# Acute cerebellar ataxia associated with intermittent ECG pattern similar to Wellens syndrome and transient prominent QRS anterior forces

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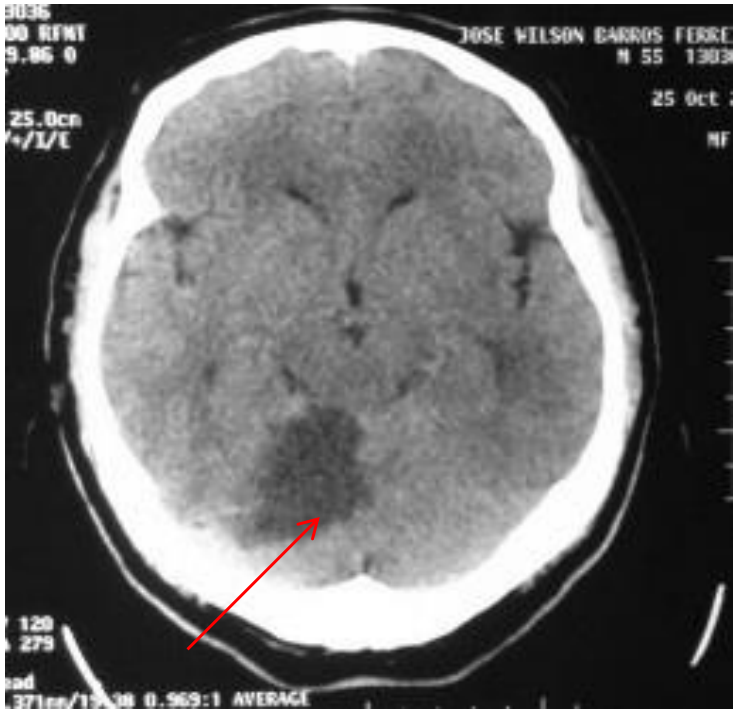
Male patient, 56 years old, white, uncontrolled hypertension, was admitted to our emergency department (ED) with reports of sudden dizziness, headache of abrupt onset, nausea, vomiting and weakness in the lower limbs.

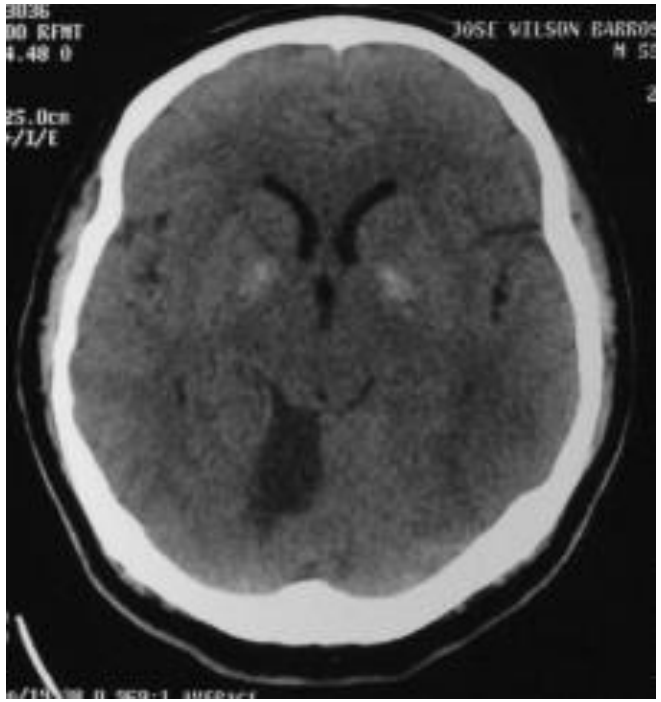
Physical examination drew attention to the presence of manifestations suggestive of cerebellar syndrome: impaired coordination in the trunk or arms and legs, inability to coordinate balance, gait, extremity, uncontrolled or repetitive eye movements, (nystagmus), dyssynergia, dysmetria, dysdiadochokinesia, dysarthria (cerebellar ataxia).

