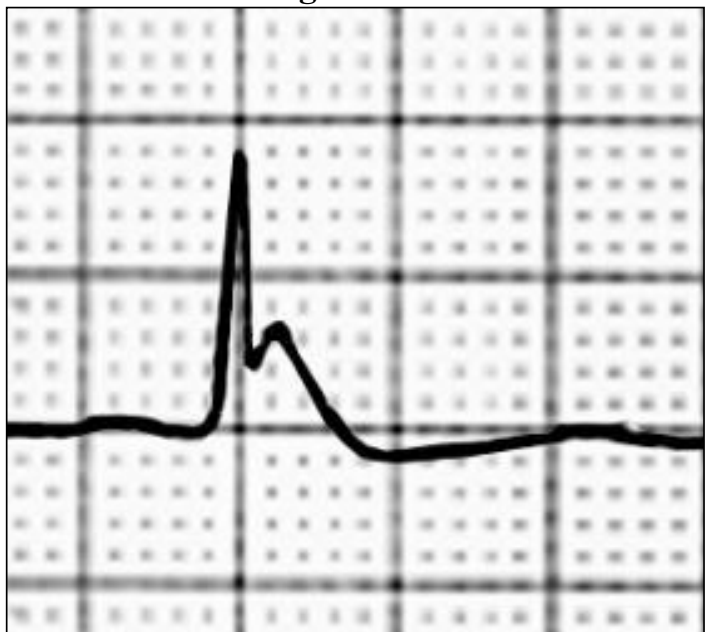




Notching J-wave

Slurring J-wave, Lambda-like or Gussak wave





J-wave syndromes are thus termed a seemingly dissimilar set of clinic-electrocardiographic entities, such as channelopaties Brugada syndrome (BrS), early repolarization syndrome (ERS) (**Gussak 2000**) idiopathic ventricular fibrillation (IVF), short QT syndrome, hypothermia mediated, ischemic heart disease/ ischemia/reperfusion-induced VF, head injuries, severe hypocalcaemia and others miscellaneous that clinically share the tendency for outbreaks of ventricular tachyarrhythmia events that may lead to syncope or sudden cardiac and the presence of J-wave on the surface 12 leads electrocardiogram. These entities represent a continuous spectrum of phenotypic expression that Gan-Xin Yan (**Yan 2004**) proposes be termed J wave syndromes in Chinese journal.

J-wave syndrome classification proposal

A) Hypothermic mediated
B) Normothermic conditions

I) Channelopaties
- Early repolarization syndrome (ERS)
- Brugada syndrome(BrS)
- ERS + BrS in association
- Idiopathic ventricular fibrillation with or without ER Pattern
- Short QT syndrome with or without ERP

II) Acquired forms of J-Wave syndrome
- Ischemia-mediated "J waves" induced by ischemia:
  - ✓ Acute myocardial infarction,
  - ✓ Variant angina or Pinzmetal angina,
  - ✓ Ischemic heart disease (i.e. Takotsubo cardiomyopathy)
- Neurogenic: head injuries, brain injury, subarachnoid hemorrhage, cardiopulmonary arrest from over sedation,
- Severe hypocalcaemia
- Miscellaneas

Electrocardiogram waves classification

1. ECG Normal waves

I. Constant and visible

a) P-wave

b) QRS complex: Q/q; R/r; S/s; R'/r'; S'/s'

c) T-wave

II. Constant and invisible

a) T-a or T-P-wave

III. Inconstant

a) The "enigmatic" U-wave (**Pérez-Riera 2008**)

2. ECG Pathological waves

I. Delta (δ) – wave of ventricular preexcitation (Wolff-Parkinson-White (WPW) syndrome)

II. Pseudo delta (δ) –waves:

a) Wolffian PVCs: PVCs from basal portion of the ventricles – QRS complexes predominantly positive in all precordial leads (V1-V6) (**Rosenbaum 1969**)

b) Epicardial ventricular tachycardias

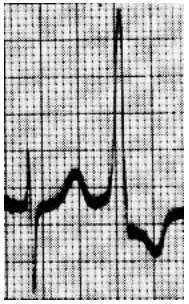
c) Slurred QRS upstroke mimicking delta (δ) waves in hypertrophic cardiomyopathy (**Marine 2013**)

III. J-wave, J deflection, "the camel's hump"/ camel-hump sign, "late δ wave", elevated J-point, hathook junction, hypothermic wave, K wave, H wave, current of injury, or Osborn wave: a J wave is defined as either notching or a slur at the QRS terminal > 0.1 mV above the isoelectric line or without ST segment elevation at least in two contiguous leads.

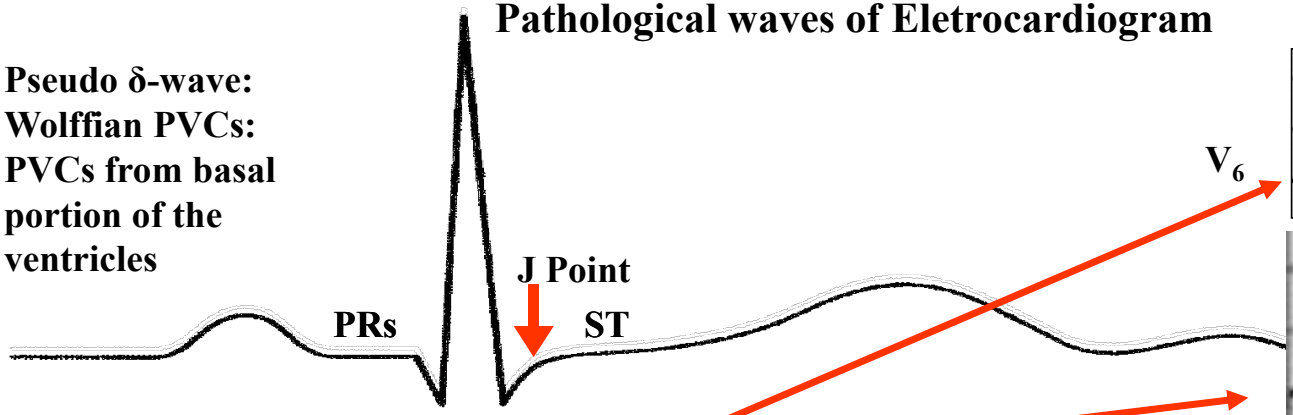
IV. Lambda (λ)-wave or Gussak wave (**Gussak 2004**). Does it exist?: Peculiar shape of J wave? Slurring J-wave

V. Epsilon (ε) wave, epsilon potential or Fontaine wave

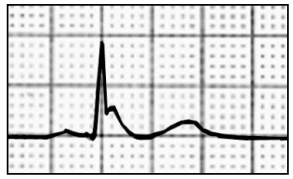
Pathological waves of Eletrocardiogram

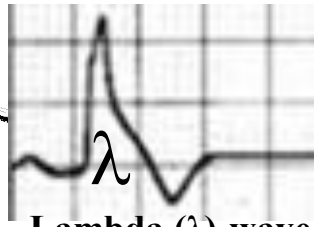


Pseudo δ-wave:
Wolffian PVCs:
PVCs from basal portion of the ventricles



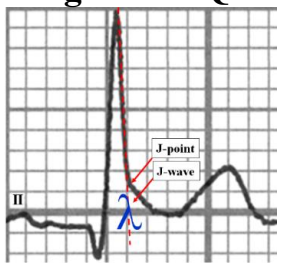
Idiopathic VF



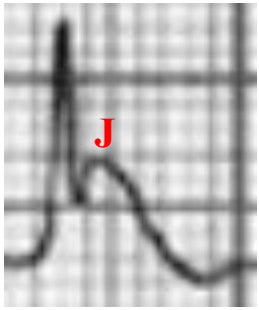


Lambda (λ)-wave
or Gussak wave or
slurring J-wave

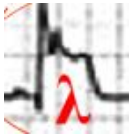
Congenital SQTS



Brain injury



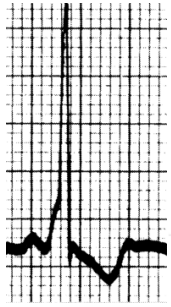
Prinzmetal



CAD

δ-wave and pseudo δ-wave

WPW

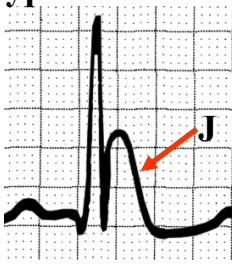


δ- wave

Epsilon wave

ARVC/D

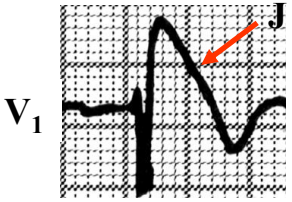
Hypothermia

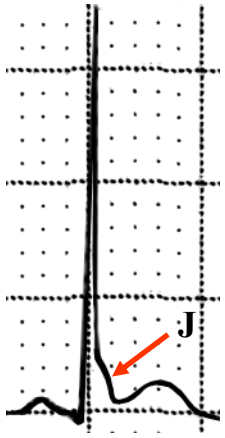


50mm/sec
2N

Hypercalcemia

Brugada syndrome





Short QT interval
The ST segment is almost absent

Ja Point: end of ST segment and beginning of QRS complex
J Point: end of QRS complex and beginning of ST segment

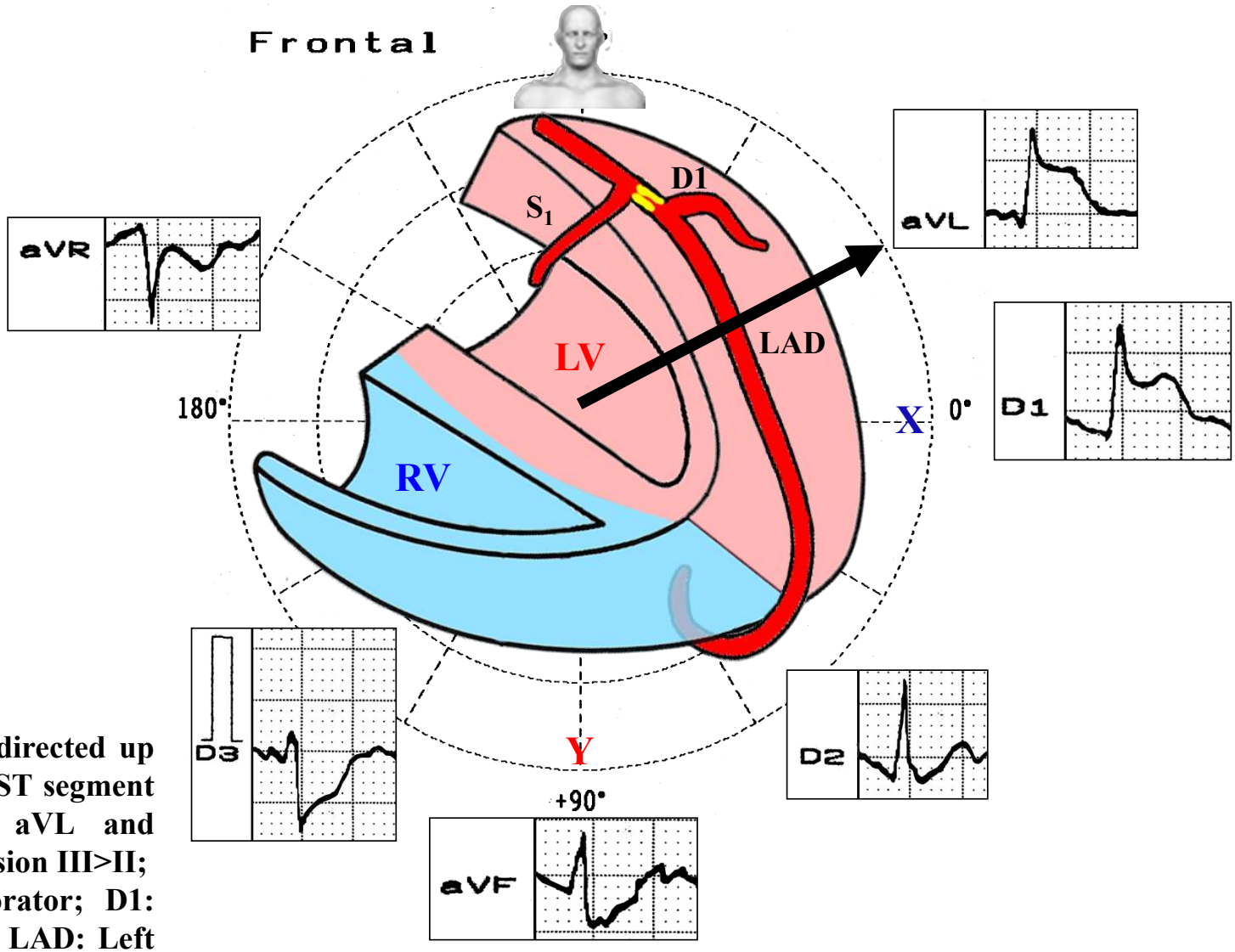
Differential Diagnosis between Left Anterior Myocardial Infarction and Takotsubo Cardiomyopathy

Kosuge et al (**Kosuge 2010**) analyzed the differential ECG diagnosis between TCM from anterior AMI by ECG criteria. The authors do not report how the TCM diagnosis was established. Coronary angiography (CAG) was not performed in 24% of the patients. In this regard, the presence of a normal coronary tree (**Prasad 2008**) does not confirm the diagnosis, because there are other causes of LV apical ballooning (**Ibanez 2006**). A group of patients with anterior AMI were used by the authors for comparison without taking into account the site of occlusion of the LAD artery (if proximal or distal to first diagonal branch D1), which is of capital importance for the interpretation of ECG features.

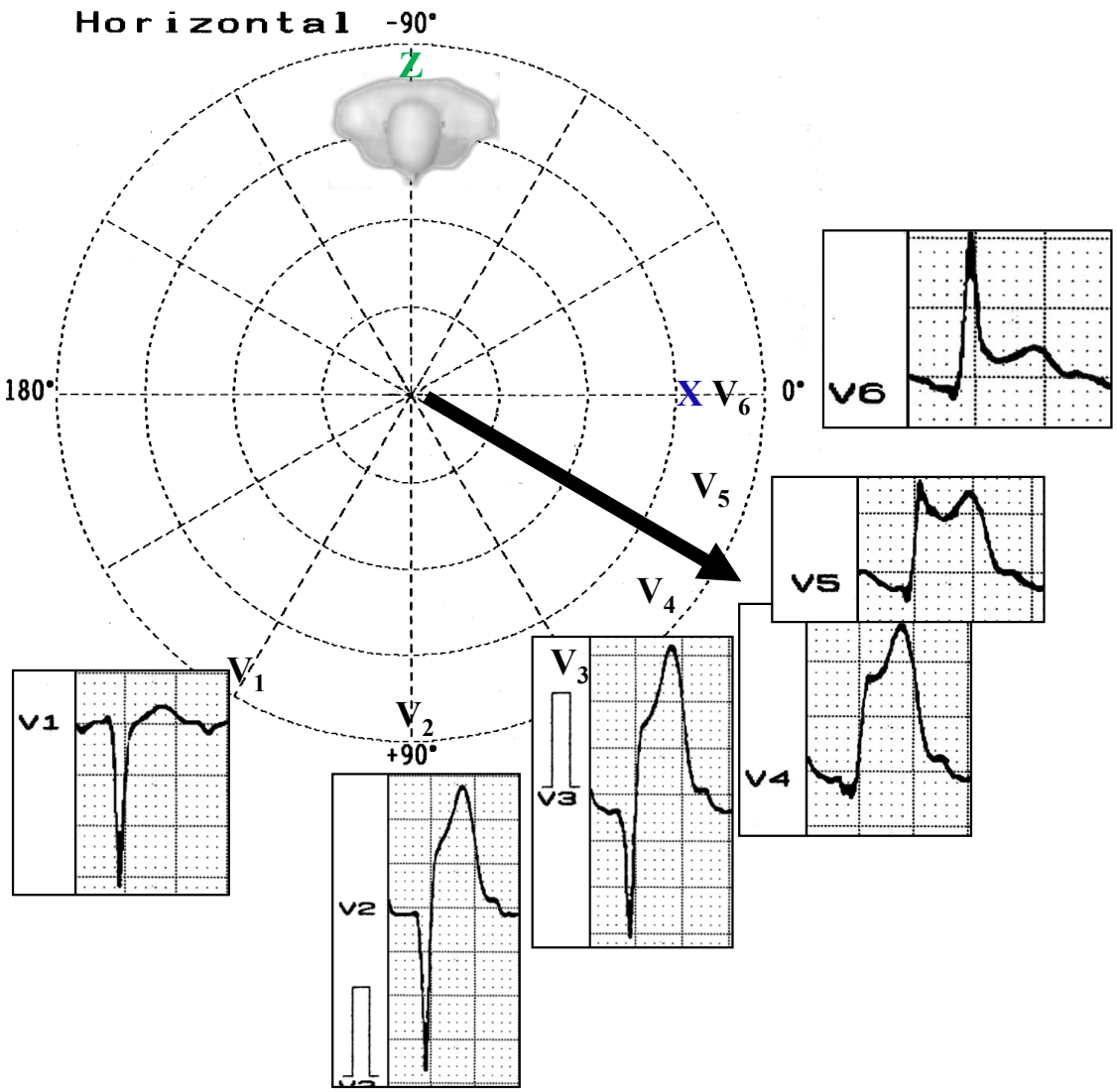
The relationship of ST-SE in V1-V2 to V4-V6 with the pattern of the ST Segment in inferior leads II, III, and aVF allows determining whether the occlusion is proximal or distal to the first diagonal branch (D1) (**Fiol 2009**). If it is proximal, the anterior muscle mass affected is large, and the injury vector (lesion dipole) is directed forward and upward; that explains the reciprocal or mirror image of ST-segment depression in II, III, and aVF. Conversely, if the occlusion is distal to D1, the lesion dipole is directed anteriorly and slightly downward, generally resulting in an isoelectric or ST-SE in II, III, and aVF. The TCM ECG pattern by Kosuge et al is also typical of ST-SE MI due to occlusion that is distal to D1 (**Bayés de Luna 2008**). Carrillo et al (**Carrillo 2010**) believe that the ST-segment shift in leads aVR and V1 can help to differentiate TCM from anterior AMI due to LAD occlusion that is proximal to D1, but not distal, in patients admitted in the early hours of the of the onset of symptoms. Dr Masami Kosuge against argued that Dr. Carrillo et al assert incorrectly the number of patients who underwent CAG because in his study, all patients with TCM underwent CAG during hospitalization, and “emergency” CAG was performed in 25 patients (76%). Formal diagnostic criteria for TCM have yet to be established, and TCM was diagnosed according to the Mayo Clinic diagnostic criteria. Dr Kosuge agrees that, deviation of the ST segment in anterior AMI is influenced by the site of the “culprit” obstruction of the LAD artery. They assert that the ECG of TCM, which fulfills our ECG criteria—namely, the presence of ST-segment depression in lead aVR (ST-segment elevation in lead aVR) and the absence of in lead V1—is typical of anterior AMI with LAD coronary artery occlusion distal to D1. However, they assume that the presence of LAD coronary artery occlusion distal to D1 alone does not result in this ECG pattern. Because lead aVR faces the apical and inferolateral regions, ST-SE in this lead would require that the LAD has a large perfusion territory, including these regions. In addition, the absence of ST-SE in lead V1, which faces the right paraseptal region, would require occlusion of the LAD distal not only to D1, but also to the first septal perforator branch (S1). **Perhaf** among patients with anterior AMI, those who have all of these coronary anatomical findings are relatively rare. Therefore, Dr Kosuge believes that their ECG criteria can help to accurately differentiate TCM from anterior AMI in patients who are admitted within 6 h after symptom onset. However, they agree that it might be difficult to distinguish patients with TCM from some patients who have anterior AMI with distal occlusion of the LAD artery, which extends to the apical and inferolateral regions,

Left Anterior Descending Artery (LAD) occlusion after first septal perforator (S1) and before first diagonal branch (D1)

Explanation

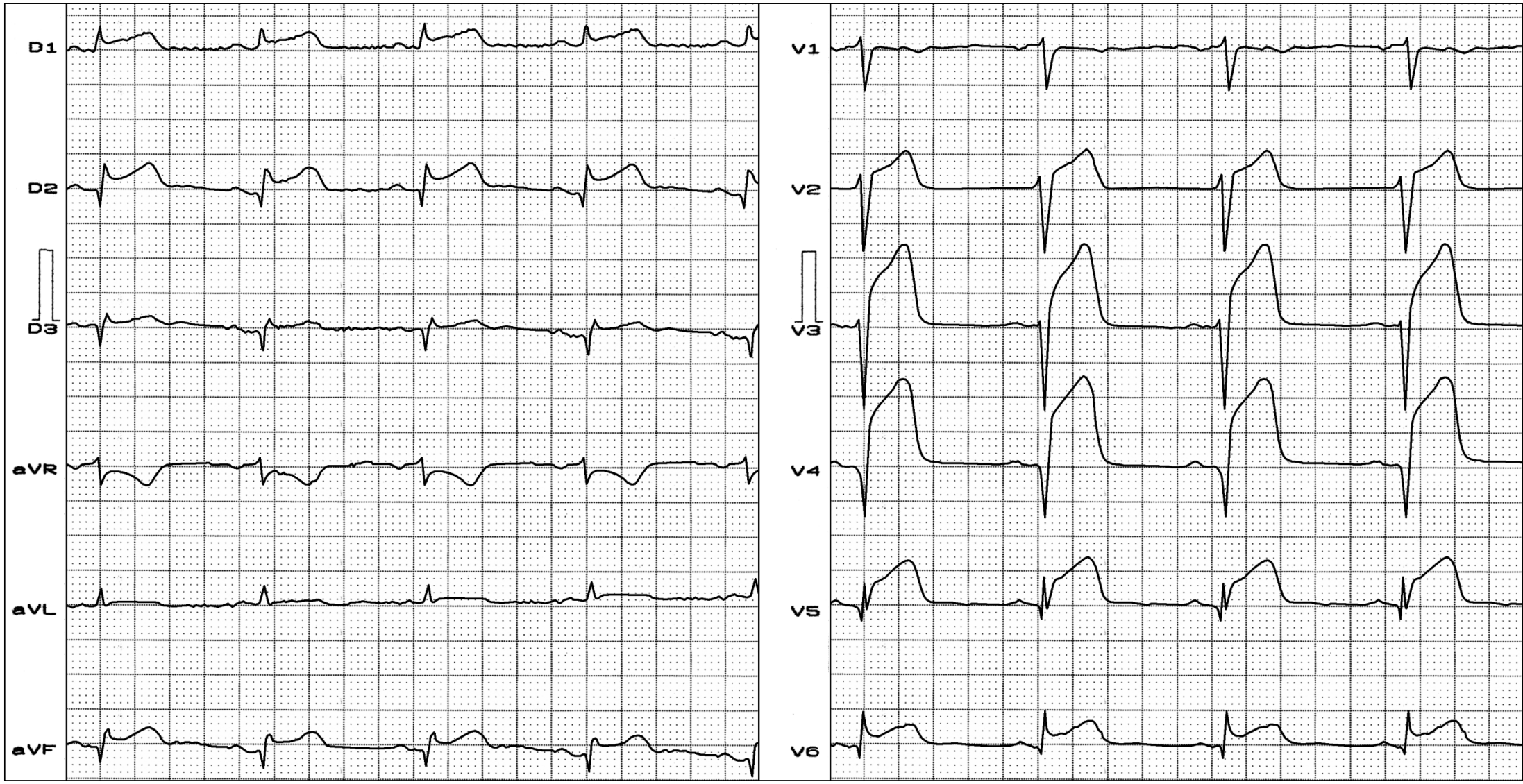


The ST injury vector directed up and leftward (arrow): ST segment elevation in I and aVL and concomitant ST depression III>II; S_1: First septal perforator; D1: First diagonal branch; LAD: Left Anterior Descending Artery.

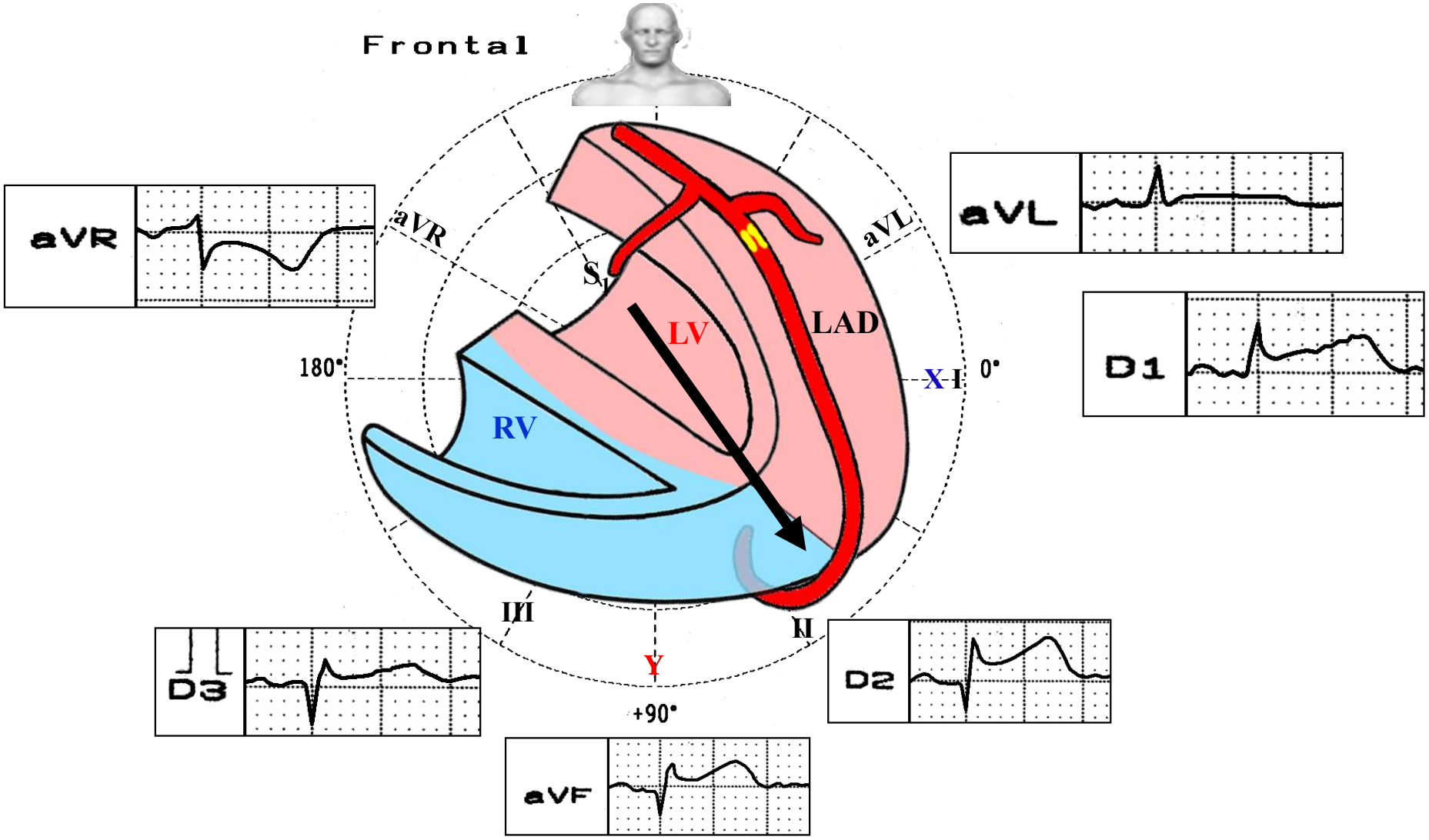


The ST injury vector directed to front and leftward(arrow): STSE from V_2 to V_6 and isoelectric in V_1

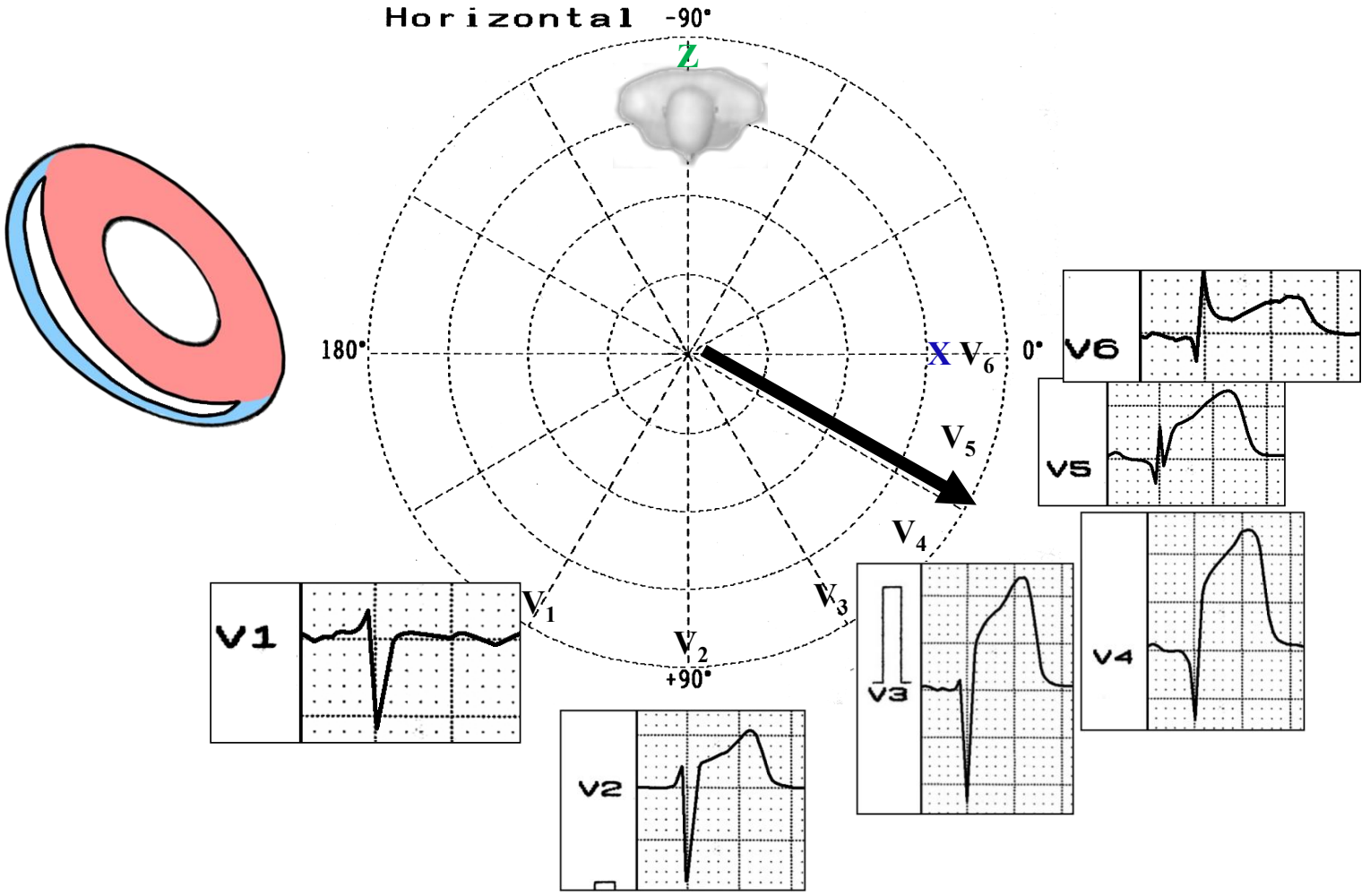
Left Anterior Descending Artery (LAD) occlusion after both first septal perforator and first diagonal branch (LAD distal obstruction)



ST segment elevation in inferior leads: II > III. ST and STSE from V_2 to V_6 Why this pattern ?