Normal myocardial necrosis markers and normal electrolytes

ECO 1: anteroseptal-apical akinesis; LVEF = 30%

ECO 2 (third day): anteroapical akinesis; LVEF = 47%

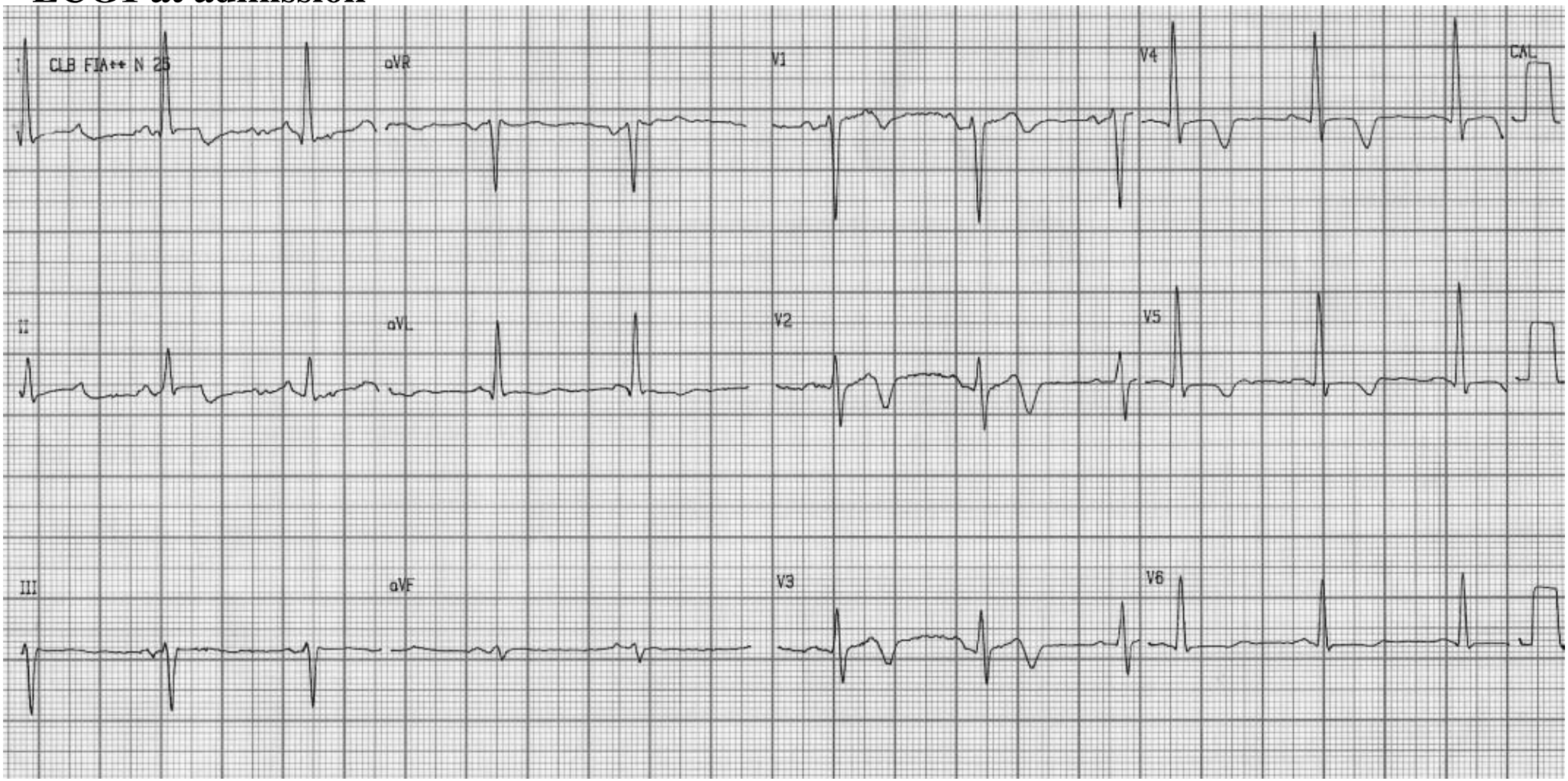


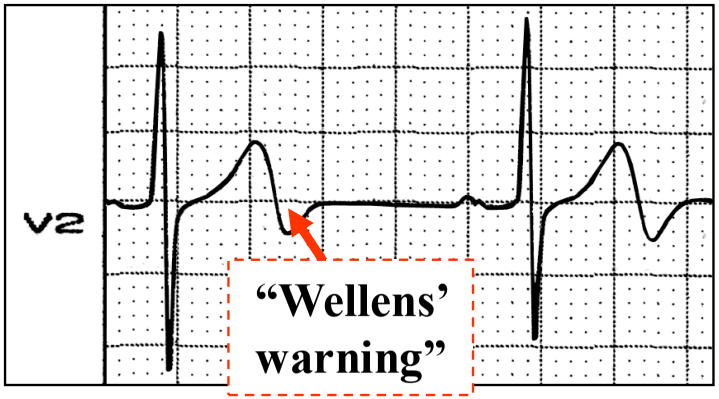

Cranial CT scan: regions of hyperdensity within the right cerebellar hemisphere

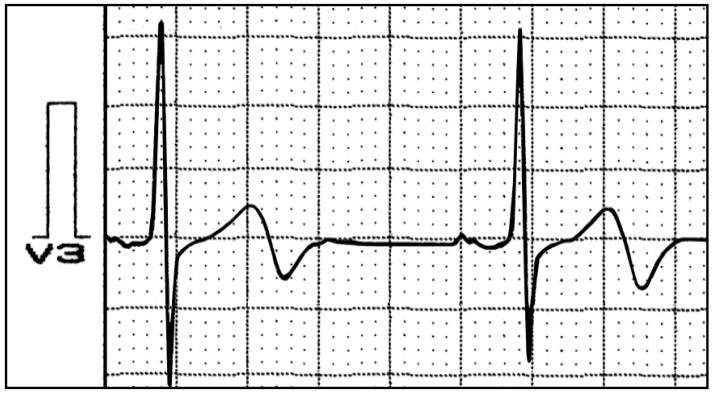
Coronary angiography: coronary lesions with minimal irregularities