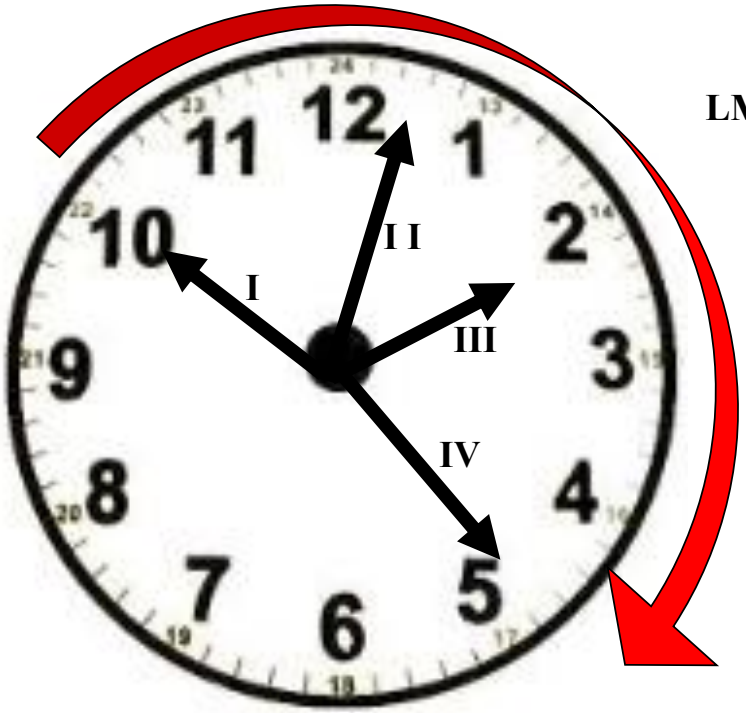


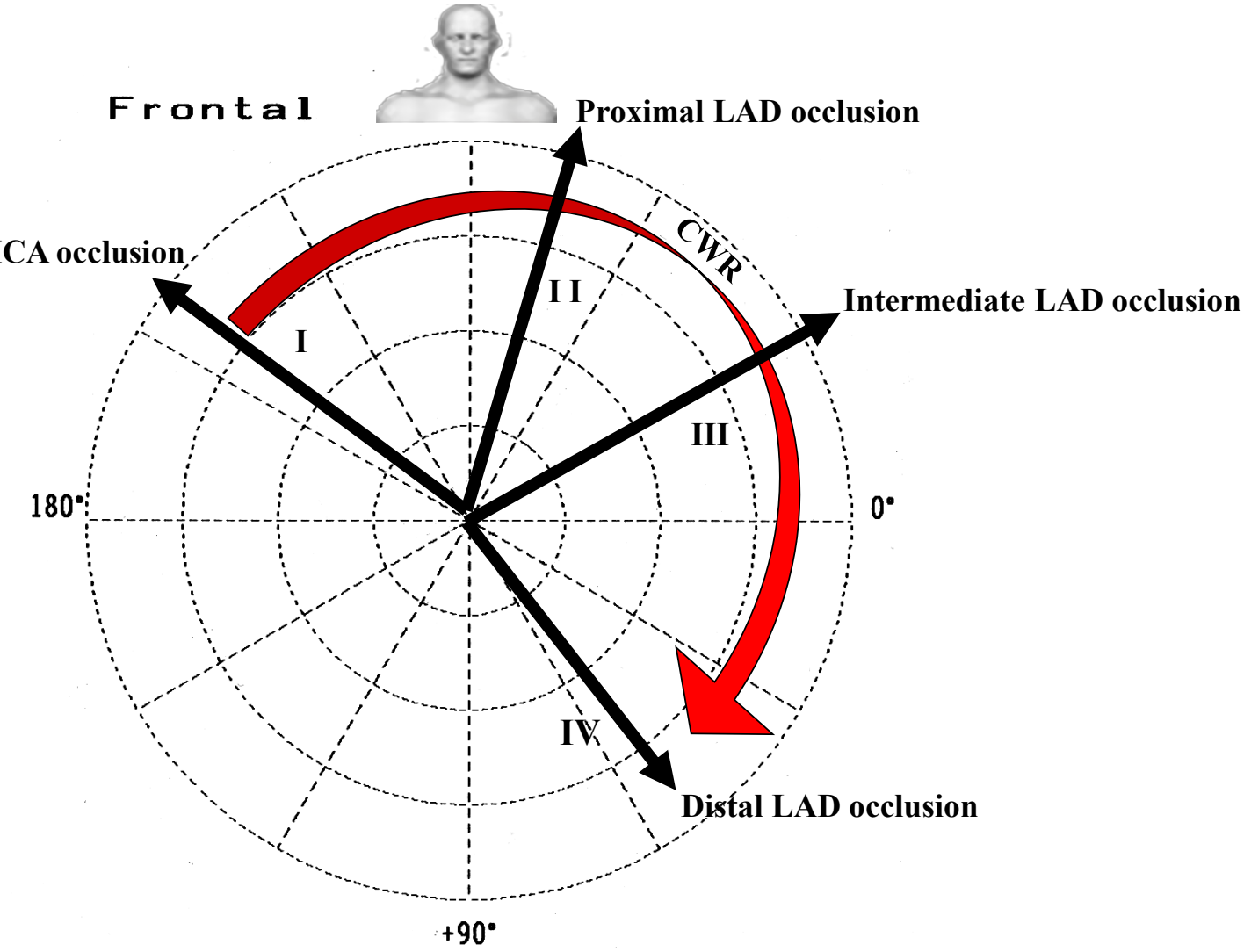
ST-SE in inferior leads: ST II > ST III and ST-S depression in aVR because the injury vector (arrow) is directed downward and leftward



The ST injury vector (arrow) directed to front and leftward: ST-SE from V2 to V6

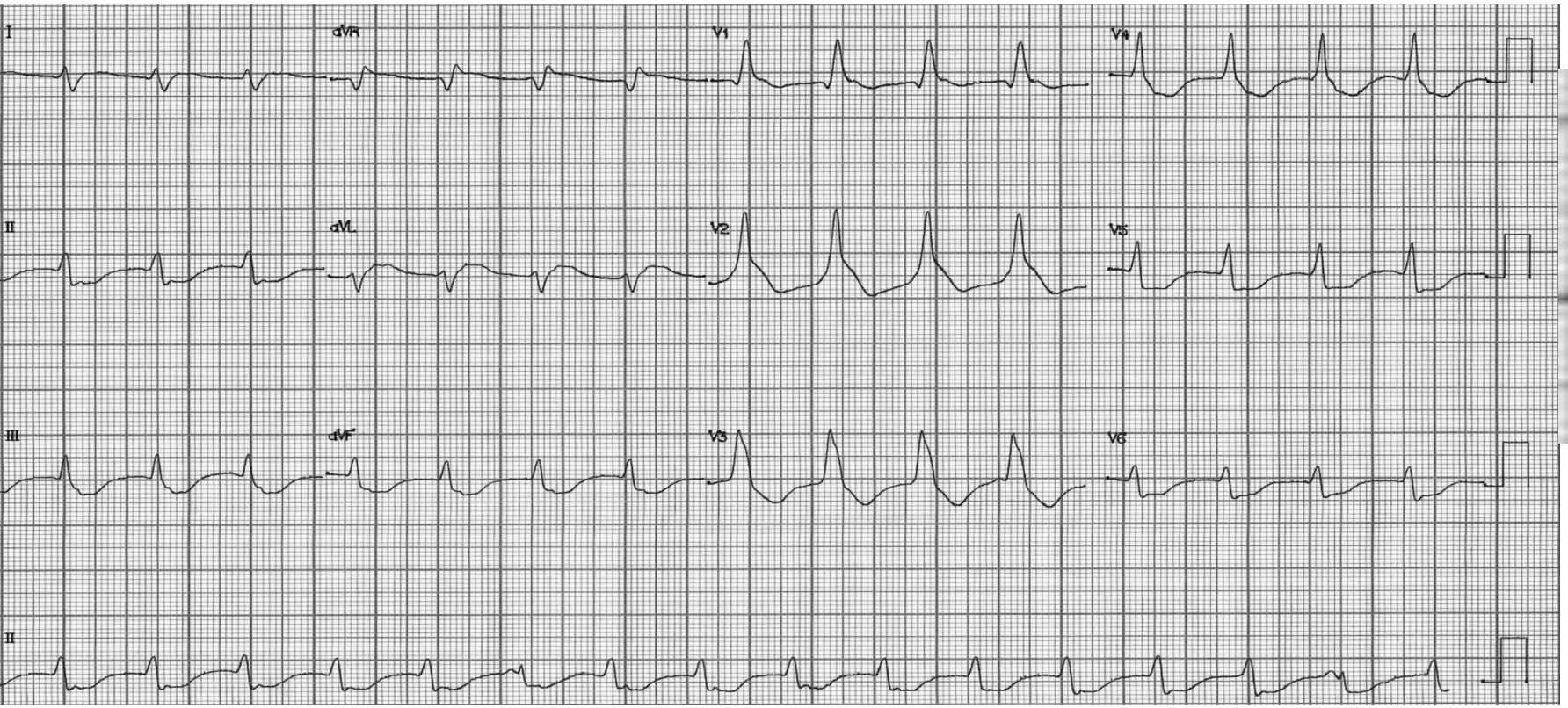
Summary of the ST injury vector direction on FP: Mnemonic method "clockwise"

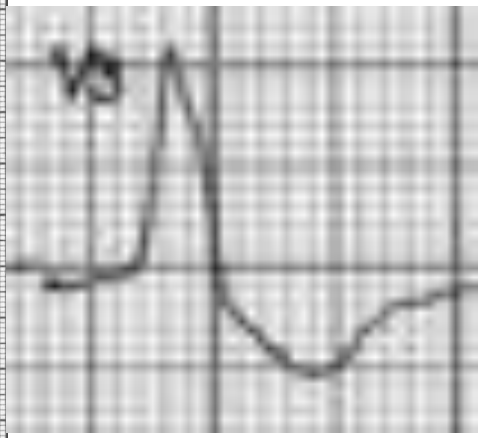




Injury vector (arrows) with CWR: Clock Wise Rotation

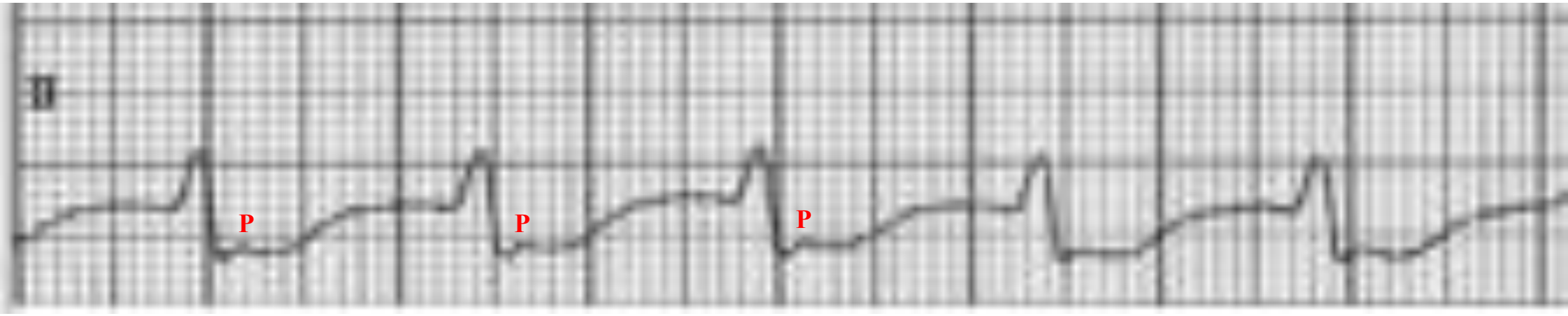
ECG-2 performed before angiography - Antes da coronariografia





QRS duration
Complexes ≥ 120ms

ECG-2 diagnosis: Sustained Accelerated Ventricular Rhythm (AKA), Accelerated Idioventricular Rhythm (AIVR), non-paroxysmal VT, slow ventricular tachycardia (**Leitz 2008**), ventricular rhythm with isorhythm, benevolent rhythm (**Martinez-Lopez 1993**). In the present case Possibly having as underlying mechanism triggered activity mechanism. This mechanism may play a role especially in ischemia. AIVR is classically seen in the reperfusion phase of an acute STEMI, e.g. post thrombolysis. Usually a well-tolerated, benign, self-limiting arrhythmia. This is a regular rhythm, HR between 50 to 110 130 bpm (in this case near 100bpm), QRS duration complexes ≥ 120ms and sinus and ventricular complexes occurring at identical rates (see next slide). This is in contrast to complete heart block, where the atrial rate is usually faster than the ventricular rate. Isorhythmic AV dissociation (see next slide) is usually due to functional block at the AV node due to retrograde ventricular impulses. These ventricular impulses depolarize the AV node, leaving it refractory to incoming sinus impulses (= “interference-dissociation”).



Isorhythmic AV dissociation is usually due to functional block at the AV node due to retrograde ventricular impulses. These ventricular impulses depolarize the AV node, leaving it refractory to incoming sinus impulses (= “interference-dissociation”).

AIVR is a ventricular rhythm with a sequence of ≥ 3 consecutives monomorphic ectopic ventricular beats, lasting less than 30 s gradual onset with a long coupling interval and the end by a gradual decrease of the ventricular rate or increase of the sinus rate and, last but not least, by a good prognosis. Its heart rate between 50 bpm and 130 bpm. The rhythm is accelerated because it usually is ≥ to the sinus one, in this case, it is called ventricular rhythm with isorhythm. It is not an escape rhythm, it is a competing rhythms self-limited and it is usually related to myocardial ischemia. In Accelerated Idioventricular Rhythm (AIVR), the rate of cardiac contraction is determined by the intrinsic rate of depolarization of the cardiac cells. It can be present at birth. In this last case, the patient had an excellent prognosis because the tachycardias resolved, and eventually the patients were in sinus rhythm. It is important to establish the diagnosis when it occurs to differentiate this benign phenomenon from dangerous paroxysmal ventricular tachycardia (**Freire 2008**). In most cases, the mechanism of AIVR appears to be related to the enhanced automaticity in His-Purkinje fibers and/or myocardium, sometimes accompanied with vagal excess and decreased sympathetic activity (**Bonnemeier 2005**). Ischemia, reperfusion, hypoxia, drugs, and electrolyte abnormalities can all accelerate the phase 4 action potential depolarization rates in His-Purkinje fiber and myocardium, leading to faster spontaneous cell depolarization (enhanced automaticity) (**Hasin 1976**). When the enhanced automaticity in His-Purkinje fiber or myocardium surpasses that of sinus node, AIVR manifests as the dominant rhythm of the heart. Sinus bradycardia may facilitate the appearance of AIVR. Any cause that increases maximum diastolic potential (MDP) depth decreases automaticity. E.g.: acetylcholine. Abnormal enhanced automaticity generally is ascribed to phase-4 depolarization of the AP of the myocardial cell. AIVR can occur in the His-Purkinje fibers or myocardium under certain abnormal metabolic conditions. AIVR arises from second-order pacemakers and manifests itself when the patient's prevailing sinus HR becomes lower than the accelerated rate (AIVR) of the competing focus. Sinus bradycardia

combined with enhanced automaticity of the subordinate site is the common pathophysiology. AIVR was associated with higher vagal tone and lower sympathetic activity, the occurrence of AIVR had no prognostic impact on the clinical course. Under certain conditions such as acute ischemia and digoxin toxicity, triggered activity has been suggested as the mechanism for AIVR (**Holzmann 1977**).

Most AIVRs originate from a single focus. Occasionally, in patients with acute myocardial ischemia and myocarditis, AIVR can originate from multiple foci (**Sclarovski 1983; Nakayama 1988**). The ventricular rate of AIVR is generally between 40 to 100-120 bpm.

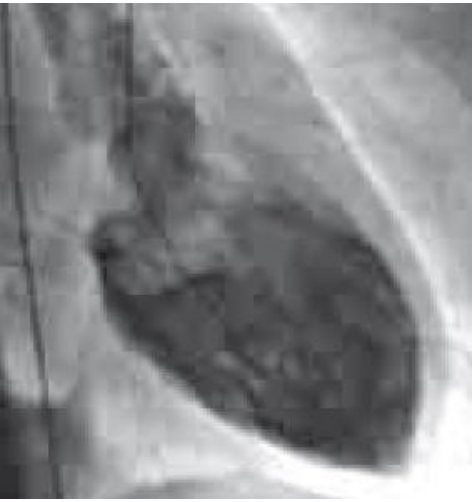
AIVR is hemodynamically well tolerated due to its slow ventricular rate. It is self-limited and resolves as sinus rate surpasses the rate of AIVR. Rarely, AIVR can degenerate into VT or VF. In patients with severe myocardial dysfunction, AIVR may lead to hemodynamic instability due to the loss of AV synchrony or relatively rapid ventricular rate. Clinically, AIVR has been best studied in patients with acute STEMI. In the thrombolysis era, AIVR was noted to be a marker of reperfusion. However, not all patients with reopened coronary artery have AIVR. In patients with AMI treated with PPCI, the reported incidence of AIVR varied significantly, raging from 15-50%, depending on methods of monitoring. Studies in patients with STEMI treated with PPCI support that AIVR is a marker of occluded coronary artery reopening, but is not necessarily a marker for complete reperfusion. In fact, AIVR seems to be associated with more extensive myocardial damage and delayed microvascular reperfusion, although the mortality rates are similar in patients with and without AIVR.

ECG characterization

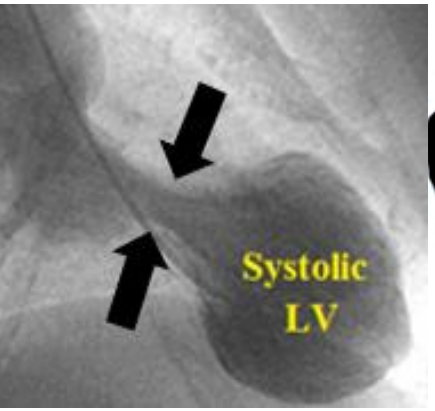
- QRS complex duration: ≥ 120 ms;
- Constant and bizarre morphology of QRS complexes (monomorphic);
- Slow rate: between 50 bpm and 130 bpm (usually between 70 and 85 bpm);
- Regular or almost regular R-R;
- Event SÂQRS different from basic rhythm SÂQRS;
- Onset and end of event, gradual and non paroxysmal. The former, marked by delayed or telediastolic premature ventricular contraction (initial beat with prolonged coupling) or with idioventricular escape if the basic rhythm was very slow; the end occurs by acceleration of sinus rhythm or by slowing of tachycardiac rhythm;
- Depressed sinoatrial activity, with frequent absence of P wave;
- AV dissociation: 70% of the cases;
- Frequent fusion beats at the onset and the end of the event;
- Capture and fusion beats, much more frequent than in paroxysmal VT;
- Frequent coexistence with extra systolic VT in its unstable form.

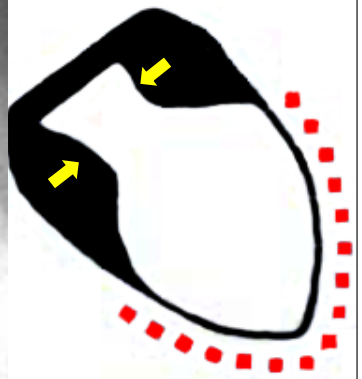
One Typical

Diastole



Systole

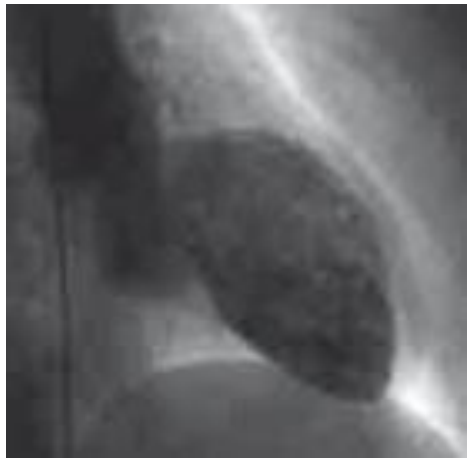




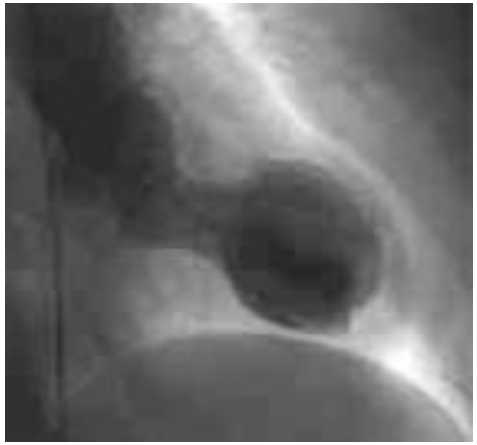
Apical akinesia and basal hyperkinesia

Three Atypical wall motion abnormalities in Takotsubo Cardiomyopathy e in acute phase

Diastole

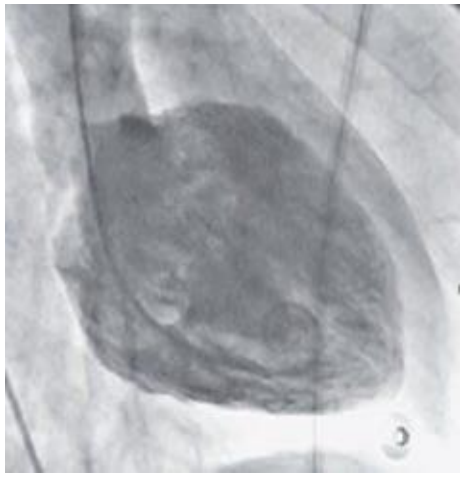


Systole

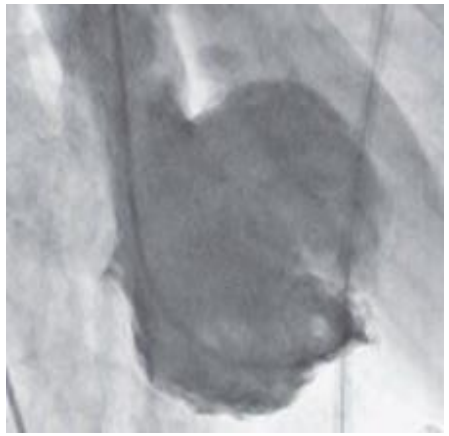


Mid-ventricular ballooning with basal and apical hyperkinesia

Diastole

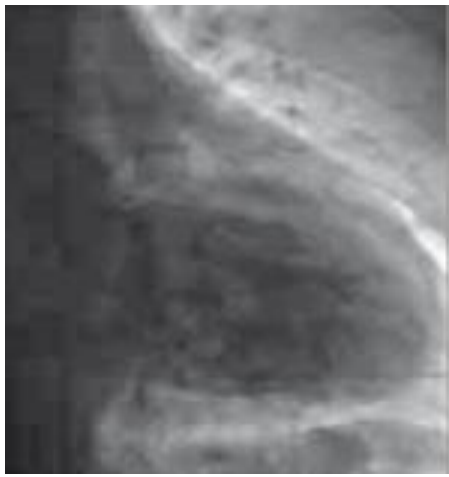


Systole

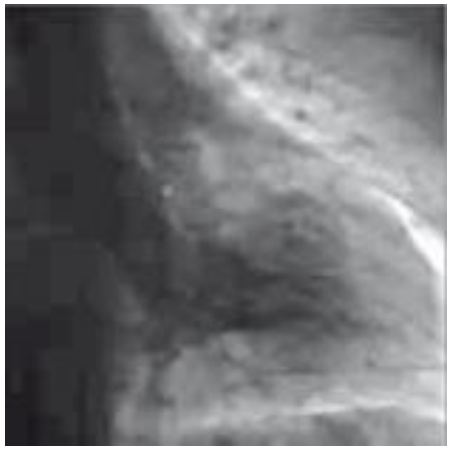


Basal, Reverse Takotsubo (Basal akinesia and apical hyperkinesia) The present case