# ECG1 at admission

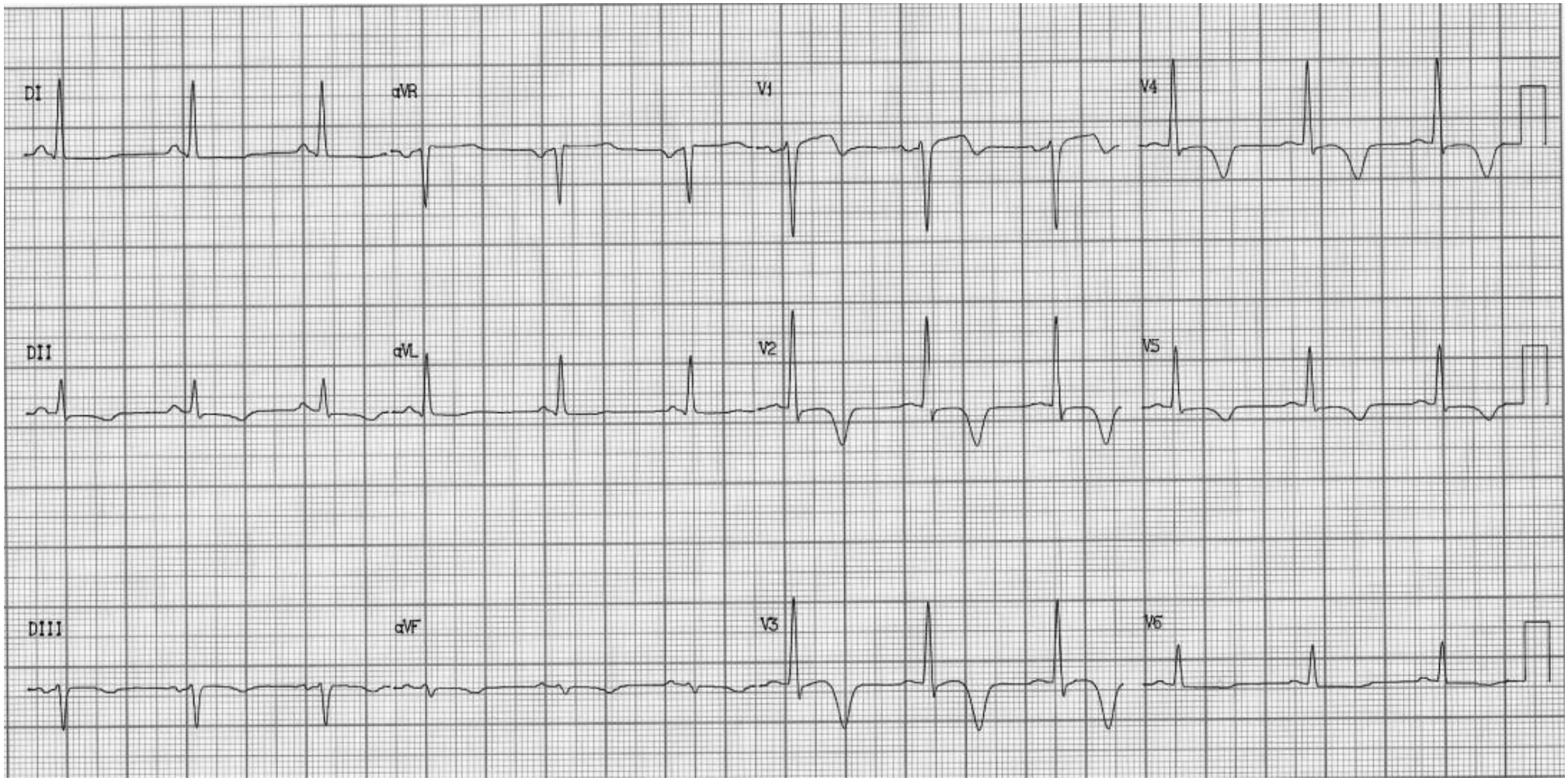



## Wellens type A or 2 pattern

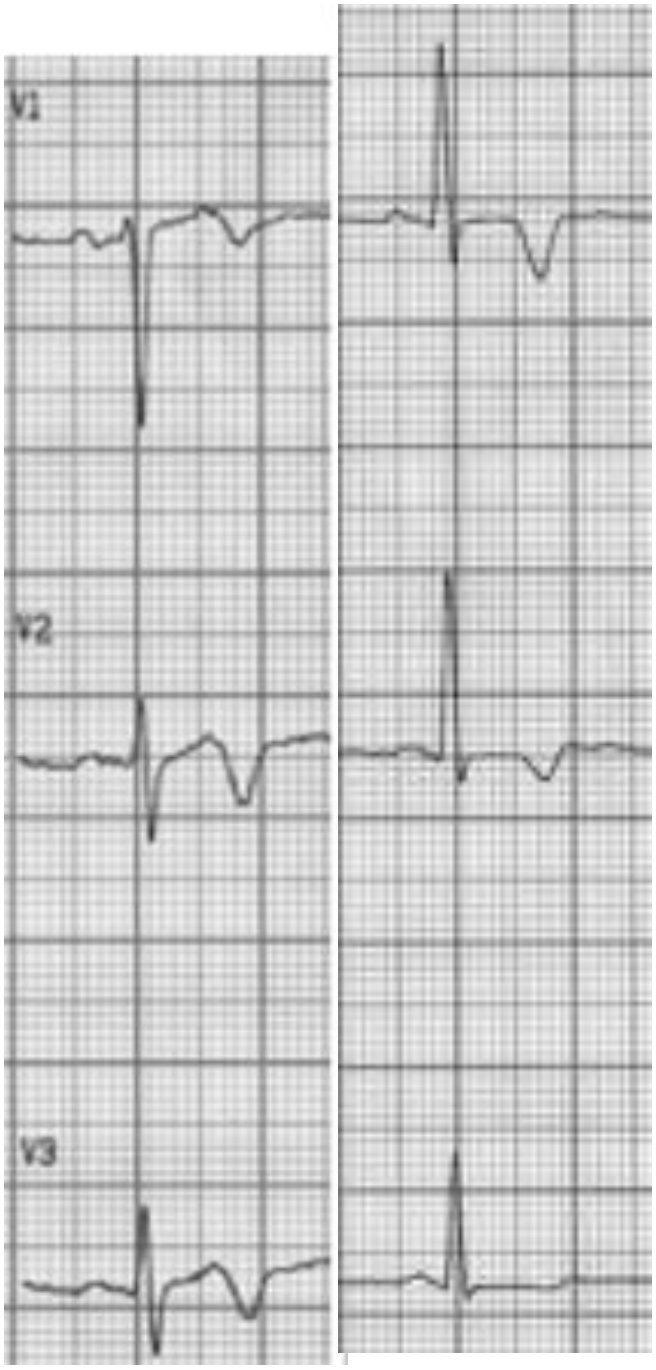


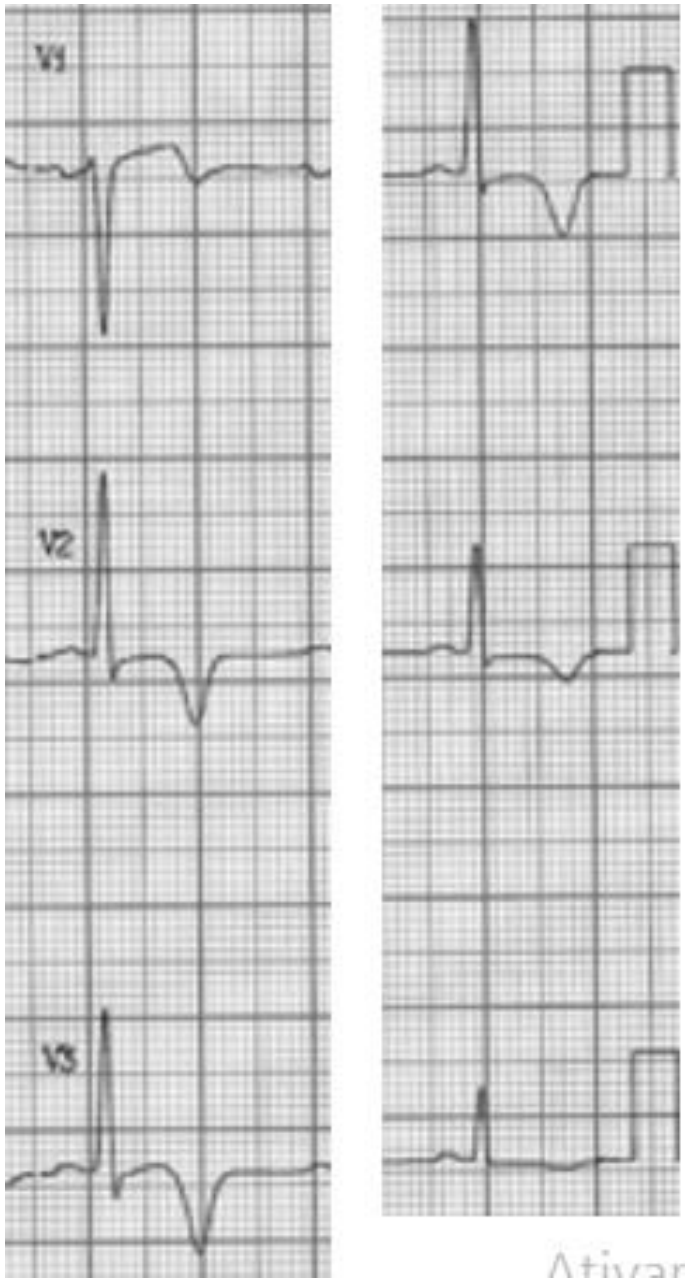
## ECG-2 3 hours later

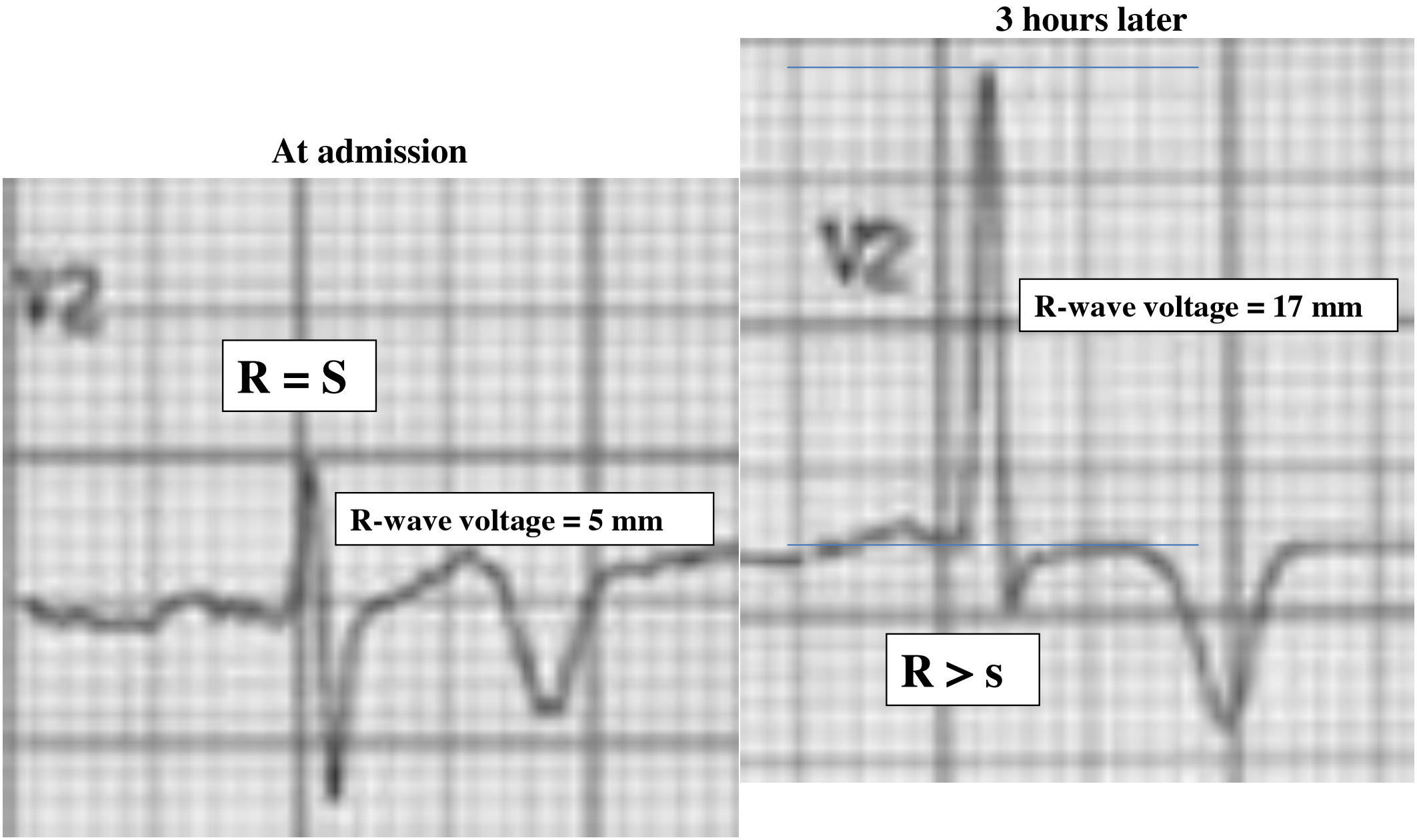


**ECG1 admission**



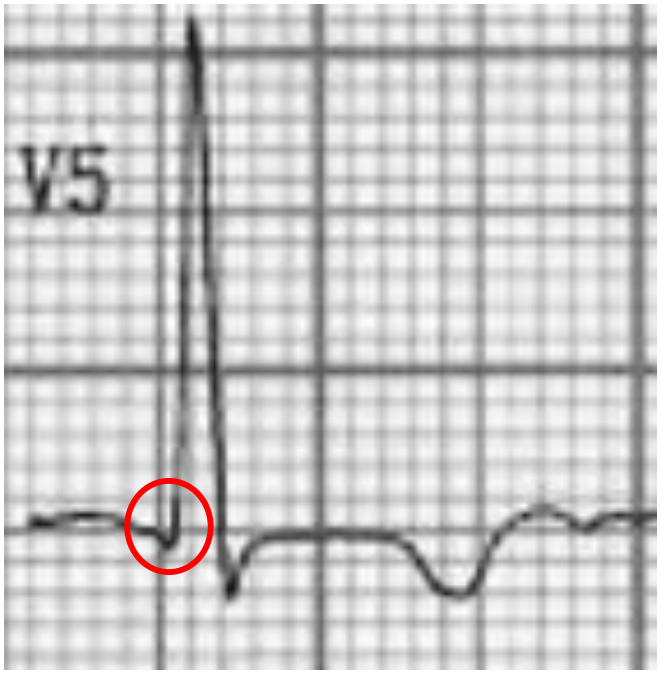

**ECG 2 three hours later**

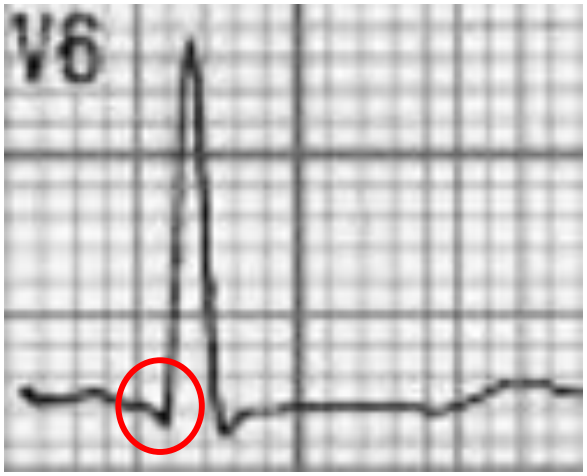





Question:
Which is the electrophysiological explanation of the transient QRS anterior forces?

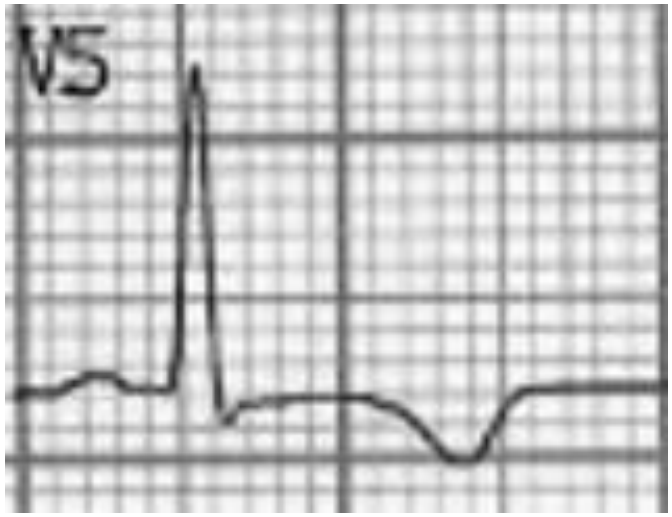