Diastole



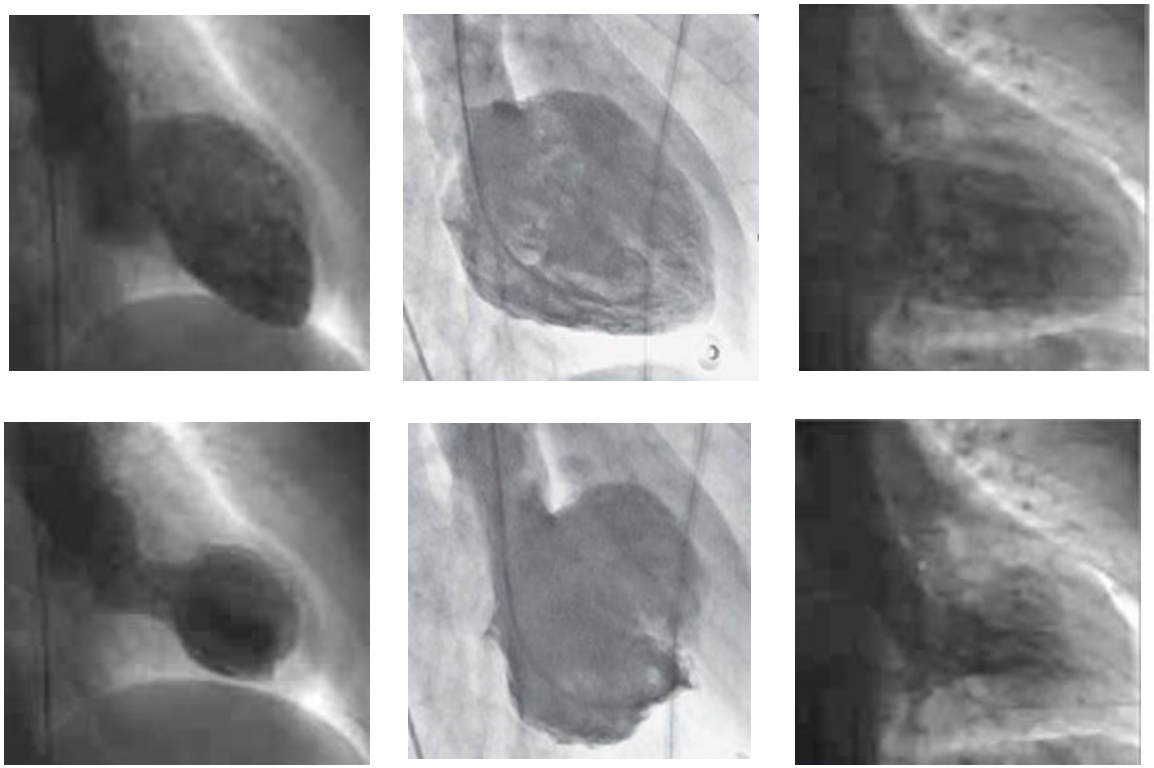
Systole



Focal TCM

Three atypical wall motion abnormalities in Takotsubo Cardiomyopathy in acute phase

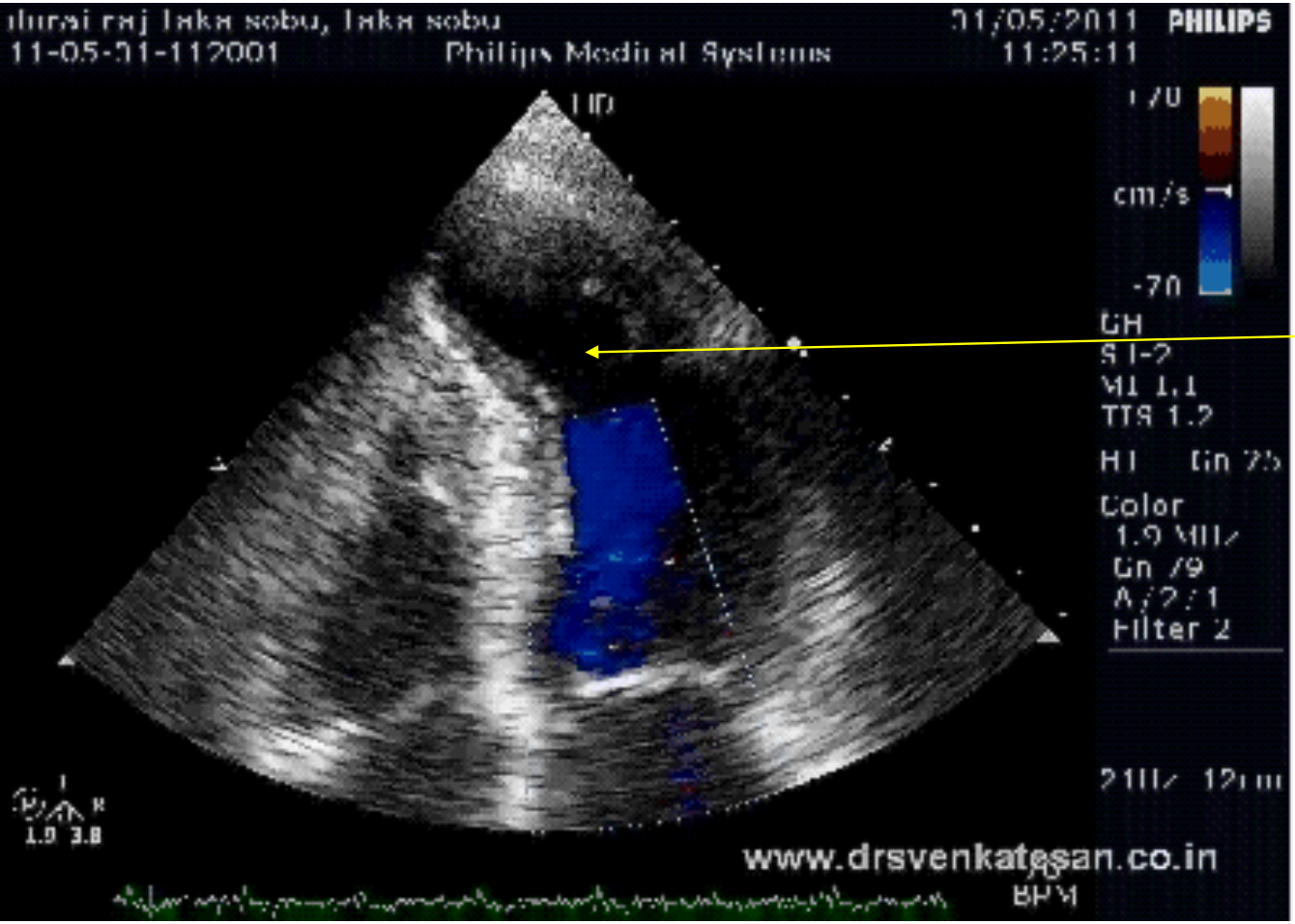
Left ventricular angiograms in right anterior oblique view (30°) during diastole and systole

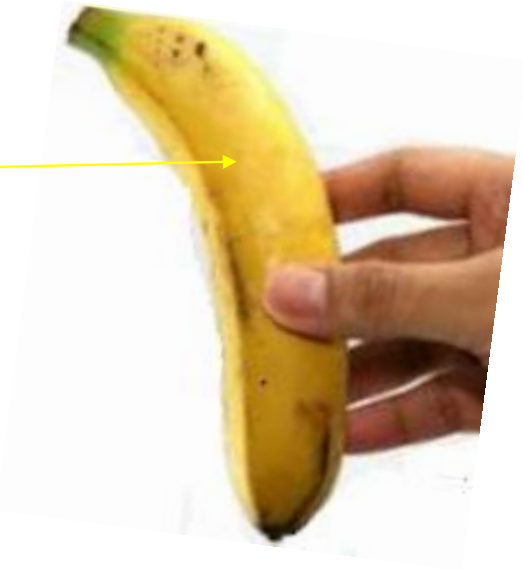


The 3 different atypical subtypes of TCM:

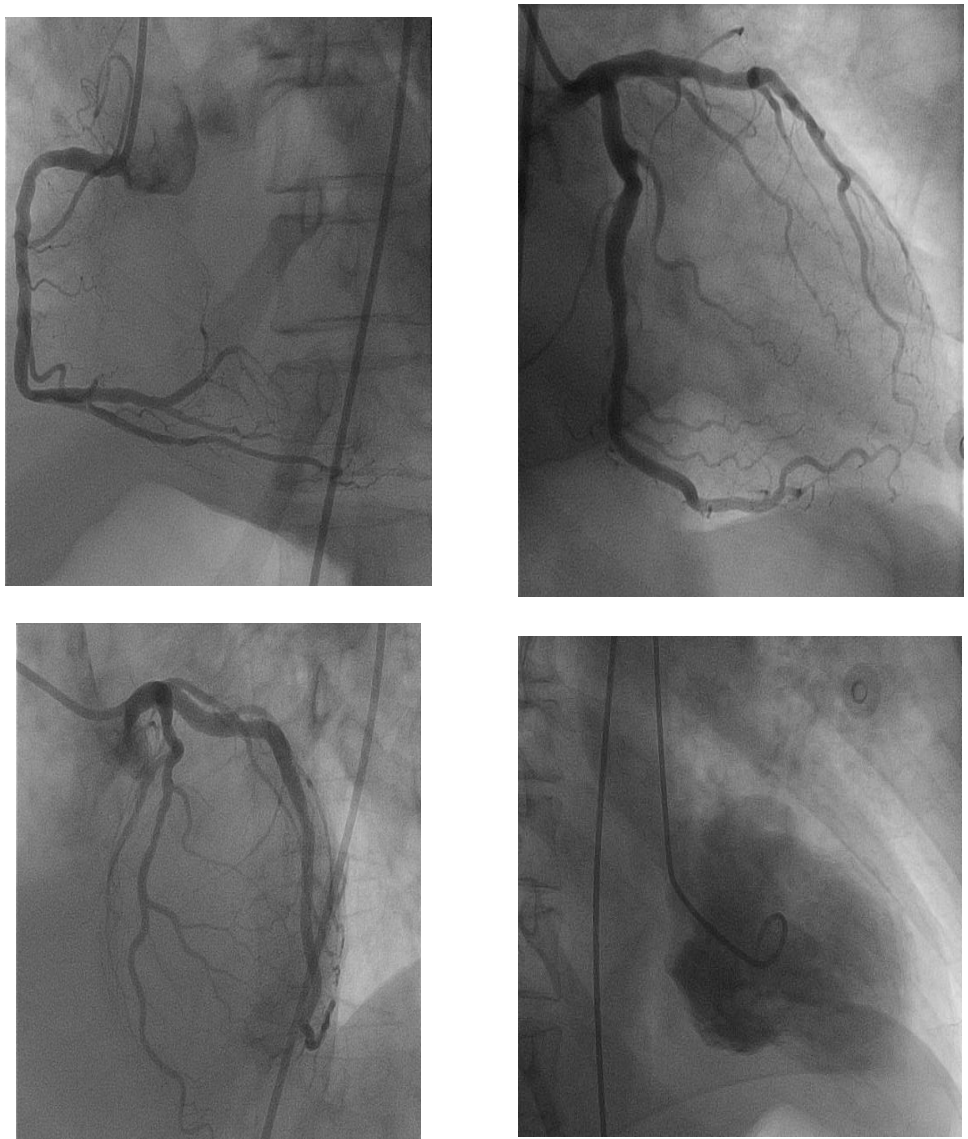
1. Midventricular,
2. Basal (the present case)
3. Focal.

The lower row shows the schematic of wall motion abnormalities corresponding to the angiograms above (blue, diastole; white, systole; blue dashed line, affected regions). LVEF indicates LVEF.

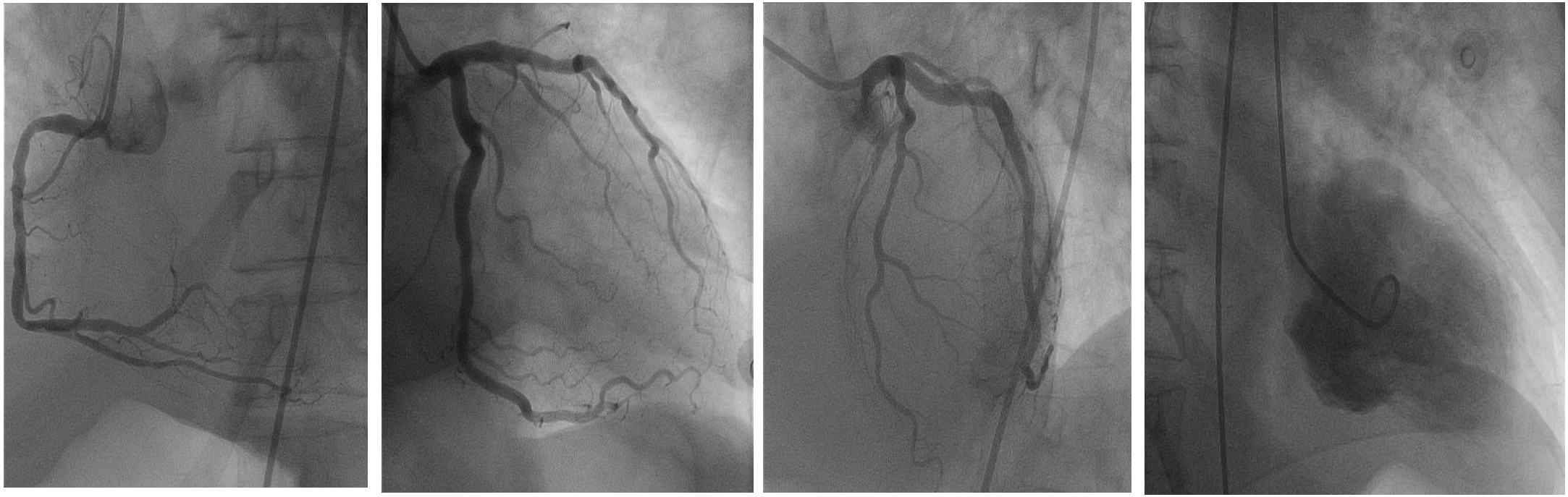




Echo show an elongated LV apex with some thinning . Note the LV apex goes out of plane with RV apex. Color Doppler revealed Trivial Mitral regurgitation. This type is called the **Banana type** (Elongation of LV apex > Widening)



LV systole - VE sístole



Coronary Angiography and ventriculography

Right coronary artery(RCA): Dominant, with multiple lesions, being greater than 40% in the proximal 1/3. **Posterior descending artery:** Moderate importance and no lesion. **Ventricular posterior branch of the RCA:** Moderate importance and no lesion. **Ventricular posterior branch of the RCA:** Moderate importance and no lesion. **Posterior descending artery:** Moderate importance and no lesion. **Predominance of coronary circulation:** Dominant right coronary artery.

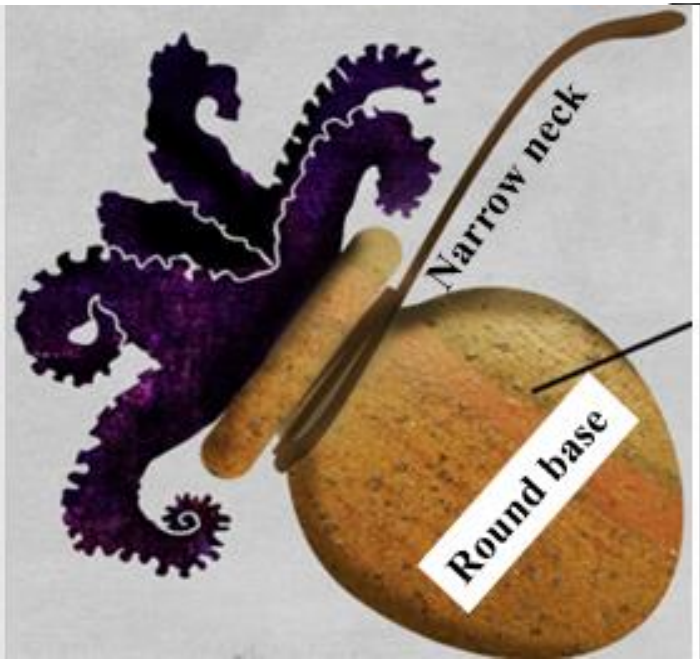
Left main coronary artery(LMCA): No lesion. **Left Anterior Descending artery(LAD):** Exceeding the apex, with multiple lesions, being greater than 40-50% in the middle 1/3. **1st diagonal artery:** Small importance and no lesion. **2nd diagonal artery:** Small importance and no lesion**. Left Circumflex artery (LCX):** It reaches the proximal 1/3 of the AV sulcus, with multiple lesions, being greater than 40% in the middle 1/3. **1st left marginal artery:** Small importance and with no lesion. **2nd left marginal artery:** Great importance and no lesion. Irregularities. **Diagonalis:** Moderate importance and no lesion. **Left ventricle:** Left ventricle with severe diffuse hypokinesis. **Conclusion:** Non-significant CAD in ADA/Cx and RCA. Severe LV systolic dysfunction. Severe mitral valve regurgitation. Hypokinesis +3/4+ middle-basal and +3/4+ basal (reverse Takotsubo syndrome?)

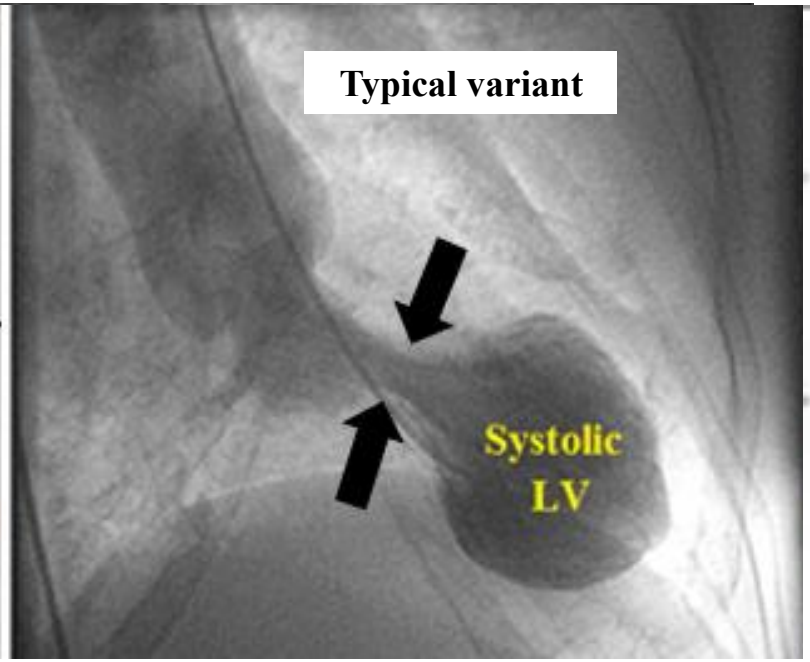
Takotsubo Cardiomyopathy (TCM)

Background

Other denominations: Takotsubo syndrome (TS), tako-tsubo-like left ventricular dysfunction, Broken heart syndrome, apical ballooning syndrome (ABS), stress-induced cardiomyopathy, transient left ventricular apical ballooning syndrome, transient left and/or right ventricular dysfunction or Gebrochenes-Herz-Syndrome.

Takotsubo cardiomyopathy (TCM) is a transient cardiac syndrome with left ventricular (LV) and or RV dysfunction characterized by apical akinesis and mimics acute coronary syndrome (ACS). It was first described in Japan in 1990 by Sato et al (**Sato 1990**). Patients often present with chest pain, have ST-segment elevation (STSE) on electrocardiogram (ECG), and have modest elevation in the cardiac enzymes and troponin levels consistent with acute myocardial infarction (AMI) (**Sato 1990; Kirusu2014**). However, when the patient undergoes cardiac angiography, LV apical ballooning is present, and there is no significant coronary artery stenosis. The Japanese word takotsubo translates to "octopus pot" resembling the shape of the LV during systole on imaging studies. The term "Takotsubo" was coined to describe the unusual shape of the LV during systole. Typically, the mid to apical segments of the LV are akinetic and the spared, basal walls exhibit compensatory hypercontractility. Takotsubo is a pot with round base and narrow neck used in Japan for trapping octopuses and has a similar appearance to this.

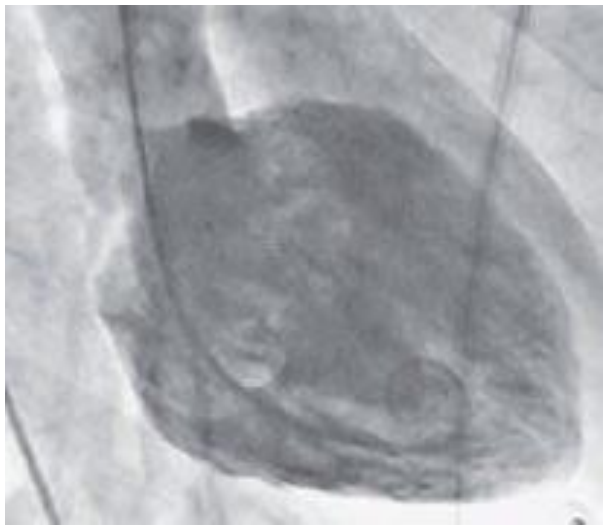


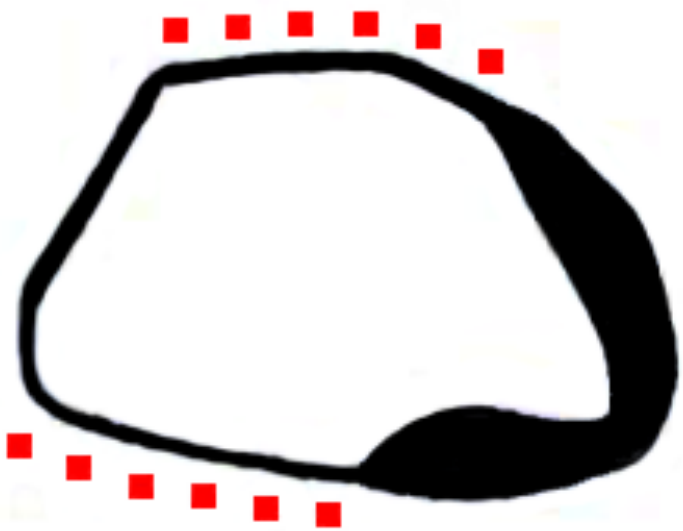


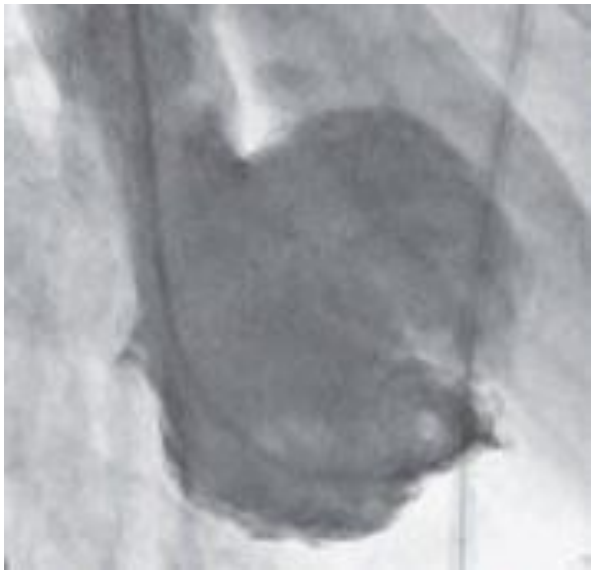
Takotsubo pot used by Japanese to trap octopus

Reversal Takotsubo cardiomyopaty or basal type (the present case)

Diastole **Diastole** **Systole**







Shimizu et al presented a 76-year-old man developed congestive HF due to severe mitral regurgitation (MR) secondary to papillary muscle dysfunction due to coronary artery spasm. after episodes of vasospastic angina. Echocardiography demonstrated LV apical akinesis with ballooning and deformity of the anterior mitral leaflet becoming concave toward the left atrium. The acetylcholine provocation test induced diffuse coronary vasospasm in the distal segments of both right and left coronary arteries and reproduced severe mitral regurgitation. Follow-up echocardiography demonstrated decreased MR with ameliorated apical wall motion. Coronary vasospasm remained refractory to antivasospastic medications and severe MR relapsed 1 month after discharge. Mitral valve annuloplasty with a Carpentier-Edwards physio ring was performed, and no recurrence of MR was observed despite some episodes of vasospastic angina. The authors speculate that vasospastic angina and the resultant apical wall motion abnormality caused tethering of the mitral subvalvular apparatus, leading to inappropriate mitral coaptation and severe regurgitation. Shimitzu (**Shimizu 2006**) described four types wall motion abnormalities in TCM in acute phase:.one typical and three atypical.

The possible underlying pathophysiology Pathophysiology

Normal myocardium utilizes approximately 90% of its energy from fatty acid metabolism at rest and with aerobic activity. During ischemia, this pathway is suppressed, and glucose is largely utilized instead, which results in impaired cardiac function. Patients with TCM are found to shift toward the glucose pathway despite relatively normal myocardial perfusion and lack of ischemia in LV segments (**Dorfman 2009**). The most commonly discussed possible mechanism for TCM is stress-induced catecholamine release, with toxicity to and subsequent stunning of the myocardium (**Boland 2015**). Other proposed mechanisms include multivessel epicardial coronary artery spasm, impairment of coronary microvascular function, and impaired myocardial fatty acid metabolism (**Sato 1990; Terefe 2007**). Myocardial regional differences in response to high levels of catecholamines (eg, apical segments more responsive to negatively inotropic epinephrine) appear to support the role of catecholamines in the pathogenesis of TCM (**Sato 1990**). Endomyocardial biopsy of patients with TCM demonstrates reversible focal myocytolysis, mononuclear infiltrates, and contraction band necrosis. The sympathetic/catecholamine theory is gaining momentum, because TCM was induced in rats exposed to physical stress and, in some instances, was prevented by pretreatment with an alpha blocker or beta blocker. Other evidence for this theory has been demonstrated through myocardial imaging studies using catecholamine analogues that evaluated cardiac sympathetic activity. Some authors have proposed a unifying hypothesis stating that in susceptible individuals, notably women, neurohormonal stimulation results in acute myocardial dysfunction, as reflected by the characteristic LV wall-motion abnormality of TCM. Whether this is triggered by multivessel spasm, thrombosis, epicardial vessel occlusion, or direct myocardial toxicity remains to be seen. These authors point out that the wall-motion abnormality of TCM can be seen in other conditions, including those with certain left anterior descending (LAD) lesions, (**Carrillo 2010**) making wall motion alone insufficient for the diagnosis of TCM (**Lindsay 2010**). Matrix metalloproteinase 8 (MMP-8) is the most potent type-I collagen protease. Such collagen mainly constitutes the transient fibrosis in TCM endomyocardial biopsies. High MMP-8 and tissue-inhibitor of matrix metalloproteinase-1 (TIMP-1) levels are implicated in ACS. Parkkonen et al (**Parkkonen 2017**) compared MMP-8 and TIMP-1 levels in consecutive TCM and ACS patients, and their association to TTC severity. Even with other differing factors considered, TIMP-1 differentiated T TCM from ACS better than TnT. In TCM, the low MMP-8/TIMP-1 molar ratio may reflect decreased proteolysis and increased transient fibrosis, perhaps in part explaining the left-ventricle impairment. Cases of TCM have been reported in the literature following cocaine, methamphetamine, and excessive phenylephrine use (**Afonso 2008; Dorfman 2009**). Exercise stress testing, which is known to cause increased levels of catecholamines, has resulted in false positives attributable to TCM (**Dhoble 2008**). Studies have found that patients with TCM have, by a statistically significant margin, higher levels of serum catecholamines (norepinephrine, epinephrine, and dopamine) than do patients with MI (**Buchholz 2007**). The apical portions of the LV have the highest concentration of sympathetic innervation found in the heart and may explain why excess catecholamine's seem to selectively affect its function (**Dorfman 2009**).

Main hypothesis related the possible underlying pathophysiology

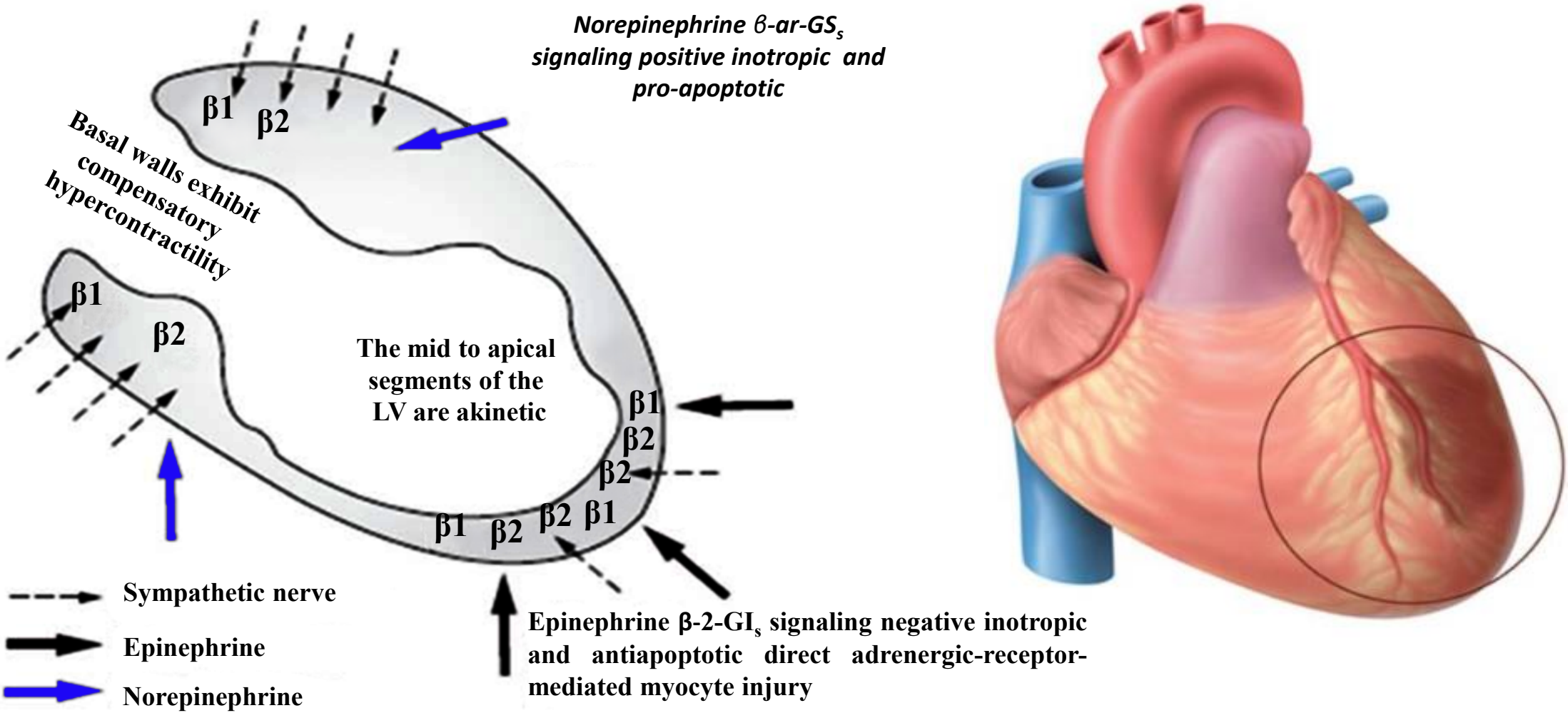
1. **Wraparound LAD**: The LAD supplies the anterior wall of the LV in the majority of patients. If this artery also wraps around the apex of the heart, it may be responsible for blood supply to the apex and the inferior wall of the heart. Some researchers have noted a correlation between TCM and this type of LAD (**Ibanez 2004**). Other researchers have shown that this anatomical variant is not common enough to explain TCM (**Inoue2005**). This theory would also not explain documented variants where the midventricular walls or base of the heart does not contract (akinesis).

2. **Multivessel Epicardial Coronary Artery Spasm (Transient vasospasm):** Some of the original researchers of TCM suggested that multiple simultaneous spasms of coronary arteries could cause enough loss of blood flow to cause transient stunning of the myocardium. Other researchers have shown that vasospasm is much less common than initially thought (**Tsuchihashi 2001**). It also has been noted that when there are vasospasms, even in multiple arteries, that they do not correlate with the areas of myocardium that are not contracting (**Abe 2003**).

3. **Microvascular dysfunction:** The theory gaining the most traction is that there is dysfunction of the coronary arteries at the level where they are no longer visible by coronary angiography. This could include microvascular vasospasm, however, it may well also have some similarities to diseases such as diabetes mellitus. In such disease conditions the microvascular arteries fail to provide adequate oxygen to the myocardium.

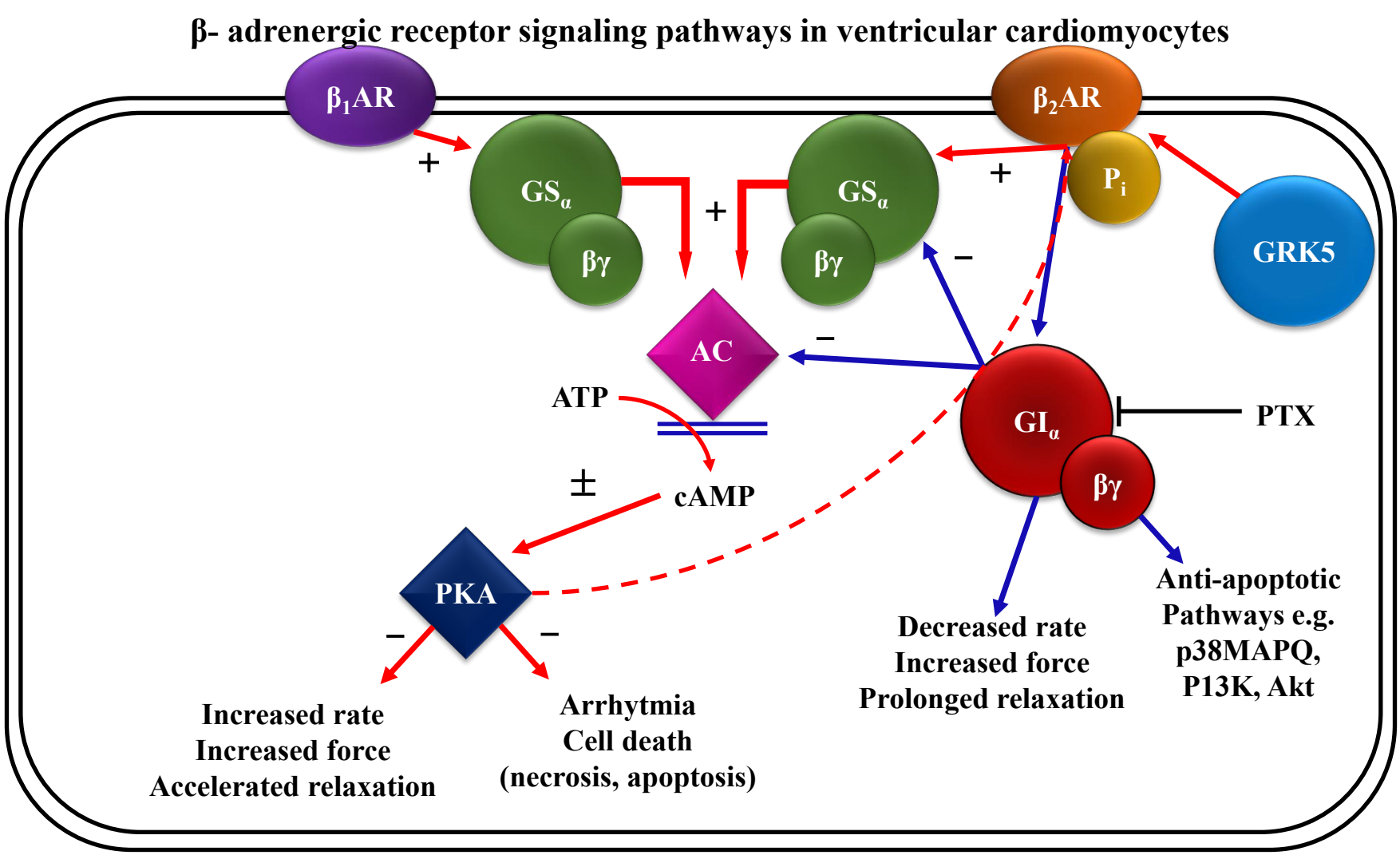
4. **Exaggerated sympathetic stimulation/catecholamine Cardiotoxicity**: TCM is a unique clinical condition of acute HF and reversible LV dysfunction frequently precipitated by sudden emotional or physical stress. There is growing evidence that exaggerated sympathetic stimulation is central to the pathogenesis. Precisely how catecholamine's mediate myocardial stunning in TCM remains incompletely understood; but possible mechanisms include epicardial spasm, microvascular dysfunction, direct adrenergic-receptor-mediated myocyte injury, and systemic vascular effects that alter ventricular-arterial coupling. Risk factors that increase sympathetic tone and/or catecholamine sensitivity may render individuals particularly susceptible to TCM during episodes of acute stress Wittstein et al (**Wittstein 2016**) compared admission plasma catecholamine concentrations between a group of 13 patients with TCM who had transient apical ballooning and a group of 7 patients hospitalized for AMI (Killip class III). The plasma levels of both epinephrine and norepinephrine were remarkably increased in the TCM patients. The authors suggested that the remarkably elevated catecholamine levels might be the main pathogenetic factor.

Mechanism of remote wall motions defects in STEMI An intrinsic Takotsubo Effect?



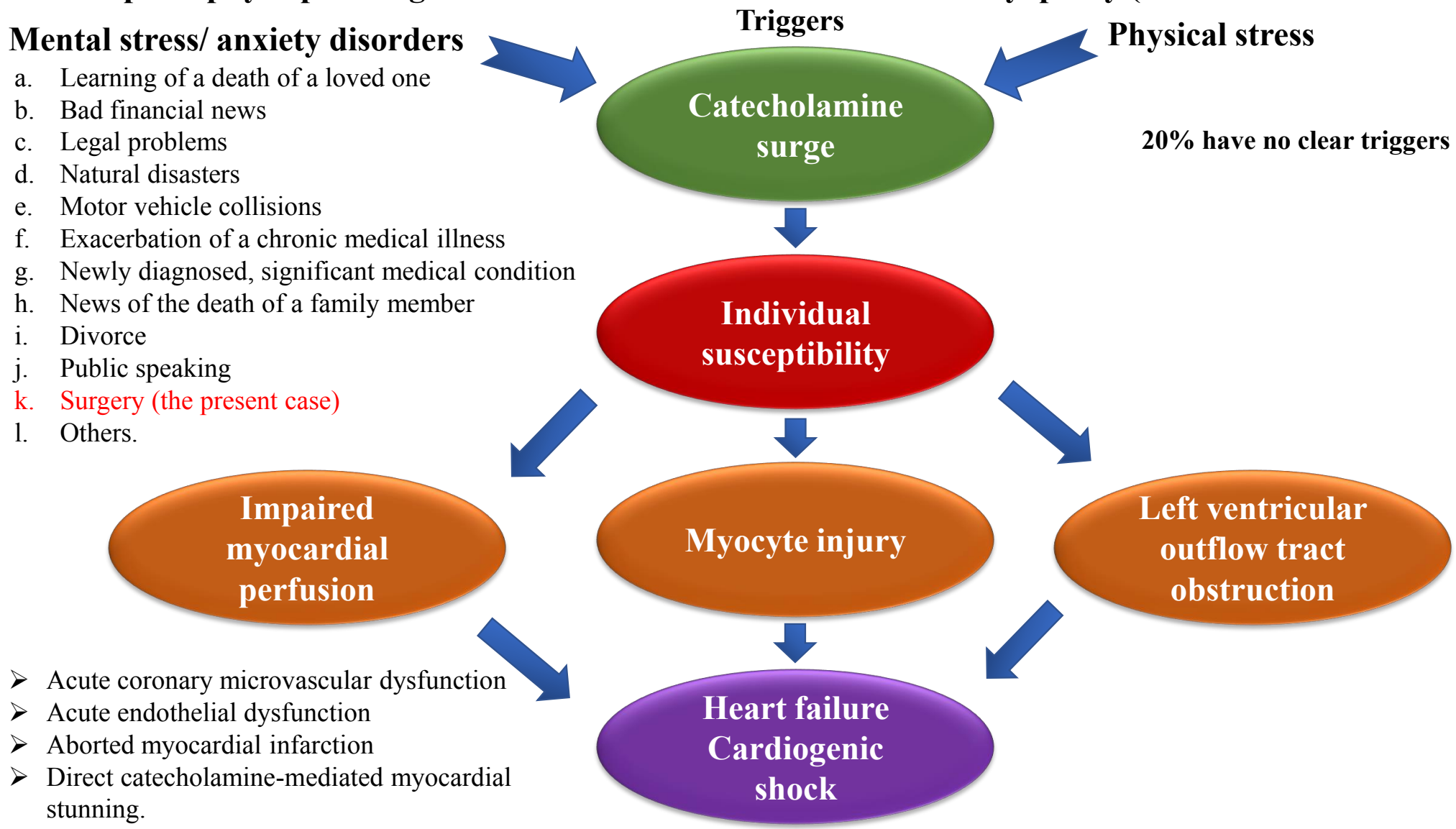
The image depicts the wide variation in the density of β-receptors in heart. The stress of MI can result in varying degrees of wall motion defect. It is important to realize the wall motion defect in STEMI has two components. One is related to ischemia and other is due to excess catecholamine's. This explains many of the unexplained remote wall motion defects during STEMI .This may be referred to as Intrinsic Takotsubo effect !

4. **Continuation:** norepinephrine might evoke basal hyperkinesis, increasing mechanical wall stress at the apex and thereby increasing end-diastolic pressure and BNP levels.() However, elevated catecholamine levels are not uniformly found in patients with TCM. High plasma catecholamine levels in patients with pheochromocytoma are well known to induce reversible cardiomyopathy (**Frustaci 1991**). The myocardial histological changes in TCM strikingly resemble those seen in catecholamine cardiotoxicity in both animals (**Movahed 1994**) and humans. These changes, which differ from those in ischemic cardiac necrosis, include contraction band necrosis, neutrophil infiltration, and fibrosis. These findings probably reflect consequences of high intracellular concentrations of Ca^{2+}, and it has been proposed that Ca^{2+} overload in myocardial cells produces the ventricular dysfunction in catecholamine cardiotoxicity (**Frustaci 1991**). Although diffuse HF can produce high circulating catecholamine concentrations, the attained levels are not nearly as high as in TCM and by definition would not explain the TCM pattern. Because circulating epinephrine exerts far more potent hormonal effects on the heart than norepinephrine does, TCM could in particular reflect epinephrine-induced toxicity. Concurrent cardiac neuronal and adreno medullary hormonal stimulation might occur, and this combination accompanies emotional distress. Lyon et al (**Lyon 2008**) have hypothesized that the high circulating epinephrine levels might trigger a switch in cardiomyocyte intracellular signaling after occupation of β_2-adrenoceptors from Gs protein to Gi protein coupling. combination of myocardial necrosis and decreased β-adrenoceptor responsiveness with high local catecholamine concentrations that cause both abnormalities. The heart stands out among organs of the body in terms of dependence on neuronal uptake for inactivating catecholamine's in the extracellular fluid (**Goldstein 2003**). High circulating catecholamine levels such as in pheochromocytoma can interfere with the neuronal uptake process (**Eldadah 2004**) and augment occupation of adrenoceptors on myocardial cells. These findings help to explain why emotional distress would induce mainly cardiac toxicity as a result of high plasma catecholamine levels despite being delivered to all organs via the arterial blood. In summary, the available pathophysiological. apical ballooning that characterizes TCM ; however, the LV apex contains a higher concentration of adrenoceptors. Thus, myocardial responsiveness to adrenergic stimulation is pronounced in the apex (**Mori 1993**). In addition, cardiac sympathectomy prevents brain-mediated cardiac injury (**Novitzky1986**). Therefore, TCM may reflect stunned myocardium from a neurogenic source. Animal studies have reported decreased inotropic responses to norepinephrine in the setting of catecholamine-induced cardiomyopathy (**Fripp1981**) that is associated with a decreased number of myocardial β-adrenoceptors. Thus, TCM might reflect a information indicates that the apical ballooning that characterizes TCM reflects toxic high local concentrations of catecholamine's, not coronary artery or microvascular disease. The pattern of LV dysfunction may result from both myocardial cellular rupture and withdrawal of β-adrenoceptors. The “first cause” would be neurogenic, with the precipitant sudden, unexpected, severe emotional distress. Stunning-like involvement at the left ventricular base also has been observed in patients with pheochromocytoma and even in TCM patients (**Bonnemeier2006**). Individual differences in the anatomy of cardiac sympathetic innervation or the distributions of adrenoceptors might result in the involvement of a variety of LV myocardial segments.



Protein kinase A **PKA**; Paclitaxeln **PTX;** G Protein-Coupled Receptor Kinase 5 **GRK5;** β-1 adreno receptor ; β-2 adreno receptor; Gsα subunit is a heterotrimeric G protein subunit that activates the **cAMP**-dependent pathway by activating adenylyl cyclase; G β γ is a tightly bound dimeric protein complex, composed of one Gβ and one Gγ subunit, and is a component of heterotrimeric G proteins; AC Adenylyl cyclase enzyme catalyse the conversion of adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate

Proposal physiopathological mechanisms for Takotsubo Cardiomyopathy (modified from Prasad 2008)



5. Neurogenic Stunned Myocardium (Mid-ventricular obstruction) apical stunning: It also has been suggested that a mid-ventricular wall thickening with LVOT obstruction is important in the pathophysiology (**Merli 2006**). The cardiac functional and ECG abnormalities in TCM might reflect activation of central neurogenic mechanisms analogous to those evoked by subarachnoid hemorrhage (**Benarroch 1993**). Intracranial pathology can produce the same myocardial histopathological findings seen in TCM. Because the basal myocardium has a somewhat higher norepinephrine content (**White 1995**) and greater density of sympathetic nerves than the apical myocardium.

6. Low MMP-8/TIMP-1: Matrix metalloproteinase 8 (MMP-8) is the most potent type-I collagen protease. It constitutes the transient fibrosis in TTC endomyocardial biopsies. High MMP-8 and tissue-inhibitor of matrix metalloproteinase-1 (TIMP-1) levels are implicated in ACS. TTC, a form of acute HF , mimics MI with similar ECG and cardiac enzyme findings (**Prasad 2008**). In an acute setting, the TTC and ACS are difficult to distinguish without a coronary angiogram. This invasive method in TTC patients show no signs of occlusive CAD, and left ventriculograms reveal a typical transient contraction abnormality which usually resolves within weeks. Previous attempts to differentiate TTC from ACS using current non-invasive methods such as ECG, cardiac enzymes, or acute-phase reactants such as C-reactive protein resulted in inadequate resolution and controversy (**Parkkonen 2014; Sharkey 2008**). Matrix metalloproteinases (MMPs) maintain extracellular matrix (ECM) under normal conditions with their ability to cleave almost all extracellular proteins such as collagens. Structurally related MMPs are secreted mainly by inflammatory cells, but also by endothelial and smooth muscle cells (**Herman 2001**). MMP activity is tightly controlled by tissue inhibitors of matrix metalloproteinases (TIMPs) (**Brew 2000; Pussinen 2013**). Disturbance in MMP and TIMP balance may raise or lower the ECM fibrotic material and accompany inflammation. Such changes, especially in MMP-8 and TIMP-1 levels, accompany the pathogenesis of atherosclerosis and ACS (**Pussinen 2013; Djuric 2010**). In myocardial ECM, an altered MMP and TIMP balance may lead to structural and functional changes, and subsequent impairment of cardiac function as seen in HF and various cardiomyopathy patients (**Spinale 2007; Spinale 2013**). LV presentation in TTC varies from normal LVEF to cardiogenic shock. Factors affecting the severity of contraction abnormality and HF in TTC are unknown (**Akashi 2015**). Endomyocardial biopsies of acute TTC patients show transient ECM fibrosis (**Nef 2007**). Altered fibrosis due to MMP-8 and TIMP-1 imbalance may play a role in pathogenesis. Reports of small TTC patient-series showed similar MMP and TIMP profiles as in hypertension- and diastolic HF patients, but include no direct comparisons to ACS (**Essa 2012**). Parkkonen et al compared MMP-8 and TIMP-1 levels in consecutive TTC and ACS patients, and their association to TTC severity. IMP-1 differentiated TTC from ACS better than TnT. In TTC, the low MMP-8/TIMP-1 molar ratio may reflect decreased proteolysis and increased transient fibrosis, perhaps in part explaining the LV impairment (**Parkkonen 2017**).

Then . . . the following questions arise
When systemic stress can have a profound effect on myocardium , what about local stress ?
Acute STEMI is a huge stress for the heart . . . isn't . If so , can it alter the wall motion defect in adjacent or remote myocardial segments independent of ischemia ?
With the distribution of adrenergic receptors showing huge variation , we do not know how an acutely ischemic heart spills the adrenaline all over . Is there a pattern to it ? or it happens at random? Further , the response to accumulated catecholamine's is not going to be uniform. This will explain why certain patients go into ischemic LVF, very early in the course of STEMI even before the myocardium is necrosed. It will also explain the benefits that accrue in selected patients who receive early IV β blockade (Which is of course currently not popular after COMET study: The Carvedilol Or Metoprolol European Trial!)

Final message

Severe transient ballooning wall motion defect in LAD region (LV apex) with isolated RCA lesion and inferior Infarct was observed.

The question raised is this

Can the stress of Inferior STEMI . . . result in apical Takotsubo like effect ?

Although the exact etiology of TCM is still unknown, the syndrome appears to be triggered by a significant emotional or physical stressor (**Boland 2015**). The stress is often emotional, neurological or general systemic stress.
The modified Mayo Clinic criteria for diagnosis of TCM (**Kawai 2007**) can be applied to a patient at the time of presentation. The diagnosis requires the presence of all four of the following (**Prasad 2008**):

1. *Transient hypokinesis, dyskinesis, or akinesis of the LV Midsegments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present*
2. *Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture*
3. *New ECG abnormalities (either ST-SE and/or T-wave inversion) or modest elevation in the cardiac troponin level*
4. *Absence of Adrenal pheochromocytoma (**Chiang 2016**) or myocarditis (**Terefe 2007**).*

In both of the above circumstances, the diagnosis of TCM should be made with caution, and a clear stressful precipitating trigger must be sought. There are rare exceptions to these criteria such as those patients in whom the regional wall motion abnormality is limited to a single coronary territory. It is possible that a patient with obstructive coronary atherosclerosis may also develop apical ballooning syndrome (ABS). However, this is very rare in our experience and in the published literature, perhaps because such cases are misdiagnosed as an ACS.

A correlation between TCM and acute emotional stress has been discussed under the context of a toxic catecholaminergic effect. Other studies have found higher incidences of anxiety disorders and major depression in patients with TCM (**Christensen 2016, Madias 2016a, Madias 2016b, El-Sayed 2012**). Müller et al studied personality traits, affective symptoms and coping with stress in a sample of 22 patients with TCM (post-acute interval: 5 years; mean age: 70.9±12 years) compared with 20 patients with major depression. The protocol for the study was approved by the Ethics Committee of the University of Erlangen-Nuremberg, and it is conformed to the provisions of the Declaration of Helsinki. All probands gave their informed consent and their anonymity was preserved.
For the study the authors used the following rating scales:

- The beck depression inventory II (beck et al. 2006, German version),
- The IKP-G and ikg-eg. (Andresen 2006, German version) and
- The SVF (janky W, Erdmann G, Kallus W & Boucsein W 1997, German version).

Depressive symptoms were significantly elevated for the patients with major depression compared with the TCM patients (finding should be addressed as part of the clinical management of TCM and its post-acute treatment through early psychotherapeutic interventions (**Müller 2017**).

Etiology

The exact etiology of TCM is still unknown, but several theories have been proposed and are being investigated (**Lindsay 2010**). These include the following (**Afonso 2008; Khallafi2008**): 1) multivessel coronary artery spasm, 2) impaired cardiac microvascular function, 3) impaired myocardial fatty acid metabolism, 4) ACS with reperfusion injury, 5) endogenous catecholamine-induced myocardial stunning and microinfarction.

Risk factors

a. A significant emotional or physical stressor or neurologic injury typically precedes the development of the TCM (**Boland 2015**). Stressors include the following:
b. Learning of a death of a loved one
c. Bad financial news
d. Legal problems
e. Natural disasters
f. Motor vehicle collisions
g. Exacerbation of a chronic medical illness
h. Newly diagnosed, significant medical condition
i. News of the death of a family member
j. Divorce
k. Public speaking
l. Surgery
m. Intensive care unit (ICU) stay
n. Use of or withdrawal from illicit drugs.
o. After near-drowning episodes.(**Citro 2008**)
p. Seizures may also trigger TCM, but it is rare for TCM to result in sudden unexpected death in epilepsy (SUDEP).(**Finsterer 2015**)

In a systematic review of 104 cases of TCM (1965-2013), investigators noted that young patients with TCM were more likely to be female and physical stress was more likely to exacerbate TCM than mental stress was.(**Wang 2015**) The clinical presentation of TCM in this patient population was similar to that of other cardiac diseases (eg, CAD) but could be differentiated from them by means of echocardiography in conjunction with ventriculography.(**Wang 2015**) Similarly, the International Takotsubo Registry reported that patients with

TCM, as compared with ACS patients, were more likely to be female (89.8%) and that physical triggers were more common than emotional triggers (36% vs 27.7%), though more than one quarter (28.5%) had no clear triggers. Patients with TCM also had higher rates of neurologic or psychiatric disorders and a significantly lower LVEF. The two groups (TCM and ACS) had similar rates of severe inpatient complications (eg, shock, death), and independent predictors of such complications included physical triggers, acute neurologic/psychiatric diseases, elevated troponin levels, and low LVEF (**Templin 2015**).

Epidemiology

I. **Prevalence:** TCM is diagnosed approximately in 1–2% of patients with history, signs and symptoms similar to acute myocardial infarction (AMI). The actual prevalence of TCM is unknown, but this syndrome likely accounts for 1%-2% of all cases of suspected AMI (**Pilgrim 2008; Kazakauskaite 2014; Kyriacou 2012** (http://www.escardio.org/communities/councils/ccp/e-journal/volume10/Pages/Takotsubo-Cardiomyopathy-identification-treatment.aspx#.VNkDbPnF_To)**; Terefe 2007**). Studies reported that 1.7-2.2% of patients who had suspected ACS were subsequently diagnosed with TCM (**Bybee 2004; 2003**).

II. **Race:** patients are typically Asian or Caucasian., 25% African American and 2.8% were other races. African American race and hypertension were found to be independent predictors of event stroke (**Dias 2016**).

III. **Age:** Literature reviews report a mean patient age of 67 years, though cases of TCM have occurred in children and young adults. Nearly 90% of reported cases involve postmenopausal women. In ≈90% of cases menopausal women.

IV. **Sex:** About 90% of cases reported are in post-menopausal women ages 58-75 years old. The diseases which predominantly occur in women are TCM, microcirculation disorders and spontaneous coronary artery dissection (**Regitz-Zagrosek 2017**). Most patients with TCM, as compared with ACS patients, were more likely to be female (89.8%) and that physical triggers were more common than TCM are postmenopausal women. A systematic review of 14 studies by Gianni et Al (**Gianni2006**) and Prasad et al showed 89% and 90% female predominance with age range of 58-77 and 58-75 years respectively.

V. **Circadian Rhythm Pattern:** unlike ACS, for which peak occurrence is the morning hours, TCM events are most prevalent in the afternoon, when stressful triggers may be more likely to take place (**Finsterer 2015**). Unlike ACS, for which the peak occurrence is during the morning hours, TCM events are most prevalent in the afternoon, when stressful triggers are more likely to take place (**Sharkey 2012**).

History

Classical Clinical complain

- Stressful trigger? One of the more unique features of TCM is its association with a preceding emotionally or physically stressful trigger event, occurring in approximately two thirds of patients.
- Patients may appear anxious
- Chest pain (64%) were reported more often than other symptoms (**Glaveckaitė 2016**)
- General weakness (45%)
- Dyspnea
- Palpitations
- Nausea
- Vomiting
- Diaphoretic
- Syncope.