**At admission**

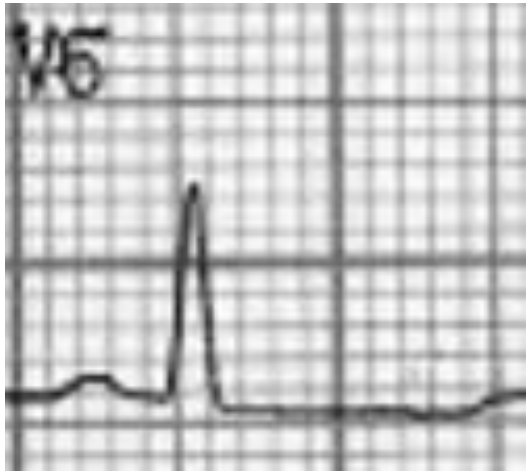



**qRs**

**3 hours later**

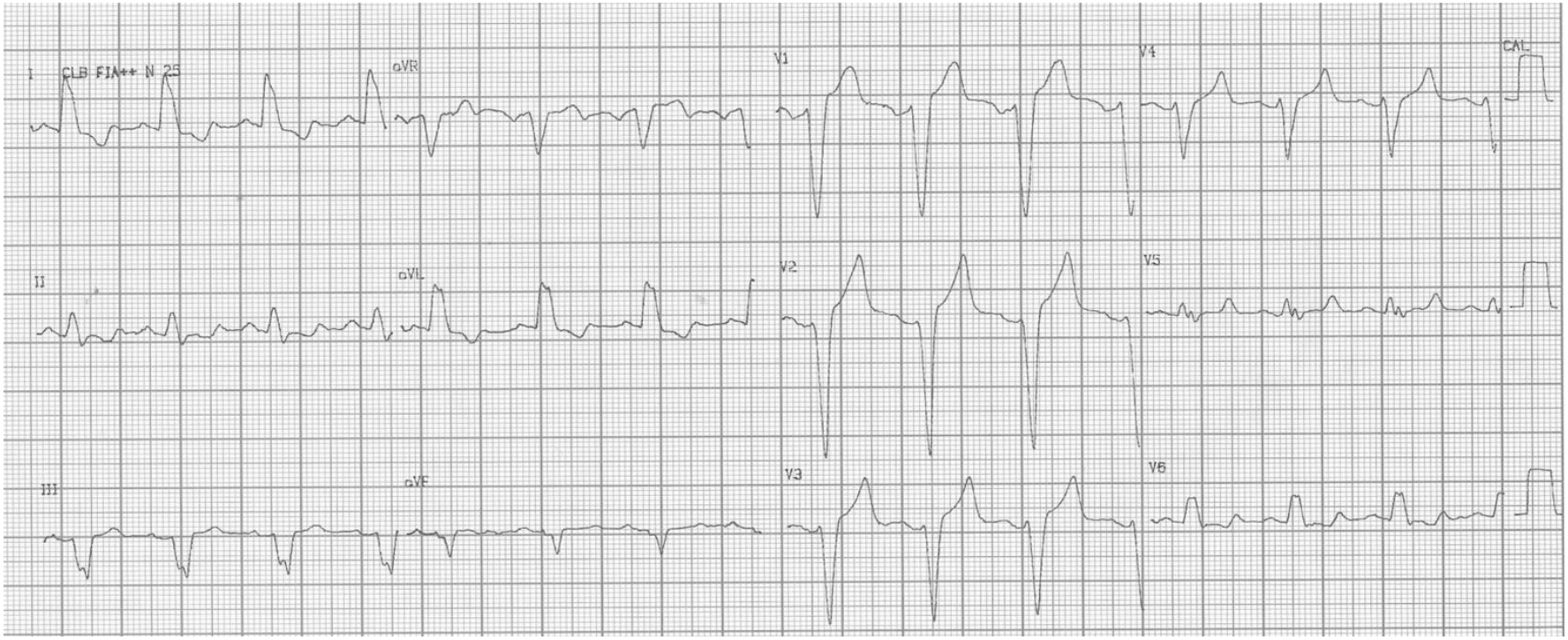



**Rs and R**

Why does the initial embryonic q-wave disappear and the R-wave voltage decreased in left precordial leads 3 hours later?