Physical examination findings are nonspecific and often normal, but the patient may exhibit the clinical appearance of ACS or acute congestive heart failure (CHF). Tachydysrhythmias and bradydysrhythmias have been reported, but the average heart rate in one review was 102 bpm (**Dorfman 2009**). Hypotension can occur from a reduction in stroke volume because of acute LV systolic dysfunction (acute HF in 20-40% of the cases) or acute outflow tract obstruction (LVOTO) cardiogenic shock. Why**?** Acute multivessel coronary spasm, provocation induced vasospasm(27%) (**Pilgrim 2008**), acute coronary microvascular dysfunction, acute endothelial dysfunction, aborted myocardial infarction, (spontaneous recanalization, warp around LDA), direct catecholamine-mediated myocardial stunning.

Murmurs and rales may be present on auscultation in the setting of acute pulmonary edema.

ECG repolarization changes STSE, QT prolongation, inverted T waves, arrhythmias.

Modest cardiac enzyme and troponin rise. Serum catecholamine's 30 x normal. Enter PPCI protocol Normal coronary angiography (no culprit coronary disease , no coronary intervention, apical and usually mid LV wall motion abnormality > 1 coronary territory, preserved basal LV contraction, LV dysfunction recovers over days-weeks, myocardial stunning. A large systematic review found that patients with TCM tend to have a lower incidence of traditional cardiac risk factors, such as hypertension, hyperlipidemia, diabetes, smoking, or positive family history for cardiovascular disease (**Pilgrim 2008**). Moreover, patients with TCM may have a lower incidence of traditional cardiac risk factors (eg, hypertension, hyperlipidemia, diabetes, smoking, positive family history for cardiovascular disease) (**Wang 2015**).

Physical Examination

Differential diagnosis

With Acute coronary syndrome. TCM can mimic both STEMI and NSTEMI but management is different. Several ECG abnormalities have been identified which might help to differentiate TCM with and without from STEMI and NSTEMI, respectively.

1. The distribution of the wall-motion abnormality does not conform to any major coronary vessel bed.
2. If the LAD occlusion is distal to first diagonalis (D1), the injury vector (lesion dipole) is directed anteriorly and slightly downward, resulting in an isoelectric or STSE in II, III, and aVF. In TCM the ECG pattern is also typical of STSEMI due to occlusion that is distal to the first diagonal branch (Dg1) (**Bayés de Luna 2008**). Consequently, distal occlusion of LAD is not easy for differential diagnosis with TCM (**Carrillo 2010**).

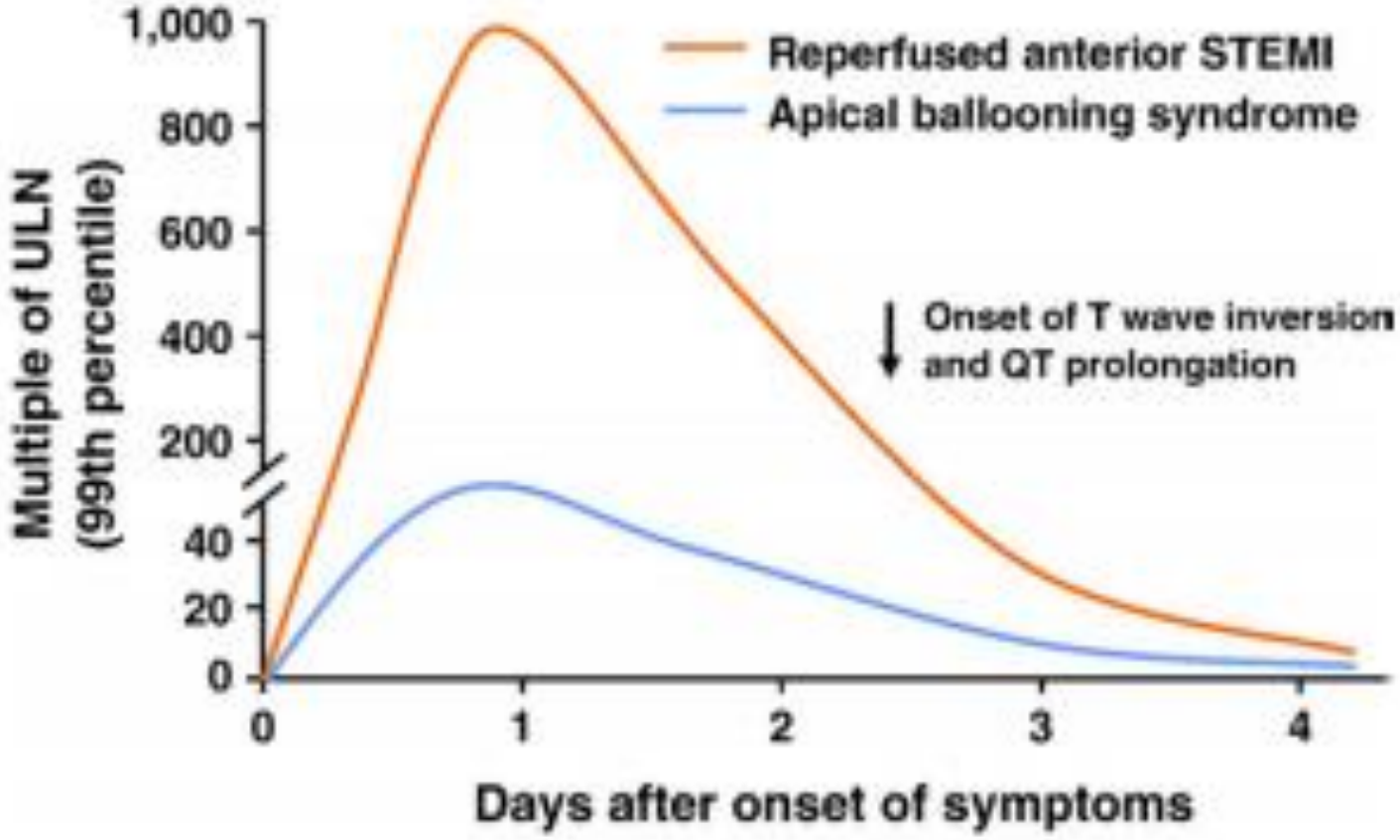
3. There are several reasons why the ECG is still not considered a useful tool in differential diagnosis between TCM and ACS. These include recent awareness of the syndrome, lack of evidence-based therapy, and, a wide range of ECG features according to race, patient characteristics, wall motion abnormalities, triggers, and time from symptoms onset. at the moment, only coronary angiography can rule out one of the two diagnoses with good certainty (**Guerra 2017**).

4. Looi et al studied 35 TCM patients had STE on admission. Compared with STEMI patients they had less prominent STE (median peak elevation 2mm vs. 3mm), less reciprocal ST-segment depression and no abnormal Q-waves. By Day 2 all STEMI patients had pathological Q-waves but none of the TCM patients. Compared with NSTE-TC patients, NSTEMI patients had more ST-segment depression (28.2% vs. 0%, P), but less T-wave inversion on admission. By Day 2 the ECG criterion which best distinguished NSTE-TC from NSTEMI was the presence of T-wave inversion in ≥6 leads (sensitivity 74%, specificity 92%) (**Loi 2015**).

5. Retrospective analysis of the ST-segment changes was done by Vervaat et al (**Vervaat 2015**) on the triage ECGs of 37 patients with TCM (34 female) and was compared to the triage ECGs of 103 female patients with acute anterior STEMI. The latter group was divided into the following subgroups: 46 patients with proximal, 47 with mid and 10 with distal LAD occlusion. Three ST-segment based ECG features were investigated: Existing criterion for differentiating anterior STEMI from TC: ST-segment depression >0.5mm in lead aVR + ST-SE ≤1mm

5. Continuation….. in lead V1, frontal plane, ST-vector, and mean amplitude of ST-segment deviation in each lead. Given the consequences of missing the diagnosis of an acute anterior STEMI the diagnostic accuracy of the ECG criteria investigated in this retrospective study were insufficient to reliably distinguish patients with TCM from patients with an acute anterior STEMI. To definitely exclude the diagnosis of an acute anterior STEMI coronary angiography, which remains the gold standard, will need to be performed.
6. Tamura et al retrospectively examined whether ECG, using the magnitude of STSE measured at the J point, could differentiate 62 patients with TCM from 280 with acute anterior STEMI. Patients with acute anterior STEMI were divided into following subgroups: 140 with LAD occlusions proximal to the first diagonal branch (STEMI-P), 120 with LAD occlusion distal to and proximal to the second diagonal branch (STEMI-M), and 20 with LAD occlusions distal to the second diagonal branch (STEMI-D). TCM had a much lower prevalence of STSE ≥1 mm in lead V1 (19.4%) compared to acute anterior -STEMI (80.4%), acute anterior -STEMI-P (80.7%,), acute anterior -STEMI-M (80%), and acute anterior-STEMI-D (80%). STSE≥1 mm in ≥1 of leads V3 to V5 without STSE≥1 mm in lead V1 identified TCM with sensitivity of 74.2% and specificity of 80.6%. Furthermore, this criterion could differentiate TCM from each acute anterior-STEMI subgroup, with similar diagnostic values. The authors concluded that using the magnitude of ST-SE measured at the J point, a new ECG criterion is proposed with an acceptable ability to differentiate TC from acute anterior-STEMI (**Tamura 2011**).
7. A mild to moderate increase in cTnI is found as in the TCM.
8. Complete recovery of LV function in days or weeks
9. Patients with TCM exhibit a typical cardiac biomarker profile, which might serve as an additional tool to distinguish these patients from those with STEMI or NSTEMI at an early stage. Nevertheless, obstructive coronary artery disease has to be ruled out in any case, but preferably, with non-invasive imaging modalities. Ratios of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and myoglobin, NT-proBNP and troponin T (TnT), NT-proBNP and creatinekinase-MB (CK-MB) were compared in patients with TCM (n=39), patients with ACS STEMI, (n=48) and patients with ACS NSTMI (NSTEMI, n=34). Biomarkers were recorded serially at admission and at the three consecutive days. Optimal cut-off values to distinguish TCM from STEMI and NSTEMI At admission a NT-proBNP (ng/l)/myoglobin (µg/l) ratio of 3.8, distinguished TCM from STEMI (sensitivity: 89%, specificity: 90%), while a NT-proBNP (ng/l)/myoglobin (µg/l) ratio of 14 separated well between TCM and NSTEMI (sensitivity: 65%, specificity: 90%). Best differentiation of TCM and ACS was possible with the ratio of peak levels of NT-proBNP (ng/l)/TnT (µg/l). A cut-off value of NT-proBNP (ng/l)/TnT (µg/l) ratio of 2889, distinguished TCM from STEMI (sensitivity: 91%, specificity: 95%), while a NT-proBNP (ng/l)/TnT (µg/l) ratio of 5000 separated well between TCM and NSTEMI (sensitivity: 83%, specificity: 95%). Conclusions: TCM goes along with a singular cardiac biomarker profile, which might be useful to identify patients with TCM among patients presenting with ACS (**Fröhlich2012**).

10. Using Magnetic resonance image, TCM was associated with a significantly lower left atrium emptying fraction (LA-EF) compared to anterior STEMI patients with a deterioration of both the passive and the active phase of LA function. However, data indicate that in TCM the LA performance recovers during follow-up similar to the LV contraction abnormalities. Consequently, transient LA dysfunction seems to be an additional feature of TCM together with the distinct impairment of LV and/or RV function (**Stiermaier 2017**).



Kinetics of cardiac troponin T release in patients with TCM versus acute anterior STEMI treated with mechanical reperfusion within 3 hours of symptom onset. ULN, Upper limit of normal.

Major, minor and exclusion criteria diagnosis for Takotsubo Cardiomyopathy

I. Major criteria

a) Transient apical ballooning with hypercontractility of the basal segments

b) ST-T abnormalities on ECG mimicking acute coronary infarction

c) No evidence of coronary obstruction or plaque rupture

II. Minors criteria

a) Physical or emotional stress as triggering factors

b) Minor cardiac enzyme elevation

c) Chest pain and shortness of breath after sever stress emotional or physical

III. Exclusion criteria

a) Subarachnoid hemorrhage

b) Pheochromocytoma crisis

c) Acute myocarditis

d) Tachycardiomyopathy

e) Ischemic myocardial stunning

The electrocardiographic pattern of Takotsubo cardiomyopathy

The electrocardiographic pattern of TCM has 3 successive stages or phases (**Kosuge 2010;Bybee 2004; Sclarowsky 2010;Kuisu 2004**)

- **First stage**: characterized by discrete ST segment elevation, usually in the precordial leads but also sometimes in the lateral and inferior leads as in the cases. The magnitude of ST elevation is usually less than ST segment elevation in STEMI. T waves are tall but do not exceed 12-15 mm as is sometimes seen in STEMI where they may exceed 18 mm. The maximal ST segment alteration usually occurs in leads V3-5.

- **Second stage:** seen after 2-3 days; ST segment elevation resolves with appearance of diffuse, deep and inverted T waves except in lead aVR where T waves are positive. The presence of positive T waves in aVR is a valuable sign in differentiating TCM from MI. The non-segmental distribution of T wave alterations is a characteristic of this syndrome. The QT and QTc intervals may also be prolonged. Pathological Q waves are rarely seen.

- **Third stage:** T wave inversion and QT prolongation typically resolves after 3-4 months, but in some cases these changes may last up to 1 year. Resolution of changes may sometimes occur earlier after 3-4 weeks.

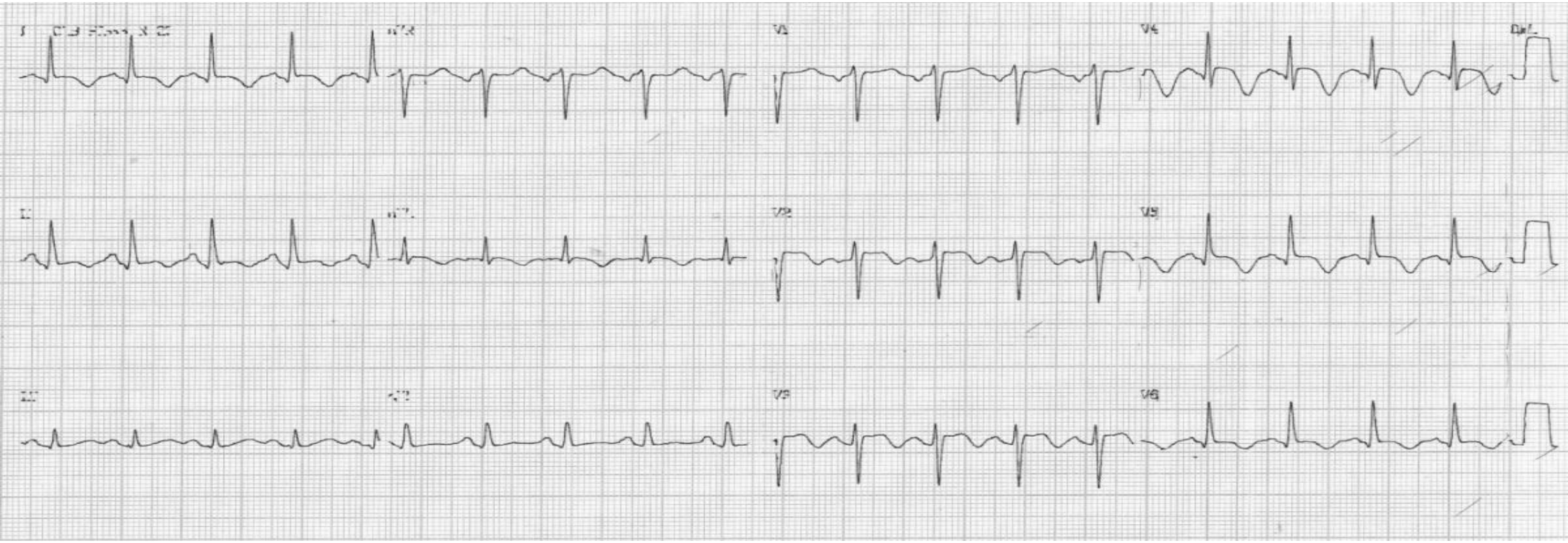
The combination of ST segment depression in aVR along with absent ST segment elevation in V1 has 91% sensitivity, 96% specificity and 95% predictive accuracy for TCM (**Kosuge 2010**).

A summary of the significant electrocardiographic criteria for diagnosis is indicated below (**Omar 2013**).

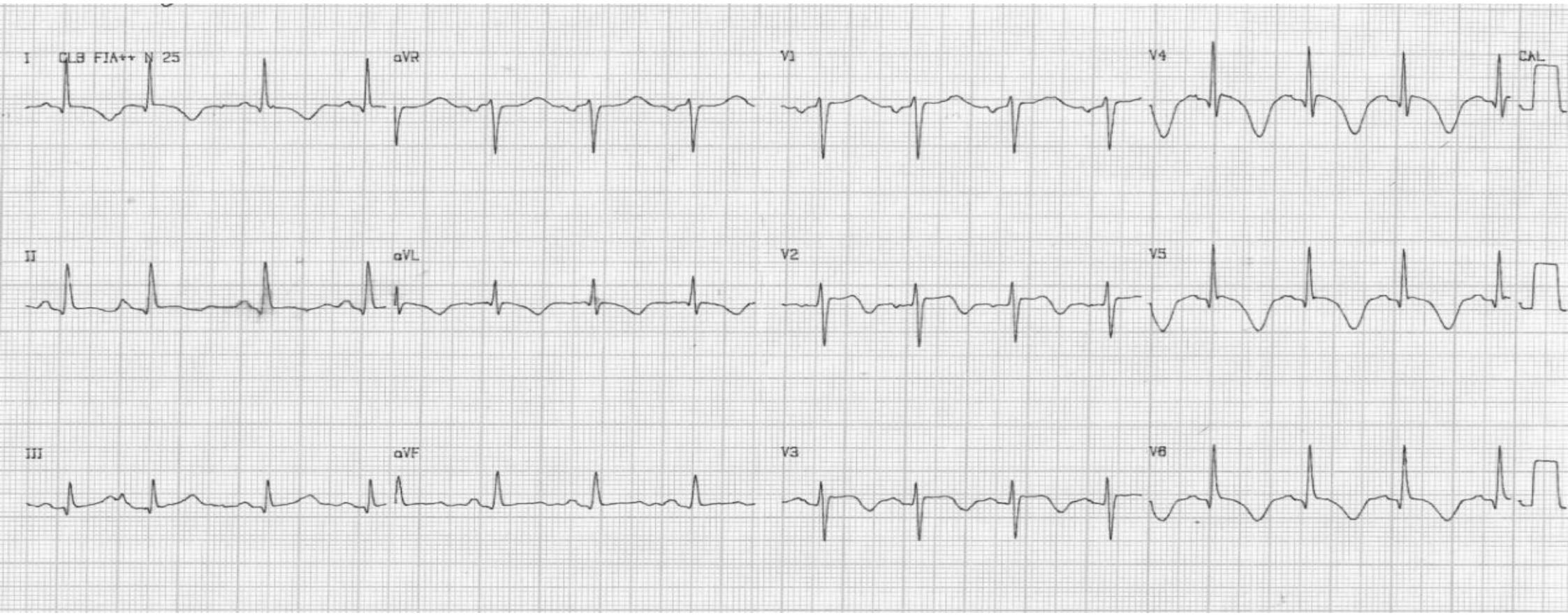
- Absence of ST segment elevation in V1
- Absence of reciprocal changes in inferior leads
- Presence of ST segment elevation in inferior leads, especially in II
- Sum of ST segment elevation in V4-6 ÷ V1-3 ≥1.
- ST segment depression in aVR.
- Deep negative T waves associated with prolonged QTc. Another characteristic of the negative T waves is that they remain negative in spite of regression of myocardial contractile dysfunction, unlike what happens in segmental ischemia where T waves became positive with the recovery of myocardial contractility. This evolution of ECG changes is illustrated in another case of TCM shown in the following ECGs. See next slides.

Low QRS voltage and shortening of QRS duration are highly prevalent ECG signs in patients with TCM. This is a reason why these ECG characteristics are useful in differentiating it from ACS during the first contact with the patient in the ED. This sign along with the echocardiogram and coronary angiography could be of great diagnostic importance.

Malignant ventricular arrhythmias, including torsade de pointes (TdP) associated with QT prolongation, may occur in 8% of the cases, especially when QTc > 500 ms (**Madias2014**). ICD implant should be considered in cases of persistent QTc > 500 ms with a previous history of syncope or cardiac arrest (**Sclarowsky 2010**). In a systematic review of TCM the incidence of late SCD is 0.5% (**Syed 2011**).

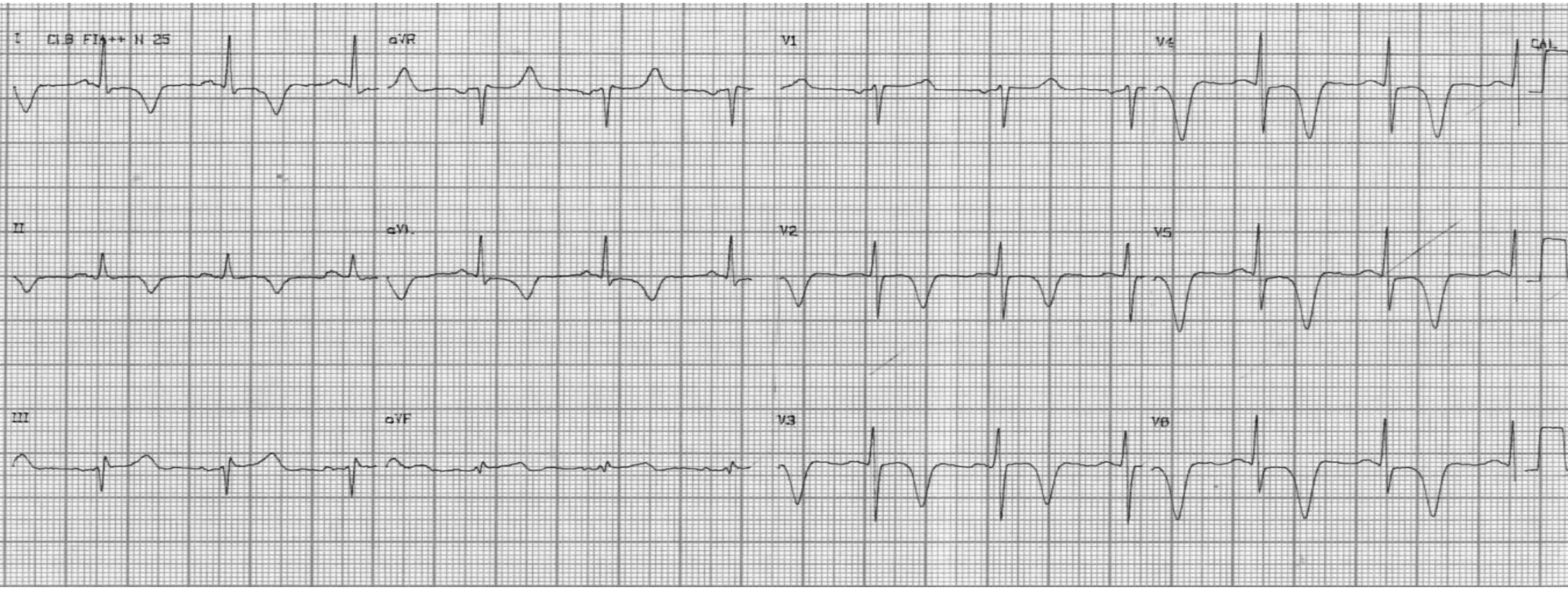


Electrocardiographic diagnosis: discrete ST segment elevation followed by negative T waves in V2-V3 (Wellens-like pattern), deeply negative T waves in anterolateral wall (from V4-6 and I and aVL: anterolateral ischemia.



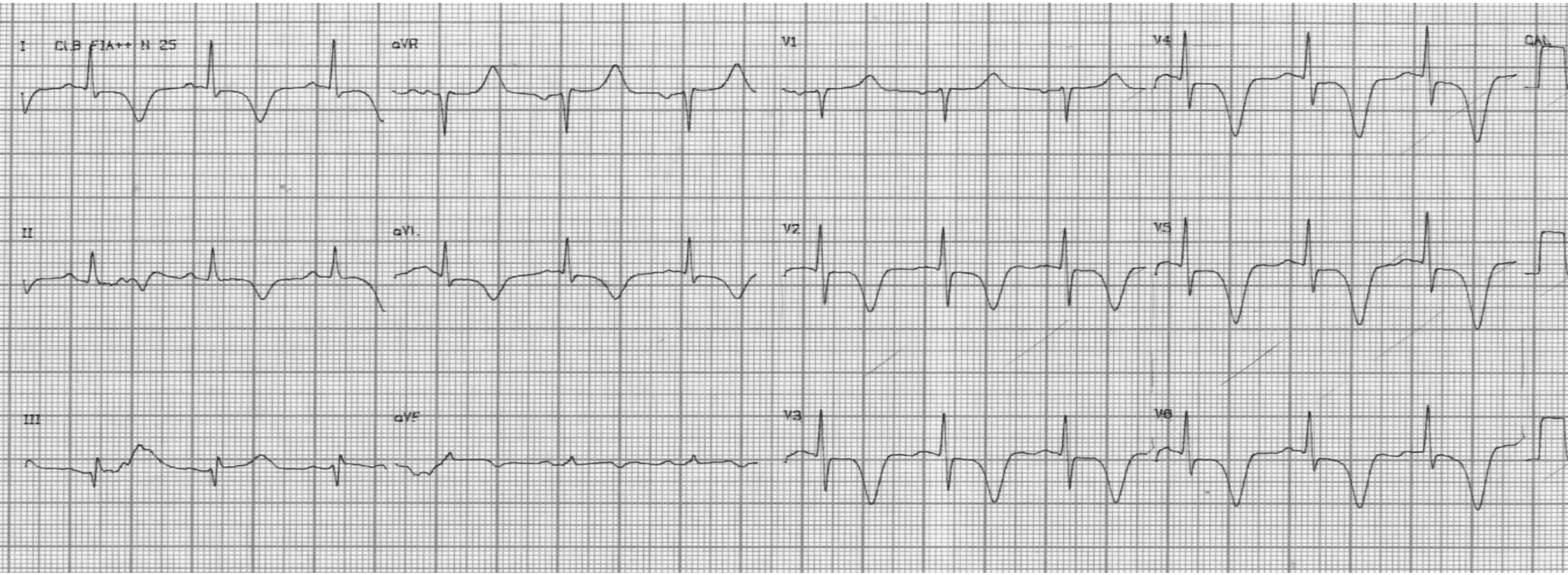
Electrocardiographic diagnosis: plus-minus T wave in V2 (Wellens-like syndrome pattern), deeply negative T waves in anterolateral wall (V3 to V6, I and aVL). Prolonged QT interval.

ECG performed after one week. In this phase, echocardiogram was already normal



Electrocardiographic diagnosis: Persistent deeply negative T waves in anterolateral wall (V2 to V6, I and aVL) and II in spite of the regression of ventricular dysfunction. These ECG findings are very important in differentiating TCM from acute MI.

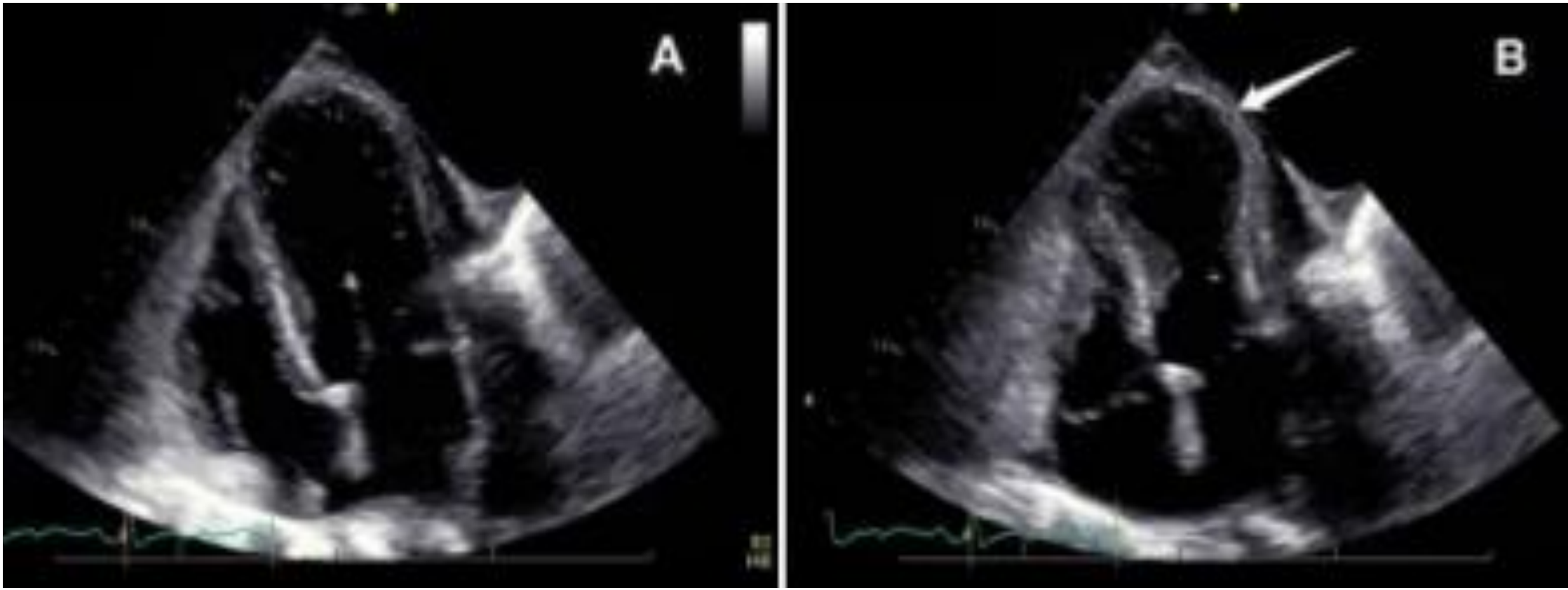
ECG performed after 2 weeks



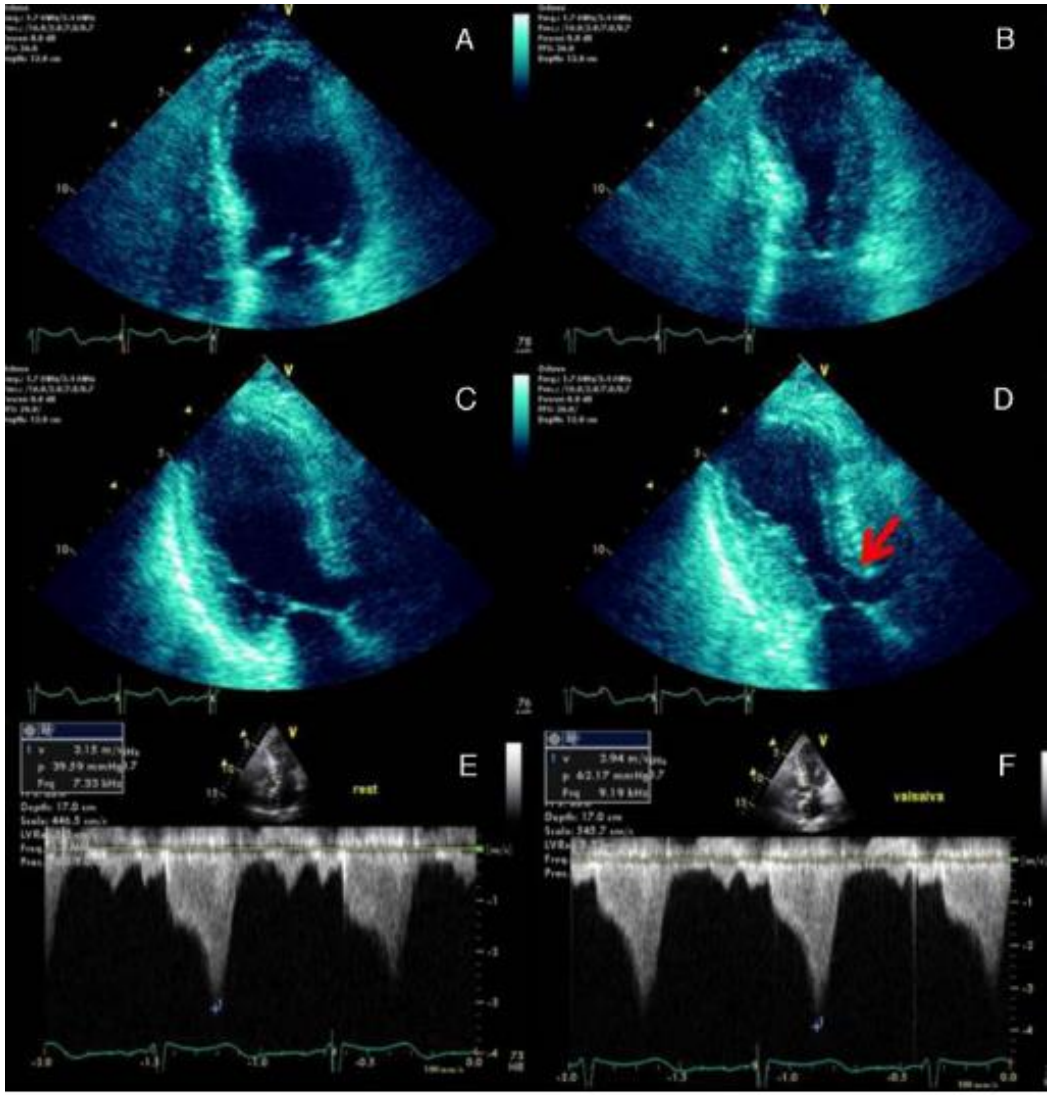
Electrocardiographic diagnosis: Persistent deeply negative T waves in anterolatral wall (V2 to V6, I and aVL) in spite of ventricular dysfunction regression. This ECG finding has a important diagnostic significance, because in segmental ischemia, T waves became positive concomitantly to myocardial contractility recovery.

ECG-nuclear magnetic resonance (NMR) correlation

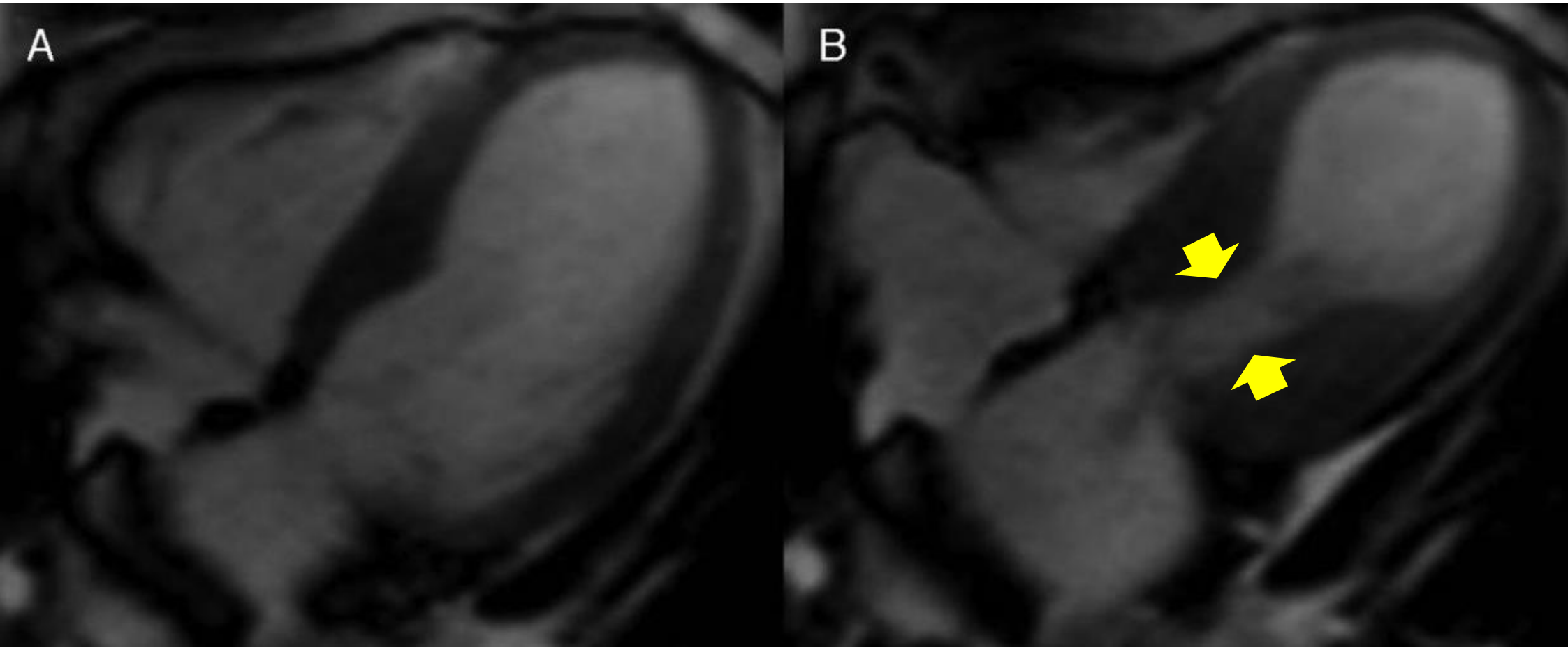
In addition to wall motion abnormalities seen NMR there is also the presence of circumferential myocardial edema in the apical and mid-ventricular region of the LV. This myocardial edema is responsible for the presence of an intracardiac gradient between the apical and basal regions which, in turn, causes a regional dispersion in action potential durations responsible for T wave inversion and QTc prolongation. Furushima et al (**Furushima 2008**) measured repolarization gradients between the LV apical and basal region in patients with TCM who had negative T waves and prolonged QT intervals in leads II, III, aVF and V2-V6. They showed a progressive increase in repolarization time from the basal region to the apical region, both in the endocardium and the epicardium. This observation confirms the hypothesis that inverted T waves in TCM result from repolarization dispersion caused by abnormal prolongation of action potential in the affected myocardial regions.



Panel A: Four chamber view of the heart at the end of diastole with a dilated left ventricle.
Panel B: Same four chamber view of the heart at the end of systole with a dilation and akinesis of the apical portion (arrow) of the heart consistent with apical ballooning/stress (**Chockalingam 2010**).

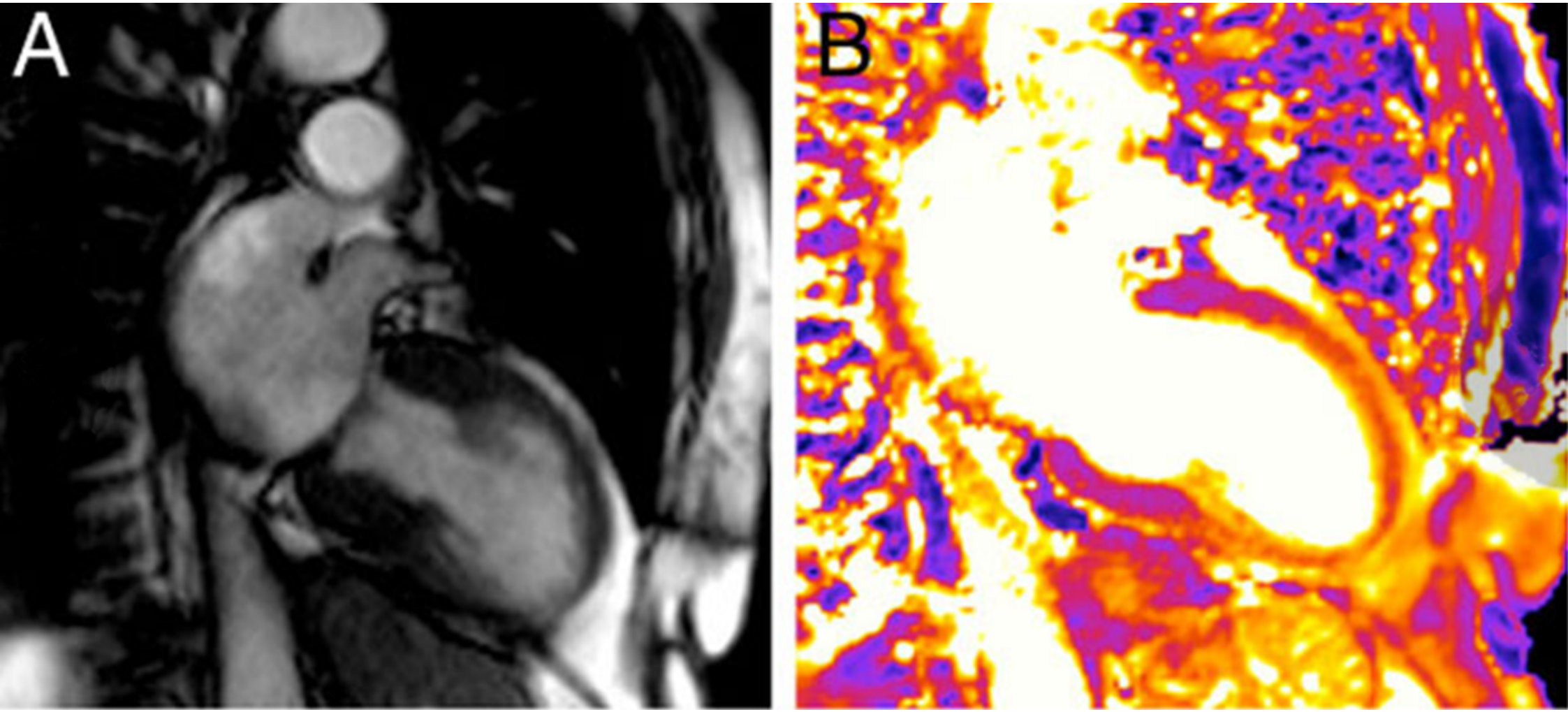


End-diastolic and end-systolic apical 4-chamber (A and B) and 3-chamber (C and D) echocardiographic views demonstrating the typical apical and mid-ventricular LV wall-motion abnormalities that raised the suspicion of TCM. SAM of the mitral valve with LVOT obstruction is signaled by the red arrow (D). Continuous-wave Doppler profile outlining the degree of LVOT obstruction at rest (E) and during the Valsalva maneuver (F).



Cardiovascular magnetic resonance (CMR) in Takotsubo cardiomyopathy. End-diastolic (A) and end-systolic (B) frames from a four-chamber cine sequence demonstrate hyperdynamic function of basal segments with apical hypokinesia.

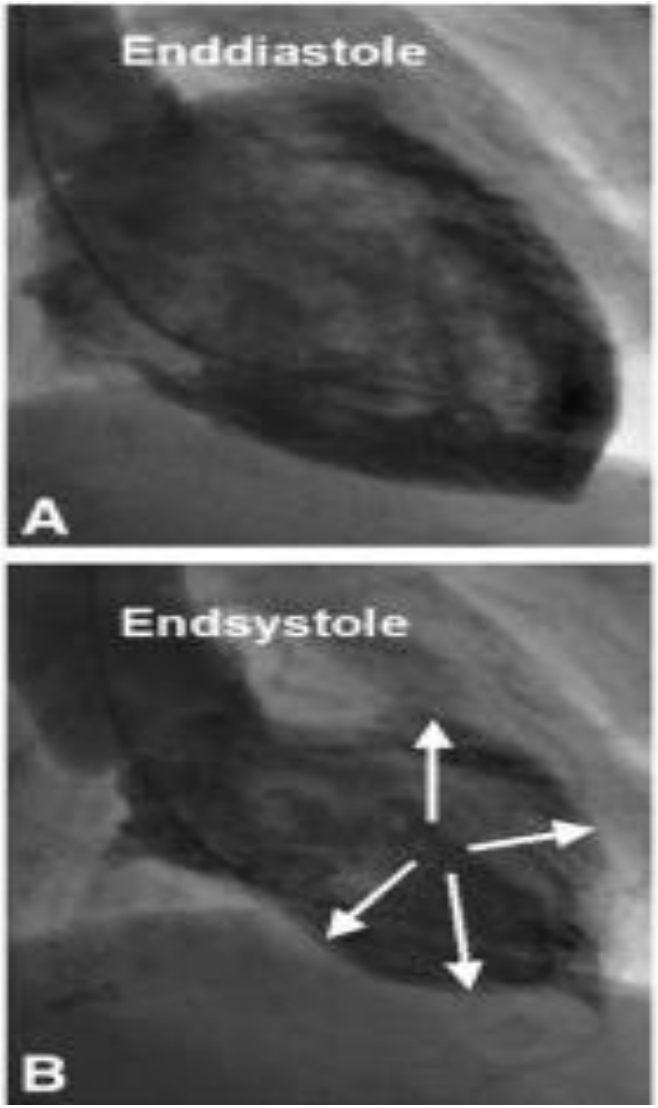
Cine magnetic resonance imaging (MRI)



A) shows apical ballooning in an 81-year-old patient with TCM. Cardiovascular MRI (CMRI) T2 (transversal relaxation time) mapping in the same patient (B) reveals elevated apical myocardial T2 signal intensity (orange). Both images are in two-chamber orientation and were obtained 3 days after the initial presentation of TCM, with transient ECG changes and elevated troponin levels following a generalized seizure.

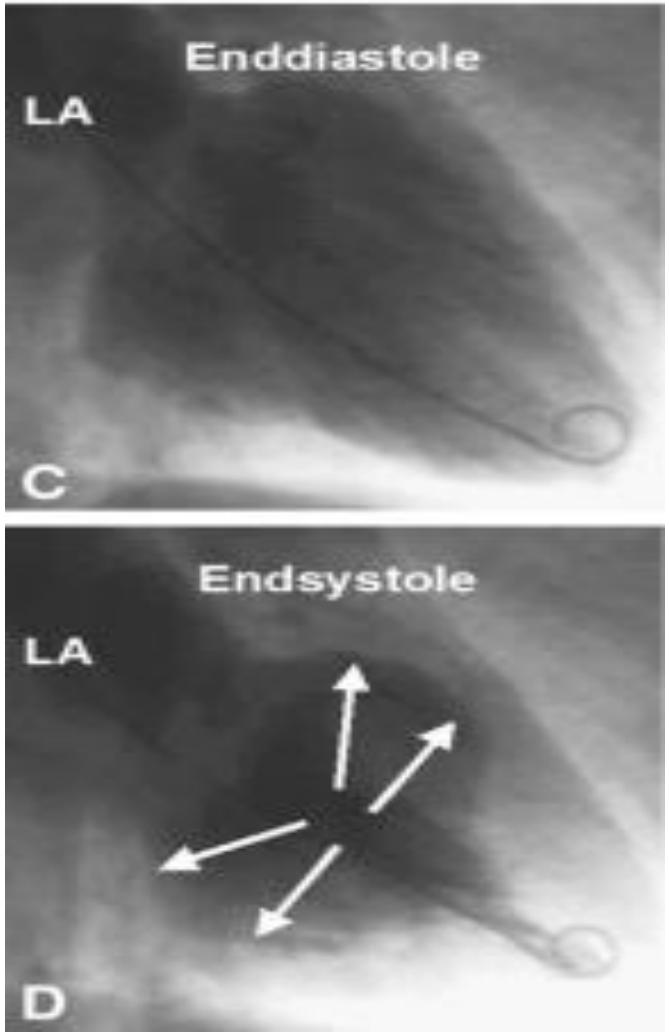
Takotsubo Cardiomyopathy Morphological types

The mid-ventricular variant

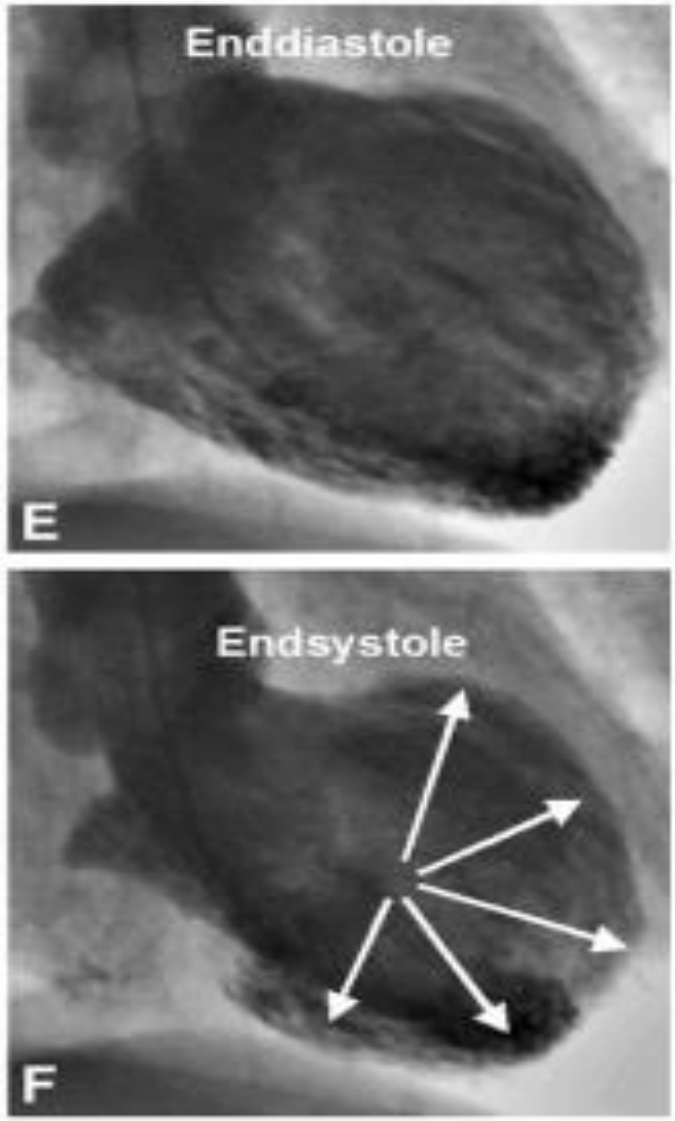


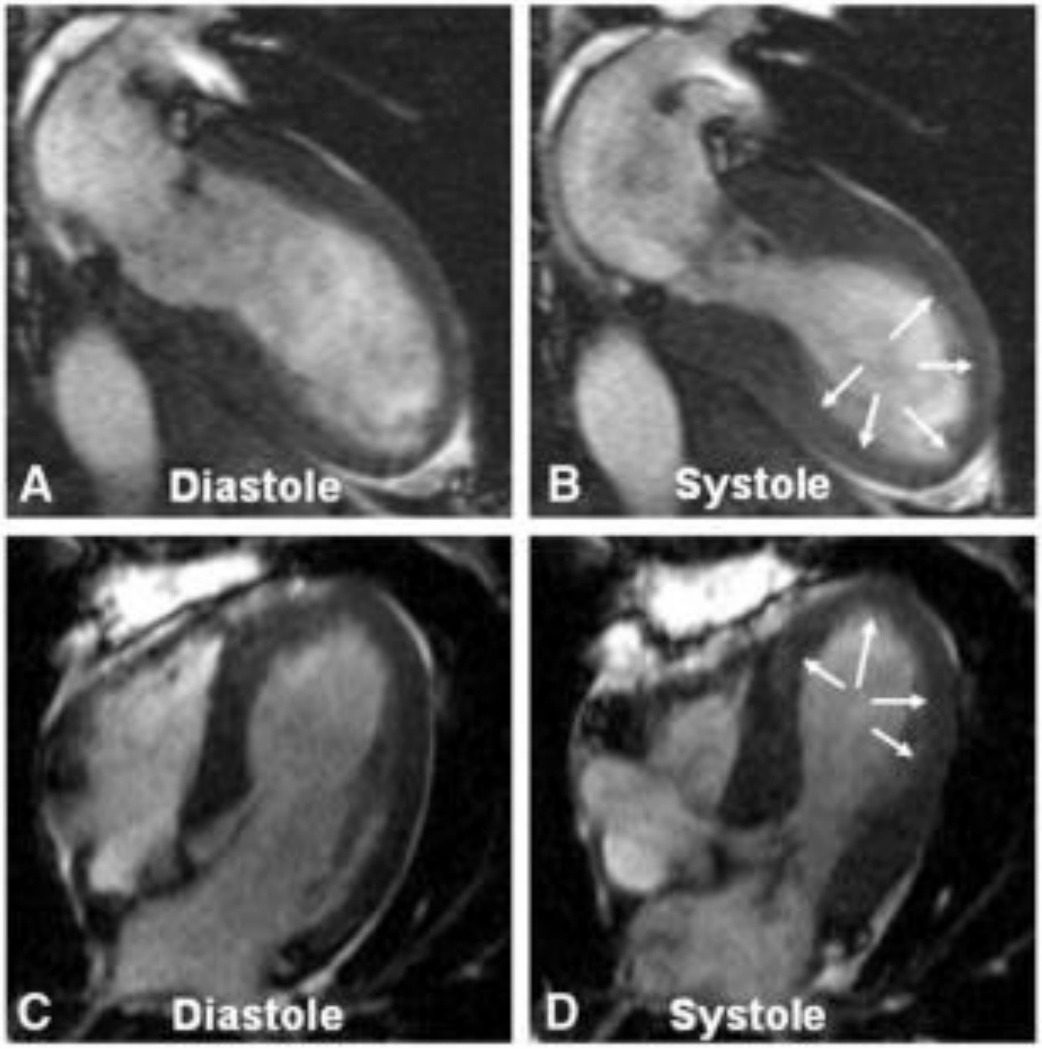
Reverse TCM

End-diastolic akinesia of the basal portions of the LV with hyperkinesia of the apex.