**2 days later**




Typical LBBB. Recently Ito et al (**Ito 2015**) presented a case of TCM with LBBB. The patient was 81-year-old man referred to ED with severe persistent chest pain. One year before, his ECG revealed a normal QRS pattern during the period of normal conduction with intermittent LBBB. His ECG immediately after arrival showed deep T-wave inversion in the precordial leads during normal conduction. During LBBB, there was mild ST-SE with poor R-wave progression across the precordial leads. Cardiac catheterization was performed to rule out ACS. Coronary angiography showed no significant stenosis, and coronary spasm was not provoked by the administration of intracoronary ergonovine. Left ventriculography demonstrated persistent LV apical akinesis with systolic ballooning. The patient was diagnosed to have TCM. After 6 months, echocardiography demonstrated the recovery of the LV regional wall motion abnormality. An ECG performed 6 months after the presentation showed incomplete resolution of T-wave inversion in the periods of normal conduction. ST-SE and poor R-wave progression were improved during LBBB. In a case with acute chest pain and an ECG changes incompatible with acute ischemia superimposed on a pattern of LBBB, TCM should be considered as a differential diagnosis. New echo: LVEF = 40%

## Discussion

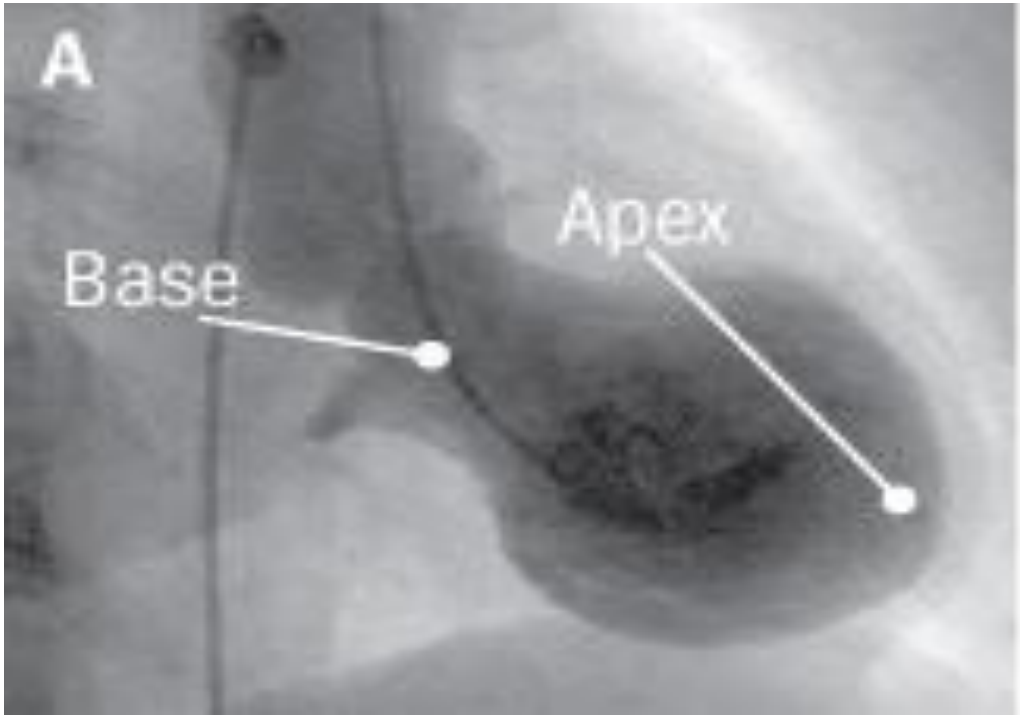
This patient has several elements to think in a "apical ballooning-like syndrome" without coronary artery stenosis, also know as Takotsubo cardiomyopathy (TCM) (**Sealove 2008**) (*takotsubo* translates to "octopus pot") transient left ventricular (LV) apical ballooning syndrome, "ampulla-shaped cardiomyopathy", transient LV dysfunction, broken heart syndrome, or stress cardiomyopathy because the very transient and dynamic changes observed on the LV function without coronary atherosclerosis obstruction (**Terefe 2007**). Here we observe the presence of the four criteria of the Mayo Clinic (**Kawai 2007**).

1. Transient hypokinesis, dyskinesia or akinesia of anteroapical wall of the LV
2. Absence of obstructive CAD
3. Dynamic modifications of T waves polarity with absence of biomarkers elevation, and
4. Absence of pheocormocitoma or myocarditis.
5. The acute encephalic event insult release large amount of endogenous catecholamine-induced neurogenic myocardial stunning (a reversible reduction of function of heart contraction) and microinfarctions. This is the explanation for the transient ventricular dysfunction as demonstrated in the present case by successive echoes with early improvement in LV ejection fraction (EF).

The apical selective commitment of this area of the LV is consequence of the highest concentration of sympathetic innervation related to the other segment of of the LV (**Aoki 2015**) which may explain that selectively affectation this segment (**Dorfman 2009**) . We must remember that the middle division of the left bundle branch is precisely located in the apical area which may explain the involvement of the middle fasciculus that would determine the prominent anterior QRS forces observed from V2 to V4 followed by negative T waves and the concomitant changes occurring in the lower lateral-apical precordial leadsV5-V6: absence of initial q wave an lower voltage of R waves. There would be transient impairment of septal division means that the path of the medium bundle is in the middle-apical region which is the region with higher concentration of sympathetic innervation as also occurs in cases of critical proximal obstruction of LAD artery.