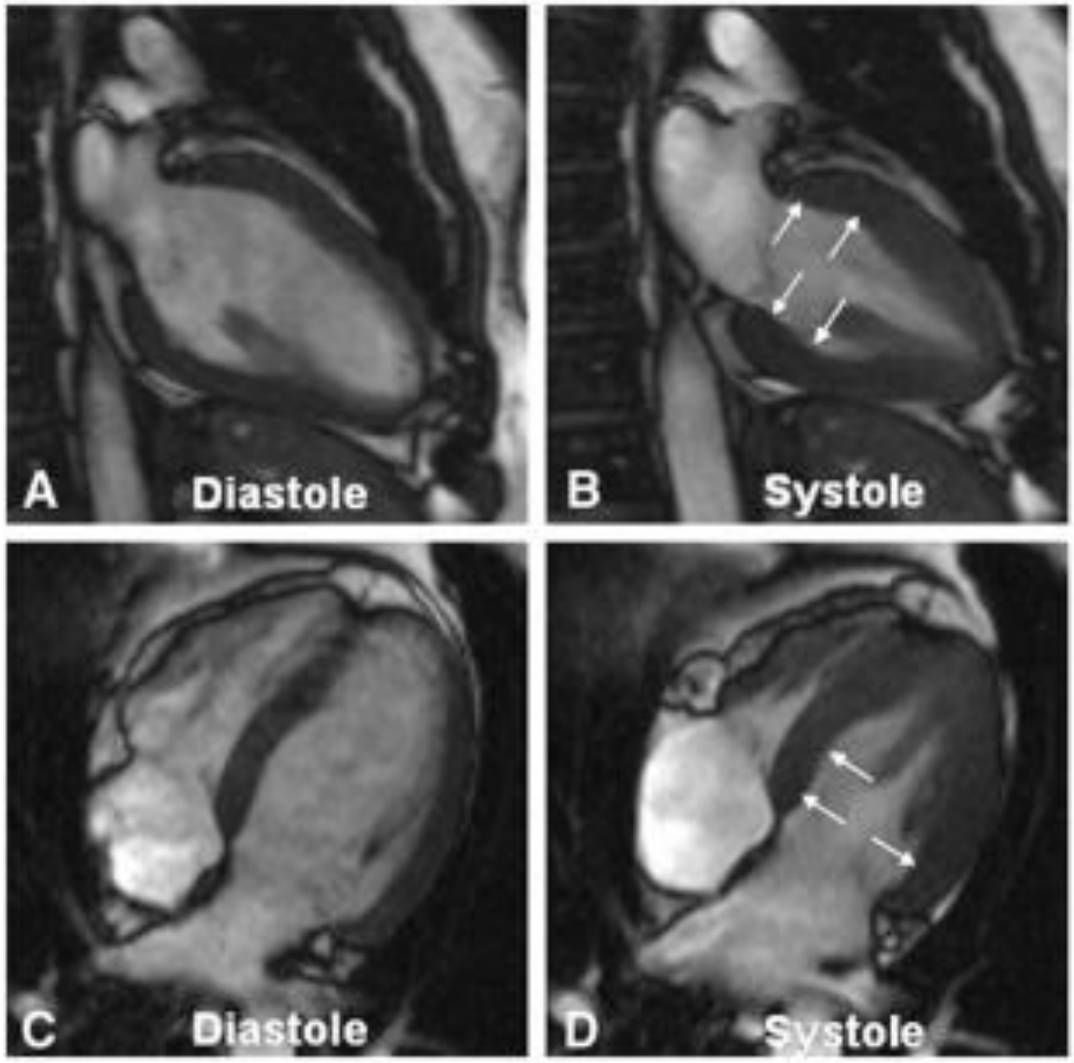


Classical TCM

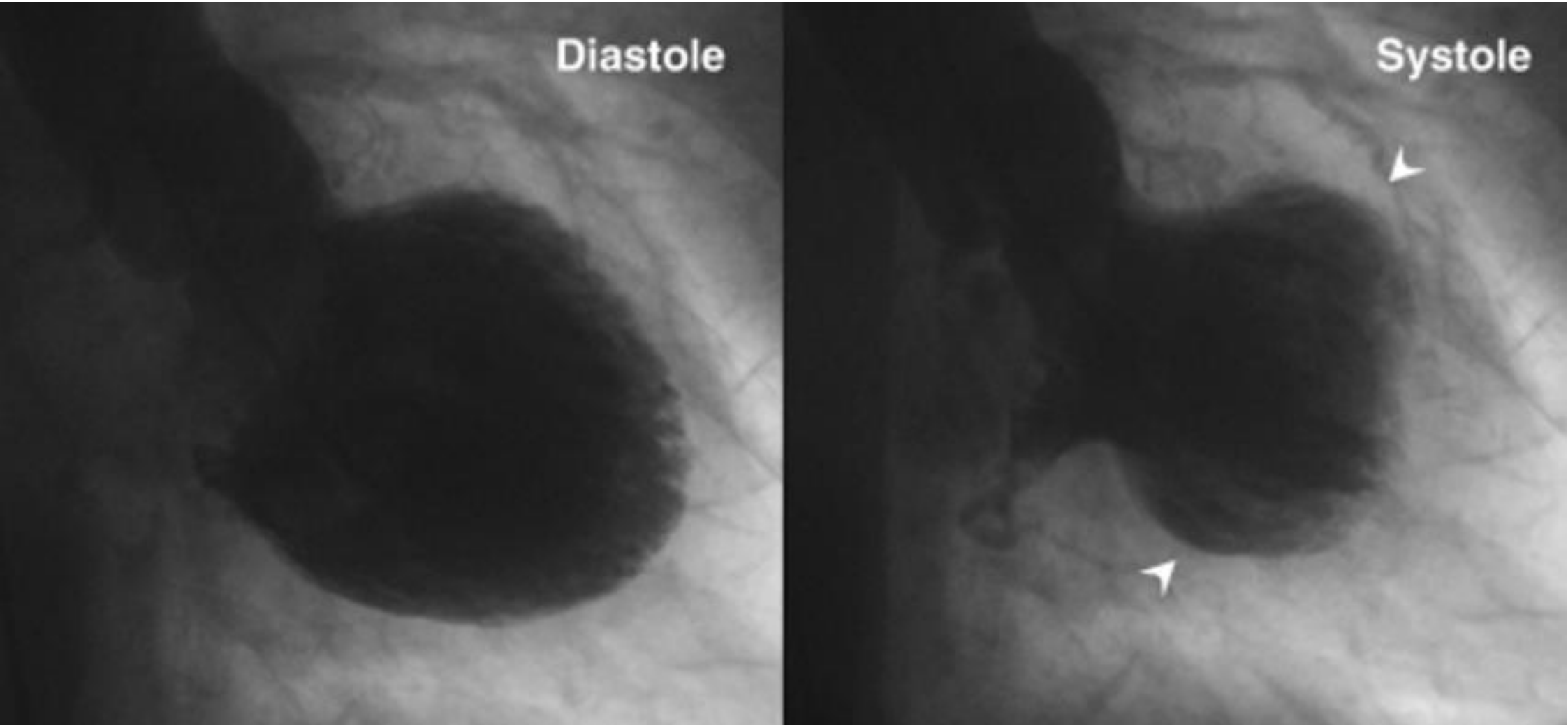




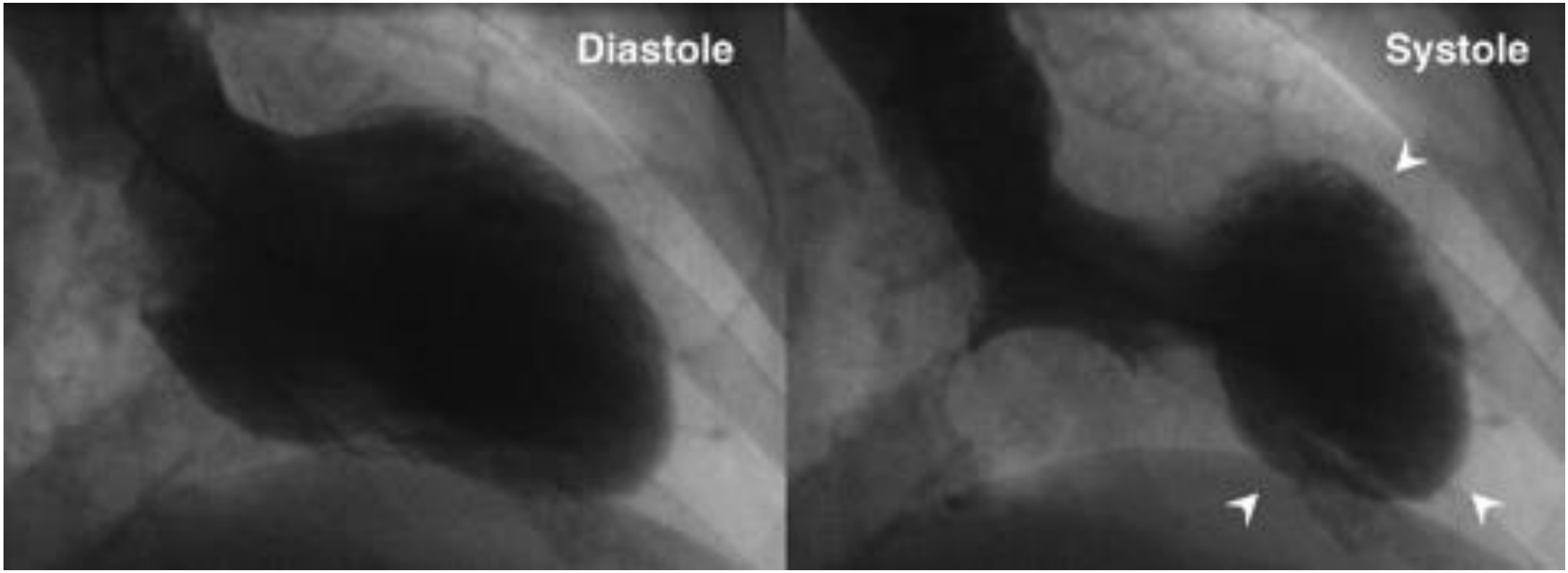
Diastolic and systolic cine CMR images from patient 9 obtained on day 4 demonstrating akinesia of distal left ventricle (arrows). Panels A and B: vertical long-axis. Panels C and D: horizontal long-axis.



Diastolic and systolic cine CMR images from patient obtained on day demonstrating mild hypokinesia of LV base (arrows). Panels A and B: vertical long-axis. Panels C and D: horizontal long-axis.

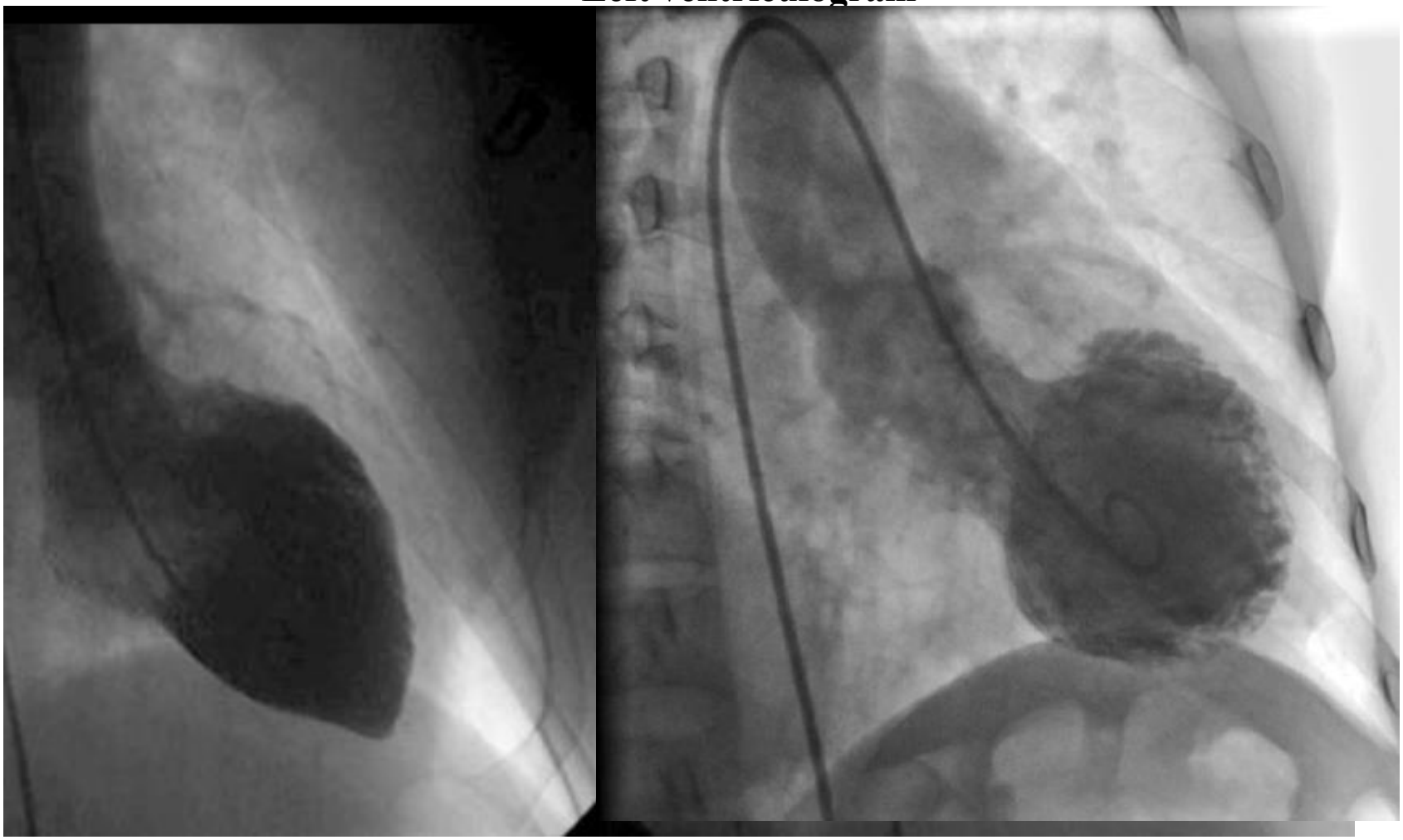


Diastolic and systolic freeze frames from a left ventriculogram of a patient with the apical sparing variant of ABS. Function at the base and apex is preserved with akinesis of the mid segments (arrows).

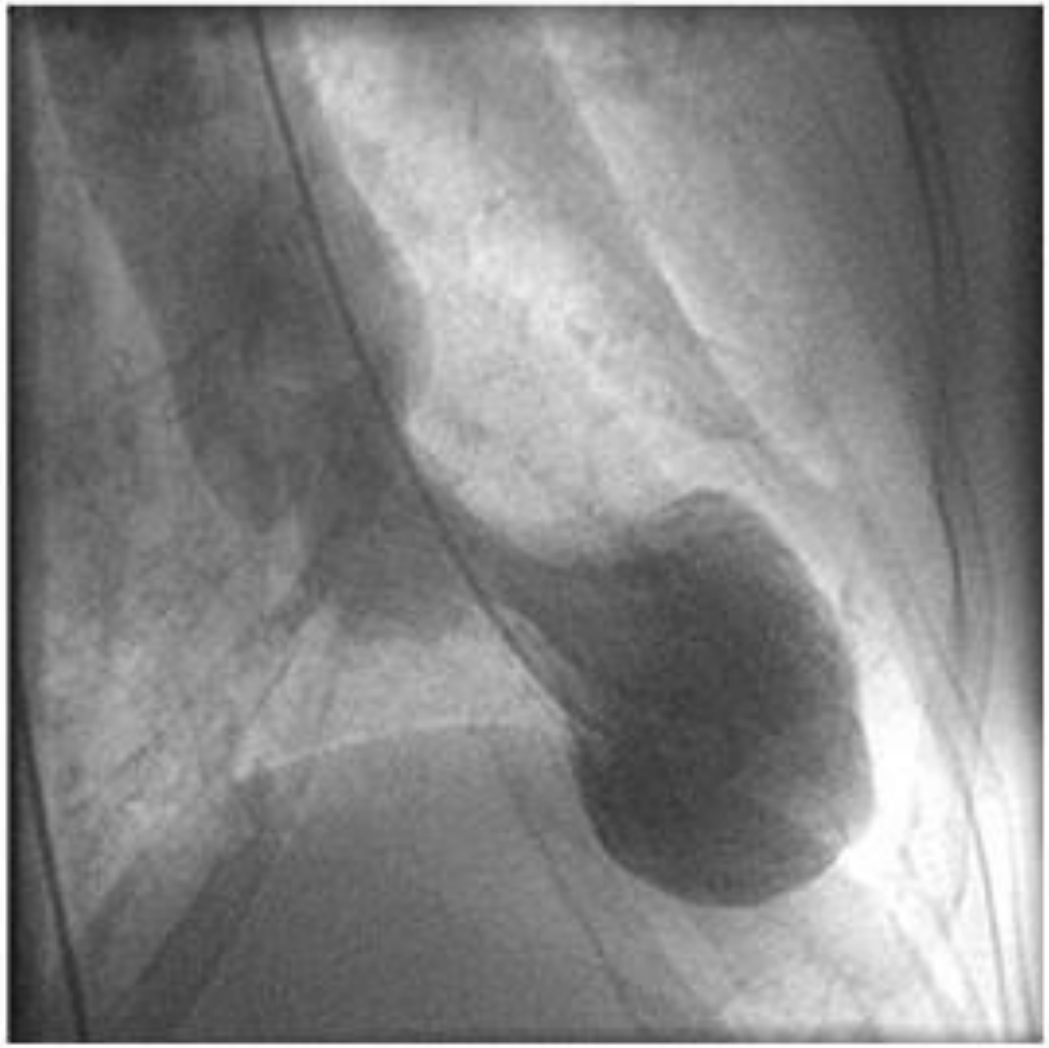


Diastolic and systolic freeze frames from a left ventriculogram of a patient with classic ABS illustrating hyperdynamic basal contraction but akinesis of the mid and apical segments (arrows).

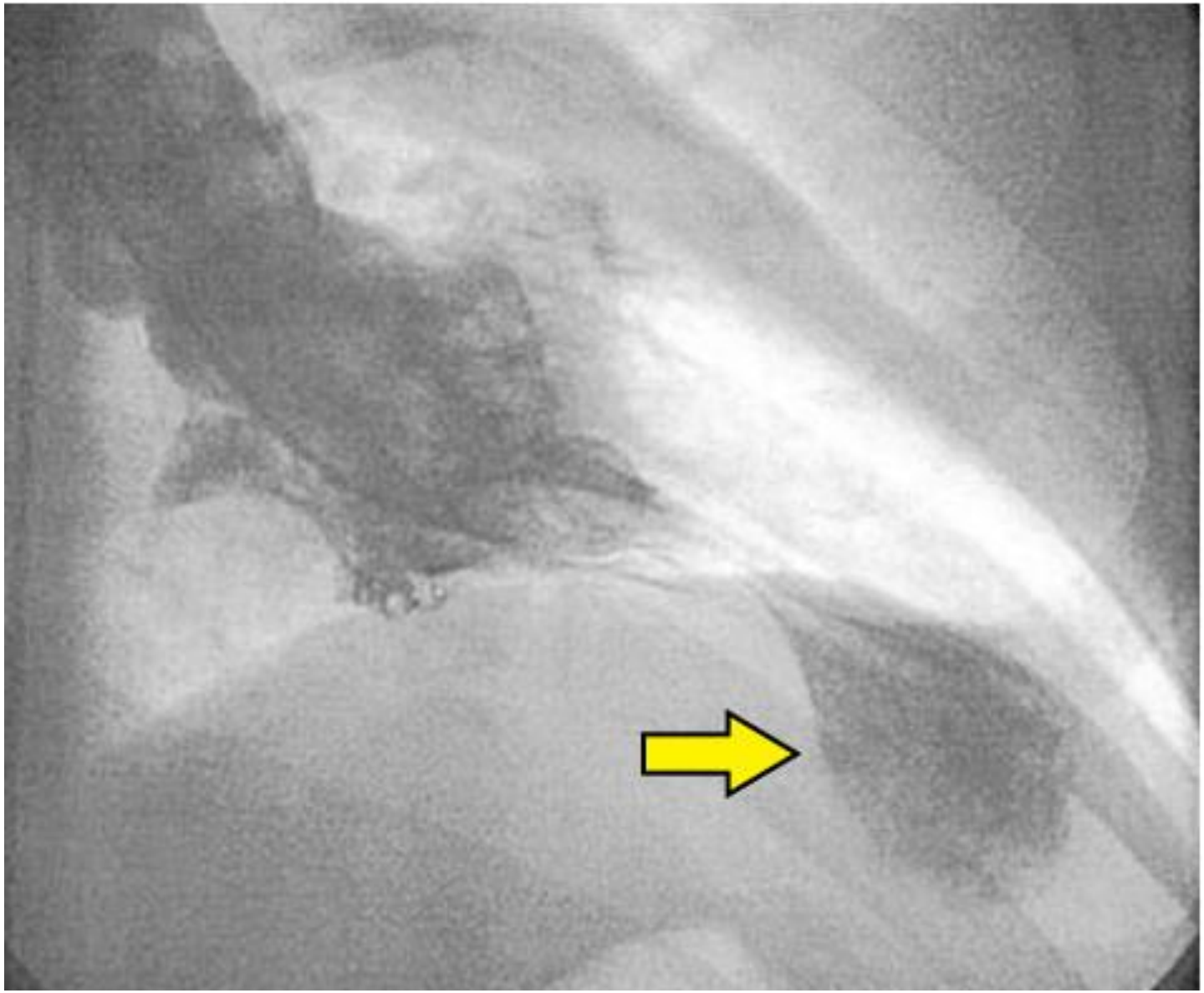
Left ventriculogram



The left ventriculogram shows the typical appearance of the LV in the mid and apical portions during diastole (A) and end-systole. In the end-systolic phase, aneurysmal dilatation (ballooning) of the anterior, apical and inferior segments of the LV is apparent; therefore, TCM has also been referred to as "apical ballooning syndrome (**Kazakauskaite 2014; Sato 2012**) http://www.escardio.org/communities/councils/ccp/e-journal/volume10/Pages/Takotsubo-Cardiomyopathy-identification-treatment.aspx#.VNkDbPnF_To.)



TCM is named for the resemblance of the LV apical ballooning (left) to the round bottoms and narrow necks of traditional Japanese octopus traps (called "takotsubo") (left)



The left ventriculogram during systole shows the characteristic apical ballooning with apical akinesis of TCM (arrow).

Complications

1) Cardiac thrombus (**Ahmed 2017**) LV mural thrombus formation
2) Embolic Events such as stroke, ventricular thrombi, and peripheral embolization, and can be present at index event of TCM as well as at any time in disease course. Patients with elevated C-reactive protein levels, markedly elevated D-dimers and severely impaired left ventricular function seem to be at higher risk of developing thromboembolic events (**El-Battrawy 2016**).
3) Ventricular wall, apex or septum rupture. LV free-wall rupture in TCM is rare, but it is a serious and potentially life-threatening complication. TCM should be considered as a differential diagnosis in cases of early-developing heart failure, and clinicians should subsequently use adequate diagnostic and therapeutic options (**Indorato 2015**).
4) Cardiac dysrhythmia(4-9%, atrial fibrillation, most common. Prolonged QT and torsade de pointes (**Ahmed 2017**).
5) Acute left heart failure with and without pulmonary edema cardiogenic shock (**Bennett 2014**).
6) Biventricular Failure (**Khamooshian 2017; Bals 2014**) (34% patients have biventricular involvement).
7) Right heart involvement (**Citro 2016**).
8) Left ventricular outflow obstruction (LVOT) (**Ozaki 2016**).
9) Mitral regurgitation (MR) (14-25% of patients) resulting from chordal tethering as well as systolic anterior motion of the anterior valve apparatus. Moderate to severe MR, and RV involvement are uncommon (**Glaveckaitė 2016**).
10) LVOT obstruction + Mitral regurgitation (MR) with systolic anterior motion of the mitral valve (SAM): Both together are severe complications of TCM and may result in HF and/or pulmonary edema. Timely and accurate identification of these complications is critical to achieve optimal clinical outcomes in patients with TCM. Treatment consist in association of β-blocker, aspirin, and ACE (**Wu 2015**).
11) Pericardial effusion (**Cortadellas 2012**).
12) Pericardial tamponade (**Jiménez-López; Yeh 2010**).
13) Death (**Bybee 2004; Merchant2008**).

While the management of TCM is mainly supportive and the outcomes are typically good, there are a variety of complications, which can increase mortality and prolong time to recovery. Patients may present in heart failure and cardiogenic shock which may be severe. While there is no definitive data to provide guidance, in general it is advised to avoid catecholaminergic inotropic agents such as dobutamine, as this may serve to exacerbate the theorized stress caused by endogenous epinephrine.

Prognosis

The prognosis in TCM is typically excellent, with nearly 95% of patients experiencing complete recovery within 4-8 weeks (**Pilgrim 2008; Prasad 2008**).

There was a significant difference in in-hospital mortality depending on the trigger type in TCM. Being male and having a physical trigger were independent risk factors of in-hospital mortality from TCM. Compared physical with emotional stress triggered TCM, patients with physical triggered TCM were more likely to have a malignancy, lower blood pressure, lower hemoglobin, higher serum creatinine and higher norepinephrine levels. During a mean hospital stay of 16±12days, 9 (20.9%) of the Physical and 1 (2.6%) of the Non-physical(emotional) patients died in-hospital. After adjusting for the age, gender, trigger, malignancy, and hemoglobin level, being male and having a physical trigger were associated with in-hospital mortality (**Sobue 2017**).

TCM is also known as stress cardiomyopathy because of the regularity with which it has been associated with physical or emotional stress. Such stress may well be a "trigger" of the syndromes howed that different triggers for TCM confer different prognoses, with medical illness conferring the worst prognosis. Overall, the in-hospital death rate was low and mostly related to non-cardiac death secondary to the underlying medical illness. Although an unidentified trigger was prevalent in a third of this population, efforts should be made to identify the triggering event to classify the risk group of patients with TCM (**Yerasi 2017**).

A study by Singh et al indicated that the annual recurrence rate is approximately 1.5% but that the frequency of ongoing symptoms is greater (**Singh 2014**). Estimates of mortality have ranged from 1% to 3.2% (**Donohue 2005; Gianni 2006**).

Complications occur in 20% of TCM cases, particularly in the early stage (**Kurisu 2011**) and include the following:

Approach Considerations

Prehospital care Because TCM mimics ACS and no initial ECG finding reliably differentiates TCM from STEMI, prehospital personnel should follow their established protocols for evaluating and transporting patients with chest pain and/ACS.

Patients with TCM will require admission to the appropriate cardiology service. Treatment options are largely empiric and supportive; however, when hemodynamics permit, beta blockers seem to be helpful. Serial imaging studies may be necessary. Patients who are found to have LV thrombus, which occurs in 5% of patients with TCM, require anticoagulation (**Kurisu 2011**). Close follow-up care with a cardiologist in the weeks after diagnosis is recommended for patients with TCM to ensure resolution of the cardiomyopathy, usually with serial echocardiograms. Thereafter, annual clinical follow-up is advised, because the long-term effects and natural history of TCM are unknown (**Prasad 2008**).

Consultation with a cardiologist is necessary, in that coronary angiography is required for the diagnosis of TCM. Patients may need to be transferred to a facility with a cardiologist and a cardiac catheterization laboratory (**Merchant 2008; Sharkey 2008.; Kolkebeck 2007**).

Medication Currently, no randomized controlled trials have been performed to evaluate medical therapies for TCM; however, it is common practice to prescribe angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), at least until LV function is restored. β-blockers are also indicated and may be useful in the long term. However, a review study and meta-analysis by Singh et al (**Singh 2014**) suggested that while ACE inhibitors and ARBs may reduce the recurrence rate of TCM, β-blockers may not.

Other standard outpatient post-STEMI medications, such as statins, aspirin, and clopidogrel, are of unknown benefit. Patients with known LV thrombus should be anticoagulated until LV function normalizes and thrombus is no longer present on echocardiogram. Chronic β-blockers therapy may reduce the likelihood of recurrent episodes.

Salicylates: These agents inhibit platelet aggregation. Aspirin is an odorless, white, powdery substance available in 81 mg, 325 mg, and 500 mg for oral use. When exposed to moisture, aspirin hydrolyzes into salicylic acid and acetic acid. It is a stronger inhibitor of prostaglandin synthesis and platelet aggregation than are other salicylic acid derivatives. The acetyl group is responsible for the inactivation of cyclooxygenase via acetylation. Aspirin is hydrolyzed rapidly in plasma, and elimination follows zero-order pharmacokinetics. It irreversibly inhibits platelet aggregation by inhibiting platelet cyclooxygenase. This, in turn, inhibits the conversion of arachidonic acid to PGI2 (a potent vasodilator and an inhibitor of platelet activation) and thromboxane A2 (a potent vasoconstrictor and platelet aggregate). Platelet inhibition lasts for life of cell (approximately 10 d). Aspirin may be used in low dose to inhibit platelet aggregation and improve the complications of venous stasis and thrombosis. It reduces the likelihood of myocardial infarction and is also very effective in reducing the risk of stroke. Early administration of aspirin in patients with acute MI may reduce cardiac mortality in the first month.

Antianginal Agents: These agents reduce blood pressure.

Nitroglycerin: topical Nitroglycerin causes relaxation of the vascular smooth muscle via stimulation of intracellular cyclic guanosine monophosphate production, causing a decrease in blood pressure.

Analgesics: Pain control is essential to quality patient care. Analgesics ensure patient comfort, promote pulmonary toilet, and have sedating properties, which are beneficial for patients who experience pain.

Morphine sulfate: This is the drug of choice for narcotic analgesia because of its reliable and predictable effects, safety profile, and ease of reversibility with naloxone. Morphine sulfate administered intravenously may be dosed in a number of ways and is commonly titrated until the desired effect is obtained.

Anticoagulants: Anticoagulants inhibit thrombogenesis. Heparin augments the activity of antithrombin III and prevents the conversion of fibrinogen to fibrin. It does not actively lyse but is able to inhibit further thrombogenesis. Heparin prevents the recurrence of a clot after spontaneous fibrinolysis.

Low Molecular Weight Heparins (LMWHs) inhibit thrombogenesis.

Unfractionated heparin (60-U/kg bolus followed by 12 U/kg/min infusion), Enoxaparin (Lovenox): It is produced by the partial chemical or enzymatic depolymerization of unfractionated heparin (UFH). LMWH differs from UFH by having a higher ratio of antifactor Xa to antifactor IIa.

The glycoprotein IIb/IIIa inhibitor eptifibatide (180-µg/kg bolus followed by 2-µg por kg x min1 infusion), and 300 mg of clopidogrel by mouth.