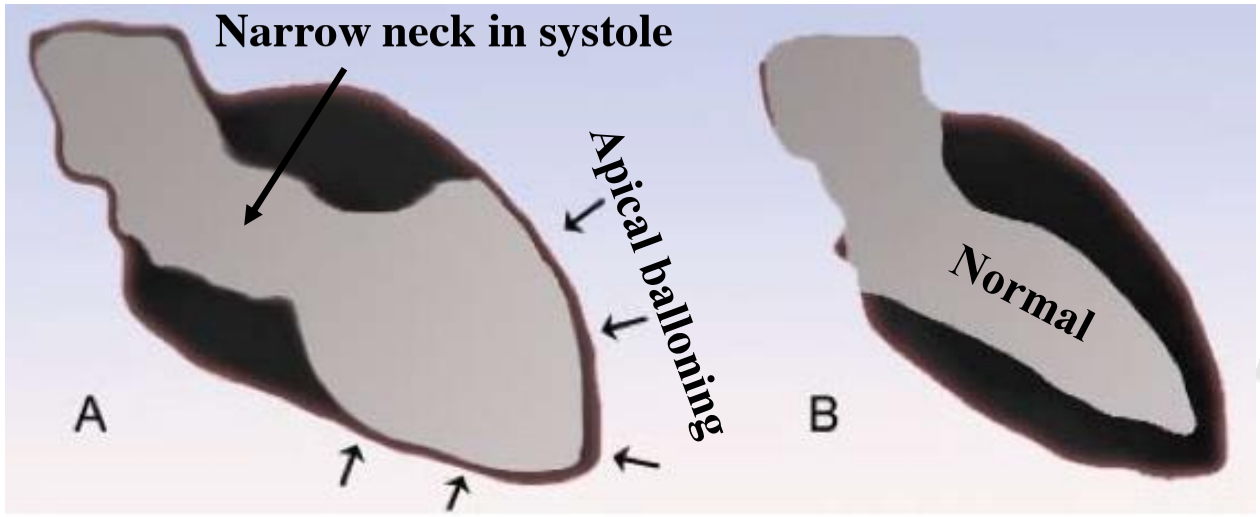
Stress cardiomyopathy is a form of myocardial stunning, but with different cellular mechanisms to those seen during transient episodes of ischemia secondary to coronary stenosis. High levels of circulating epinephrine trigger a switch in intracellular signal trafficking in ventricular cardiomyocites, from $G_s$protein to $G_i$ protein signaling via the $\beta_2$-adrenoceptor (autonomic dysfunction) (**Khalid 2015**). The most commonly discussed possible mechanism for TCM is stress-induced catecholamine release, with toxicity to and subsequent stunning of the myocardium. 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 α-blocker or β-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 triggered by multivessel spasm, thrombosis, epicardial vessel occlusion, or direct myocardial toxicity remains to be seen. They point out that the wall-motion abnormality of TCM can be seen in other conditions, including those with certain LAD obstructions (**Dorfman 2009**), making wall motion alone insufficient for the diagnosis of TCM (**Carrillo 2010**). Cases of TCM have been reported in the literature following cocaine, methamphetamine, and excessive phenylephrine use ( **Khallafi 2008**) in the absence of a protective mechanism. d'Avenia et al (**d'Avenia 2015**) sequenced BAG3 gene in 70 TCM patients and in 81 healthy donors with the absence of evaluable cardiovascular disease. Mutations and polymorphisms detected in the BAG3 gene included a frequent nucleotide change g2252c in the BAG3 3'-untranslated region (3'-UTR) of TCM patients, resulting in loss of binding of microRNA-371a-5p (miR-371a-5p) as evidenced by dual-luciferase reporter assays and argonaute RNA-induced silencing complex catalytic component 2/pull-down assays. The authors describe a novel signaling pathway in cardiomyocytes that leads to BAG3 upregulation on exposure to catecholamine through an ERK-dependent upregulation of miR-371a-5p. They concluded that the presence of a g2252c polymorphism in the BAG3 3'-UTR determines loss of miR-371a-5p binding and results in an altered response to catecholamine, potentially representing a new molecular pathogenesis for TCM.