Enoxaparin binds to antithrombin III, enhancing its therapeutic effect. The heparin-antithrombin III complex binds to and inactivates activated factor X (Xa) and factor II (thrombin). It does not actively lyse but is able to inhibit further thrombogenesis, preventing clot reaccumulation after spontaneous fibrinolysis. The advantages of enoxaparin include intermittent dosing and a decreased requirement for monitoring. Heparin anti–factor Xa levels may be obtained if needed to establish adequate dosing. There is no utility in checking activated partial thromboplastin time (aPTT); the drug has a wide therapeutic window, and aPTT does not correlate with the anticoagulant effect. The maximum antifactor Xa and antithrombin activities occur 3-5 hours after administration. Enoxaparin is indicated for the treatment of acute STEMI managed medically or with subsequent percutaneous coronary intervention (PCI). It isalso indicated as prophylaxis for ischemic complications caused by unstable angina and non-Q-wave MI.

Antiarrhythmic Agents reduce episodes of chest pain.

Esmolol (Brevibloc) it is an ultra–short-acting agent that selectively blocks β-1 receptors with little or no effect on β-2-receptor types. It is particularly useful in patients with elevated arterial pressure, especially if surgery is planned. Esmolol has been shown to reduce episodes of chest pain and clinical cardiac events compared with placebo. It can be discontinued abruptly if necessary.

Esmolol is useful in patients at risk of experiencing complications from β blockade, particularly those with reactive airway disease, mild-moderate LV dysfunction, and/or peripheral vascular disease. The drug's short, 8-minute half-life allows for titration to the desired effect and for quick discontinuation if needed.

Platelet Aggregation Inhibitors: These agents reduce platelet aggregation.

Abciximab (ReoPro) It is a chimeric human-murine monoclonal antibody that has been approved for use in elective/urgent/emergent PCI. It binds to the receptor with high affinity and reduces platelet aggregation by 80% for up to 48 hours following infusion.

Eptifibatide (Integrilin) is an antagonist of the GP IIb/IIIa receptor; it reversibly prevents von Willebrand factor, fibrinogen, and other adhesion ligands from binding to the GP IIb/IIIa receptor. Eptifibatide inhibits platelet aggregation. Its effects persist over the duration of maintenance infusion and are reversed when infusion ends.

Tirofiban (Aggrastat) is a nonpeptide antagonist of the GP IIb/IIIa receptor. It is a reversible antagonist of fibrinogen binding. When tirofiban is administered intravenously, more than 90% of platelet aggregation is inhibited. The drug is approved for use in combination with heparin for patients with unstable angina who are being treated medically and for those undergoing PCI.

Clopidogrel (Plavix) selectively inhibits adenosine diphosphate (ADP) binding to the platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. The drug may have a positive influence on several hemorrhagic parameters and may exert protection against atherosclerosis not only through the inhibition of platelet function but also through changes in the hemorrhagic profile. Clopidogrel has been shown to decrease cardiovascular death, MI, and stroke in patients with ACS (ie, unstable angina, non-Q-wave MI).

Loop diuretics reduce blood pressure. Furosemide (Lasix) Furosemide increases the excretion of water by interfering with the chloride-binding cotransport system, which, in turn, inhibits sodium and chloride reabsorption in the ascending loop of Henle and distal renal tubule. It increases renal blood flow without increasing the filtration rate. The onset of action generally is within 1 hour. Furosemide increases potassium, sodium, calcium, and magnesium excretion. The dose must be individualized to the patient. Depending on the response, administer furosemide at increments of 20-40 mg, until the desired diuresis occurs. When treating infants, titrate with 1-mg/kg/dose increments until a satisfactory effect is achieved. Diuretics have major clinical uses in managing disorders involving abnormal fluid retention (edema) or in treating hypertension, in which their diuretic action causes decreased blood volume.

Thiazide Diuretics: These agents reduce blood pressure. Hydrochlorothiazide inhibits the reabsorption of sodium in distal tubules, causing the increased excretion of sodium and water, as well as of potassium and hydrogen ions.

Spironolactone (Aldactone) is used for the management of edema resulting from excessive aldosterone excretion. It competes with aldosterone for receptor sites in the distal renal tubules, increasing water excretion while retaining potassium and hydrogen ions.

References

1. Abbas A, Sonnex E, Pereira RS, Coulden RA. Cardiac magnetic resonance assessment of takotsubo cardiomyopathy. Clin Radiol. 2016;71(1):e110-9.
2. Abe Y, Kondo M, Matsuoka R, Araki M, Dohyama K, Tanio H. "Assessment of clinical features in transient left ventricular apical ballooning". J Am Coll Cardiol. 2003;41(5):737-42
3. Afonso L, Bachour K, Awad K, Sandidge G. Takotsubo cardiomyopathy: pathogenetic insights and myocardial perfusion kinetics using myocardial contrast echocardiography. Eur J Echocardiogr. 2008;9(6):849-54.
4. Ahmed AE, Serafi A, Sunni NS, Younes H, Hassan W. Recurrent takotsubo with prolonged QT and torsade de pointes and left ventricular thrombus. J Saudi Heart Assoc. 2017;29(1):44-52.
5. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T.Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation. 2008;118(25):2754-62.
6. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. Nat Rev Cardiol. 2015;12(27): 387–97.
7. Ter Bals E, Odekerken DA, Somsen GA. Takotsubo cardiomyopathy complicated by cardiac tamponade. Neth Heart J 2014;22(5):246-8.
8. Bayés de Luna A, Fiol-Sala M. Electrocardiographic pattern of injury: ST-segment abnormalities. In: Electrocardiography in Ischemic Heart Disease. Oxford: Blackwell/Futura; 2008:80.
9. Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc. 1993;68(10):988–1001.
10. Bennett J, Ferdinande B, Kayaert P, et al. Left ventricular function and clinical outcome in transient left ventricular ballooning syndrome. Acta Cardiol. 2014;69(5):496-502.
11. Boland TA, Lee VH, Bleck TP. Stress-induced cardiomyopathy. Crit Care Med. 2015;43(3):686-93.
12. Bonnemeier H, Ortak J, Wiegand UK, et al. Accelerated idioventricular rhythm in the post-thrombolytic era: incidence, prognostic implications, and modulating mechanisms after direct percutaneous coronary intervention. Ann Noninvasive Electrocardiol. 2005;10(2):179-87.
13. Bonnemeier H, Schafer U, Schunkert H. Apical ballooning without apical ballooning. Eur Heart J. 2006;27(18):2246.
14. Botto F, Trivi M, Padilla LT. Transient left midventricular ballooning without apical involvement. Int J Cardiol. 2008;127(3):e158-9.
15. Brew K, Dinakarpandian D, Nagase H. Tissue inhibitors of metalloproteinases: evolution, structure and function. Biochim Biophys Acta. 2000; 1477(1-2):267-83.

16. Buchholz S, Rudan G. Tako-tsubo syndrome on the rise: a review of the current literature. Postgrad Med J. 2007;83(978):261-4.
17. Budnik M, Kochanowski J, Piatkowski R, et al. Simple markers can distinguish Takotsubo cardiomyopathy from ST segment elevation myocardial infarction. Int J Cardiol. 2016;219:417-20.
18. Bybee KA, Kara T, Prasad A, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med. 2004;141(11):858-65.
19. Carrillo A, Fiol M, Garcia-Niebla J, Bayes de Luna A. Electrocardiographic differential diagnosis between Takotsubo syndrome and distal occlusion of LAD is not easy. J Am Coll Cardiol. 2010;56(19):1610-1; author reply 1611.
20. Chiang YL, Chen PC, Lee CC, Chua SK. Adrenal pheochromocytoma presenting with Takotsubo-pattern cardiomyopathy and acute heart failure: A case report and literature review. Medicine (Baltimore). 2016;95(36):e4846.
21. Chockalingam A, Xie GY, Dellsperger KC. Echocardiography in stress cardiomyopathy and acute LVOT obstruction. Int J Cardiovasc Imaging. 2010;26(5):527-35.
22. Christensen TE, Bang LE, Holmvang L, et al. Neuroticism, depression and anxiety in takotsubo cardiomyopathy. BMC Cardiovasc Disord. 2016;16:118.
23. Citro R, Previtali M, Bossone E. Tako-tsubo cardiomyopathy and drowning syndrome: is there a link? Chest. 2008;134(2):469.
24. Citro R, Lyon AR, Meimoun P, et al. Standard and advanced echocardiography in takotsubo (stress) cardiomyopathy: clinical and prognostic implications. J Am Soc Echocardiogr. 2015;28(1):57-74.
25. Citro R, Bossone E, Parodi G, et al. Clinical profile and in-hospital outcome of Caucasian patients with takotsubo syndrome and right ventricular involvement. Int J Cardiol. 2016;219:455-61.
26. Cortadellas J, Figueras J, Llibre C, et al. Left ventricular dynamic gradient and pericardial effusion. A life threatening combination in patients with apical ballooning syndrome. Int J Cardiol. 2012;154(3):370-2.
27. Dhoble A, Abdelmoneim SS, Bernier M, Oh JK, Mulvagh SL. Transient left ventricular apical ballooning and exercise induced hypertension during treadmill exercise testing: is there a common hypersympathetic mechanism? Cardiovasc Ultrasound. 2008;6:37.
28. Dias A, Franco E, Janzer S, et al. Incidence and predictors of stroke during the index event in an ethnically diverse Takotsubo cardiomyopathy population. Funct Neurol. 2016,31(3):157-62.
29. Djuric T, Zivkovic M, Stankovic A, et al. Plasma levels of matrix metalloproteinase-8 in patients with carotid atherosclerosis. J Clin Lab Anal. 2010; 24(4):246-51.

30. Donohue D, Movahed MR. Clinical characteristics, demographics and prognosis of transient left ventricular apical ballooning syndrome. Heart Fail Rev. 2005;10(4):311-6.
31. Dorfman TA, Iskandrian AE. Takotsubo cardiomyopathy: State-of-the-art review. J Nucl Cardiol. 2009;16(1):122-34.
32. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. JAMA. 2011;306(3):277-86.
33. El-Battrawy I, Borggrefe M, Akin I. Takotsubo Syndrome and Embolic Events. Heart Fail Clin. 2016;12(4):543-50.
34. Eldadah BA, Pacak K, Eisenhofer G, Holmes C, Kopin IJ, Goldstein DS. Cardiac uptake-1 inhibition by high circulating norepinephrine levels in patients with pheochromocytoma. Hypertension. 2004;43(6):1227-32.
35. El-Sayed AM, Brinjikji W & Salka S. Demographic and co-morbid predictors of stress (takotsubo) cardiomyopathy. Am J Cardiol 2012;110(9):1368-72.
36. Ennezat PV, Pesenti-Rossi D, Aubert JM, et al. Transient left ventricular basal dysfunction without coronary stenosis in acute cerebral disorders: a novel heart syndrome (inverted Takotsubo). Echocardiography. 2005;22(7):599-602.
37. Finsterer J, Bersano A. Seizure-triggered Takotsubo syndrome rarely causes SUDEP. Seizure. 2015;31:84-7.
38. Fiol M, Carrillo A, Cygankievicz I, et al. New Electrocardiographic algorithm to locate the occlusion in left anterior descending coronary artery. Clin Cardiol 2009;32:E1–6.
39. Freire G, Dubrow I. Accelerated idioventricular rhythm in newborns: a worrisome but benign entity with or without congenital heart disease. Pediatr Cardiol. 2008;29(2):457-62.
40. Fripp RR, Lee JC, Downing SE. Inotropic responsiveness of the heart in catecholamine cardiomyopathy. Am Heart J. 1981;101(1):17–21.
41. Fröhlich GM, Schoch B, Schmid F, et al. Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NT-proBNP/myoglobin and NT-proBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy. Int J Cardiol. 2012;154(3):328-32.
42. Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Morgante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia: a histologic, ultrastructural, and biochemical study. Chest. 1991;99(2):382–5.
43. Furushima H, Chinushi M, Sanada A, Aizawa Y. Ventricular repolarization gradients in a patient with takotsubo cardiomyopathy. Europace. 2008;10(9):1112-5.
44. Ghadri JR, Cammann VL, Napp LC, et al. Differences in the Clinical Profile and Outcomes of Typical and Atypical Takotsubo Syndrome: Data From the International Takotsubo Registry. JAMA Cardiol. 2016;1(3):335-40.

45. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J. 2006;27(13):1523-9.
46. Guerra F, Giannini I, Capucci A. The ECG in the differential diagnosis between takotsubo cardiomyopathy and acute coronary syndrome. Expert Rev Cardiovasc Ther. 2017;15(2):137-44.
47. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol. 2000;33(4):299–309.
48. Gussak I, Bjerregaard P, Kostis J. Electrocardiographic "lambda" wave and primary idiopathic cardiac asystole: a new clinical syndrome? J Electrocardiol. 2004;37(2):105-7.
49. Hasin Y, Rogel S. Ventricular rhythms in acute myocardial infarction. Cardiology. 1976;61(3):195-207.
50. Herman MP, Sukhova GK, Libby P, et al. Expression of neutrophil collagenase (matrix metalloproteinase-8) inhuman atheroma: a novel collagenolytic pathway suggested by transcriptional profiling. Circulation. 2001;104(16):1899-904.
51. Holzmann M, Reutter FW. Accelerated idioventricular rhythm with second degree v.a.-block and reentry. Z Kardiol. 1977;66(1):52-4.
52. Ibáñez B, Navarro F, Farré J, et al. Tako-tsubo syndrome associated with a long course of the left anterior descending coronary artery along the apical diaphragmatic surface of the left ventricle. Rev Esp Cardiol. 2004;57(3):209-16.
53. Inoue M, Shimizu M, Ino H, et al. Differentiation between patients with takotsubo cardiomyopathy and those with anterior acute myocardial infarction. Circ J. 2005;69(1):89-94.
54. Ito K, Sugihara H, Katoh S, Azuma A, Nakagawa M. Assessment of Takotsubo (ampulla) cardiomyopathy using 99mTc-tetrofosmin myocardial SPECT--comparison with acute coronary syndrome. Ann Nucl Med. 2003;17(2):115-22.
55. Indorato F, Akashi YJ, Rossitto C, Raffino C, Bartoloni G. Takotsubo cardiomyopathy associated with rupture of the left ventricular apex: assessment of histopathological features of a fatal case and literature review. Forensic Sci Med Pathol. 2015;11(4):577-83.
56. Jiménez-López J, Arias MA, Casares-Medrano J, et al. Tako-tsubo cardiomyopathy with apical variant complicated by cardiac tamponade and mid-ventricular variant presentation during a delayed recurrence. Rev Esp Cardiol (Engl Ed) 2012;65(10):962-3.
57. Kato K, Sakai Y, Ishibashi I, Kobayashi Y. Transient focal left ventricular ballooning: a new variant of Takotsubo cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2015;16(12):1406.
58. Kawai S, Kitabatake A, Tomoike H. Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. Circ J. 2007;71(6):990-2.
59. Kazakauskaite E, Jankauskas A, Lapinskas T, Ordiene R, Ereminiene E. Takotsubo cardiomyopathy: the challenging diagnosis in clinical routine. Medicina (Kaunas). 2014;50(1):1-7.

60. Khallafi H, Chacko V, Varveralis N, Elmi F. "Broken heart syndrome": catecholamine surge or aborted myocardial infarction? J Invasive Cardiol. 2008;20(1):E9-13.
61. Khamooshian A, Hai T, Amador Y, Jeganathan J, Mahmood F, Matyal R. Intraoperative Challenges in the Management of Biventricular Failure in Takotsubo Cardiomyopathy. J Cardiothorac Vasc Anesth. 2016. pii: S1053-0770(16)30664-4. (in press)
62. Kohan AA, Levy Yeyati E, De Stefano L, et al. Usefulness of MRI in takotsubo cardiomyopathy: a review of the literature. Cardiovasc Diagn Ther. 2014;4(2):138-46.
63. Kolkebeck TE, Cotant CL, Krasuski RA. Takotsubo cardiomyopathy: an unusual syndrome mimicking an ST-elevation myocardial infarction. Am J Emerg Med. 2007;25(1):92-5.
64. Kosuge M, Ebina T, Hibi K, Morita S, Okuda J, Iwahashi N. Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. J Am Coll Cardiol. 2010;55(22):2514-6.
65. Kurisu S, Inoue I, Kawagoe T, Ishihara M, et al. Time course of electrocardiographic changes in patients with tako-tsubo syndrome: comparison with acute myocardial infarction with minimal enzymatic release. Circ. J. 2004;68(1):77–81.
66. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nakama Y. Incidence and treatment of left ventricular apical thrombosis in Tako-tsubo cardiomyopathy. Int J Cardiol. 2011;146(3):e58-60.
67. Kurisu S, Kihara Y. Clinical management of takotsubo cardiomyopathy. Circ J. 2014;78(7):1559-66.
68. Kyriacou C. Identifying takotsubo cardiomyopathy. E-journal of Cardiology. 2012;10(27). Available at: http://www.escardio.org/communities/councils/ccp/e-journal/volume10/Pages/Takotsubo-Cardiomyopathy-identification-treatment.aspx#.VNkDbPnF_To.
69. Lindsay J, Paixao A, Chao T, Pichard AD. Pathogenesis of the Takotsubo syndrome: a unifying hypothesis. Am J Cardiol. 2010;106(9):1360-3.
70. Looi JL, Wong CW, Lee M, Khan A, Webster M, Kerr AJ. Usefulness of ECG to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. Int J Cardiol. 2015;199:132-40.
71. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy: a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med. 2008;5(1):22–9.
72. Madias JE. Follow-up of a patient who had suffered a "heart breaking pleasure"-triggered Takotsubo syndrome. Int J Cardiol. 2016;222:1057. (a)

73. Madias JE. History of anxiety and/or depression in patients with Takotsubo syndrome: A need for further exploration. Int J Cardiol. 2016;203:600. (b)
74. Marine JE. ECG Features that suggest a potentially life-threatening arrhythmia as the cause for syncope. J Electrocardiol. 2013;46(6):561-8.
75. Merchant EE, Johnson SW, Nguyen P, Kang C, Mallon WK. Takotsubo cardiomyopathy: a case series and review of the literature. West J Emerg Med. 2008;9(2):104-11.
76. Merli E, Sutcliffe S, Gori M, Sutherland GG. "Tako-Tsubo cardiomyopathy: new insights into the possible underlying pathophysiology". Eur J Echocardiogr. 2006;7(1):53-61.
77. Mori H, Ishikawa S, Kojima S, Hayashi J, Watanabe Y, Hoffman JI, Okino H. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. Cardiovasc Res. 1993;27(2):192–8.
78. Movahed A, Reeves WC, Mehta PM, Gilliland MG, Mozingo SL, Jolly SR. Norepinephrine-induced left ventricular dysfunction in anesthetized and conscious, sedated dogs. Int J Cardiol. 1994;45(1):23–33.
79. Müller HH, Sperling W, Kornhuber J.Cluster C. Personality Accentuation in Patients with Takotsubo Cardiomyopathy Personality Traits Mark Vulnerability. Psychiatr Danub. 2017;29(1):93.
80. Nakagawa M, Hamaoka K, Okano S, et al. Multiform accelerated idioventricular rhythm (AIVR) in a child with acute myocarditis. Clin Cardiol. 1988;11(12):853-5.
81. Nef HM, Mollmann H, Kostin S, Troidl C, Voss S, Weber M, et al. Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. Eur Heart J. 2007;(20):2456-64.
82. Novitzky D, Wicomb WN, Cooper DK, Rose AG, Reichart B. Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. Ann Thorac Surg. 1986;41(5):520–4
83. Omar HR, Faibairn J, Abdelmalak HD, Delibasic M, Camporesi EM. Postoperative takotsubo cardiomyopathy: an illustration of the electrocardiographic features that raise suspicion for takotsubo. Eur Heart J Acute Cardiovascular Care. 2013 Oct 21. (in press)
84. Ozaki K, Okubo T, Tanaka K, et al. Manifestation of Latent Left Ventricular Outflow Tract Obstruction in the Acute Phase of Takotsubo Cardiomyopathy. Intern Med. 2016;55(23):3413-20.
85. Parkkonen O, Allonen J, Vaara S, et al. Differences in ST-elevation and T-wave amplitudes do not reliably differentiate takotsubo cardiomyopathy from acute anterior myocardial infarction. J Electrocardiol. 2014;47(5):692-9.
86. Parkkonen O, Nieminen MT, Vesterinen P, et al. Low MMP-8/TIMP-1 reflects left ventricle impairment in takotsubo cardiomyopathy and high TIMP-1 may help to differentiate it from acute coronary syndrome. PLoS One. 2017;12(3):e0173371.

87. Pérez Riera AR, Ferreira C, Filho CF, et al. The enigmatic sixth wave of the electrocardiogram: the U wave. Cardiol J. 2008;15(5):408-21.
88. Pilgrim TM, Wyss TR. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. Int J Cardiol. 2008;124(3):283-92.
89. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J. 2008;155(3):408-17.
90. Pussinen PJ, Sarna S, Puolakkainen M, Ohlin H, Sorsa T, Pesonen E. The balance of serum matrix metalloproteinase-8 and its tissue inhibitor in acute coronary syndrome and its recurrence. Int J Cardiol. 2013;167(2):362-8.
91. Regitz-Zagrosek V. Gender and cardiovascular diseases : Why we need gender medicine. Internist (Berl). 2017. doi: 10.1007/s00108-017-0214-3.
92. Rosenbaum MB. Classification of ventricular extrasystoles according to form. J Electrocardiol. 1969;2(3):289-97.
93. Sato H, Tateishi H, Uchida T, et al. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. Clinical Aspect of Myocardial Injury: From Ischaemia to Heart Failure. Tokyo: Kagakuhyouronsya; 1990:56-64.
94. Sattler K, El-Battrawy I, Lang S, et al. Prevalence of cancer in Takotsubo cardiomyopathy: Short and long-term outcome. Int J Cardiol. 2017. pii: S0167-5273(17)31123-3. (in press)
95. Scantlebury DC, Prasad A. Diagnosis of takotsubo cardiomyopathy. Circ J. 2014;78(9):2129-39.
96. Scheffel H, Stolzmann P, Karlo C, et al. Tako-tsubo phenomenon: dual-source computed tomography and conventional coronary angiography. Cardiovasc Intervent Radiol. 2008;31(1):226-7.
97. Sclarovsky S, Strasberg B, Fuchs J, et al. Multiform accelerated idioventricular rhythm in acute myocardial infarction: electrocardiographic characteristics and response to verapamil. Am J Cardiol. 1983;52(1):43-7.
98. Sclarovsky S, Nikus K. The electrocardiographic paradox of tako-tsubo cardiomyopathy-comparison with acute ischemic syndromes and consideration of molecular biology and electrophysiology to understand the electrical-mechanical mismatching. J. Electrocardiol. 2010;43(2):173-6.
99. Sealove BA, Tiyyagura S, Fuster V. Takotsubo cardiomyopathy. J Gen Intern Med. 2008;23(11):1904-8.
100. Sharkey SW, Lesser JR, Menon M, Parpart M, Maron MS, Maron BJ. Spectrum and significance of electrocardiographic patterns, troponin levels, and thrombolysis in myocardial infarction frame count in patients with stress (tako-tsubo) cardiomyopathy and comparison to those in patients with ST-elevation anterior wall myocardial infarction. Am J Cardiol. 2008;101(12):1723-8.

101. Sharkey SW, Lesser JR, Garberich RF, Pink VR, Maron MS, Maron BJ. Comparison of Circadian Rhythm Patterns in Tako-tsubo Cardiomyopathy Versus ST-Segment Elevation Myocardial Infarction. Am J Cardiol. 2012;110(6):795-9.
102. Shimizu M, Takahashi H, Fukatsu Y, et al. Reversible left ventricular dysfunction manifesting as hyperkinesis of the basal and the apical areas with akinesis of the mid portion: a case report..J Cardiol. 2003;41(6):285-90.
103. Shimizu M, Kato Y, Matsukawa R, et al. Recurrent severe mitral regurgitation due to left ventricular apical wall motion abnormality caused by coronary vasospastic angina: a case report. J Cardiol. 2006;47(1):31-7.
104. Singh K, Carson K, Usmani Z, et al. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. Int J Cardiol. 2014;174(3):696-701.
105. Sobue Y, Watanabe E, Ichikawa T, et al. Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality. Int J Cardiol. 2017. pii: S0167-5273(17)31120-8.
106. Song BG, Chun WJ, Park YH, et al. The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: comparison with mid or apical variant. Clin Cardiol. 2011;34(11):693-9.
107. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev. 2007; 87(4):1285-342.
108. Spinale FG, Janicki JS, Zile MR. Membrane-associated matrix proteolysis and heart failure. Circ Res. 2013;112(1):195-208.
109. Stiermaier T, Rommel KP, Eitel C, et al. Management of arrhythmias in patients with Takotsubo cardiomyopathy: Is the implantation of permanent devices necessary? Heart Rhythm. 2016;13(10):1979-86.
110. Stiermaier T, Graf T, Möller C, et al. Transient left atrial dysfunction is a feature of Takotsubo syndrome. J Cardiovasc Magn Reson. 2017;19(1):15.
111. Suzuki K, Osada N, Akasi YJ, et al. An atypical case of “Takotsubo cardiomyopathy” during alcohol withdrawal: abnormality in the transient left ventricular wall motion and a remarkable elevation in the ST segment. Intern Med. 2004;43(4):300-5.
112. Syed FF, Asirvatham SJ, Francis J. Arrhythmia occurrence with takotsubo cardiomyopathy: a literature review. Europace 2011;13(6):780–8.
113. Tamura A, Watanabe T, Ishihara M, et al. A new electrocardiographic criterion to differentiate between Takotsubo cardiomyopathy and anterior wall ST-segment elevation acute myocardial infarction. Am J Cardiol. 2011;108(5):630-3.
114. Terefe YG, Niraj A, Pradhan J, Kondur A, Afonso L. Myocardial infarction with angiographically normal coronary arteries in the contemporary era. Coron Artery Dis. 2007;18(8):621-6.

115. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med. 2015;373(10):929-38.
116. Tsuchihashi K, Ueshima K, Uchida T, et al. Angina Pectoris-Myocardial Infarction Investigations in Japan.Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. J Am Coll Cardiol. 2001;38(1):11-8.
117. Vervaat FE, Christensen TE, Smeijers L, et al. Is it possible to differentiate between Takotsubo cardiomyopathy and acute anterior ST-elevation myocardial infarction? J Electrocardiol. 2015;48(4):512-9.
118. Wang Y, Xia L, Shen X, et al. A new insight into sudden cardiac death in young people: a systematic review of cases of Takotsubo cardiomyopathy. Medicine (Baltimore). 2015;94(32):e1174.
119. Weihs V, Szücs D, Fellner B, et al. Electrocardiogram changes and wall motion abnormalities in the acute phase of Tako-Tsubo syndrome. Eur Heart J Acute Cardiovasc Care. 2016;5(6):481-8.
120. Wittstein IS. The Sympathetic Nervous System in the Pathogenesis of Takotsubo Syndrome. Heart Fail Clin. 2016;12(4):485-98.
121. White M, Wiechmann RJ, Roden RL, et al. Cardiac fl-adrenergic neuroeffector systems in acute myocardial dysfunction related to brain injury: evidence for catecholamine-mediated myocardial damage. Circulation. 1995;92(8):2183–9.
122. Wu Y, Fan W, Chachula L, Costacurta G, Rohatgi R, Elmi F. Left ventricular outflow track obstruction and mitral valve regurgitation in a patient with takotsubo cardiomyopathy. J Community Hosp Intern Med Perspect. 2015;5(6):29419.
123. Yan GX, Yao QH, Wang DQ, Cui CC. Electrocardiographic J wave and J wave syndromes. Chin J Cardiac Arrhyth. 2004;8:360–5.
124. Yeh RW, Yu PB, Drachman DE. Takotsubo cardiomyopathy complicated by cardiac tamponade: classic hemodynamic findings with a new disease. Circulation. 2010;122(12):1239-41.
125. Yerasi C, Koifman E, Weissman G, Wang Z, et al. Impact of triggering event in outcomes of stress-induced (Takotsubo) cardiomyopathy. Eur Heart J Acute Cardiovasc Care. 2016. pii: 2048872616633881. (in press)