## *Takotsubo* mean " octopus pots”



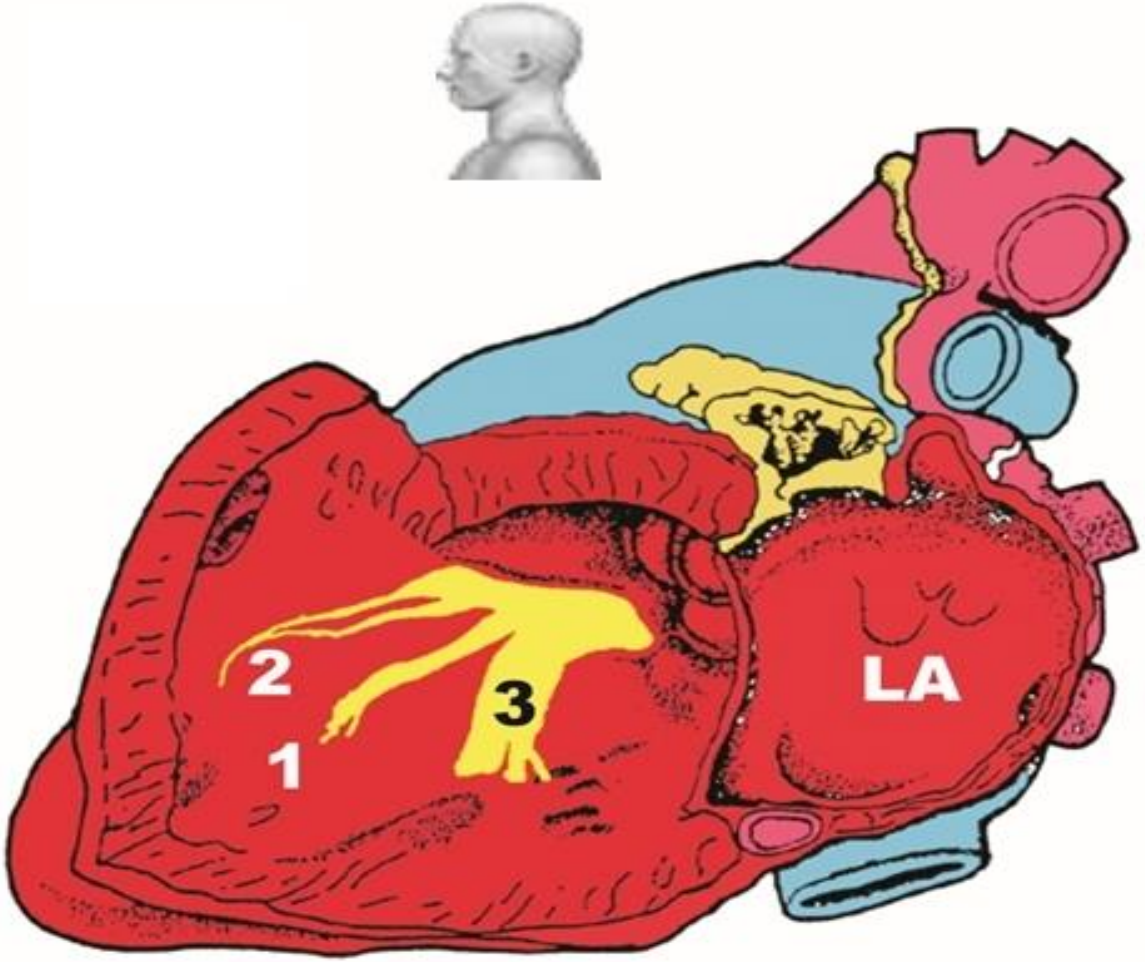


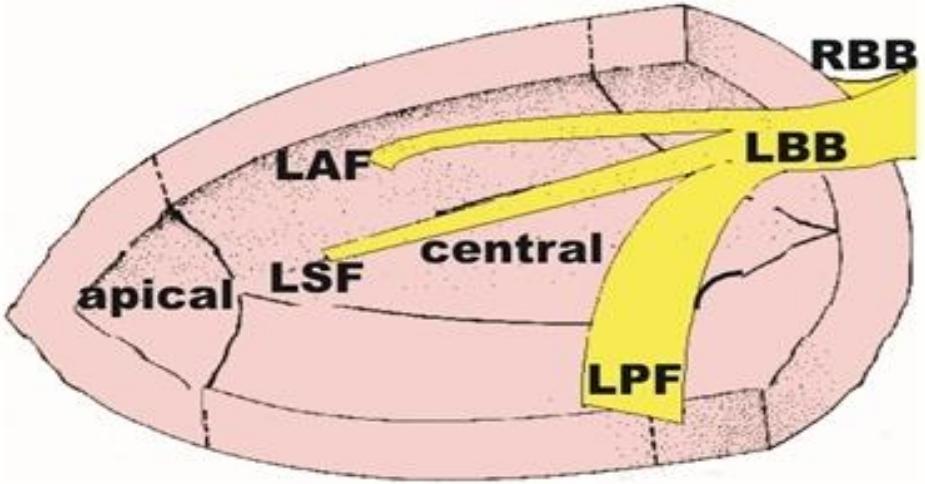
An x-ray of the LV (**A**) shows apical ballooning, a reversible abnormality characteristic of TCM. During systole (cardiac contraction) the midsection and tip (apex) of the LV balloon out, while the area above, called the base, contracts normally. The shape is similar to that of a TCM (B), a round-bottomed, narrow-necked vessel used to catch octopuses.




**octopus pots**

# Left sagital view of open LV and lefft fascicles distrubutions




1) LSF - Left Septal Fascicle
2) LAF - Left Anterior Fascicle
3) LPF - Left Posterior Fascicle

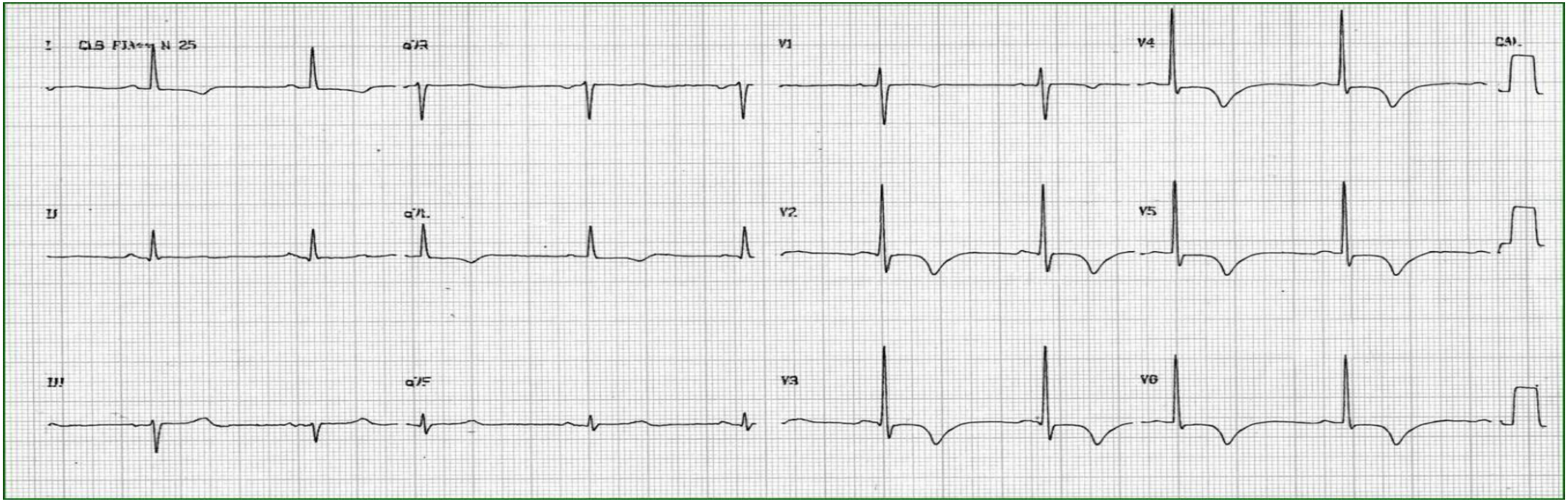
PA – Pulmonary Artery
LA – Left Atrium

LBB – Left Bundle Branch
RBB – Right Bundle Branch

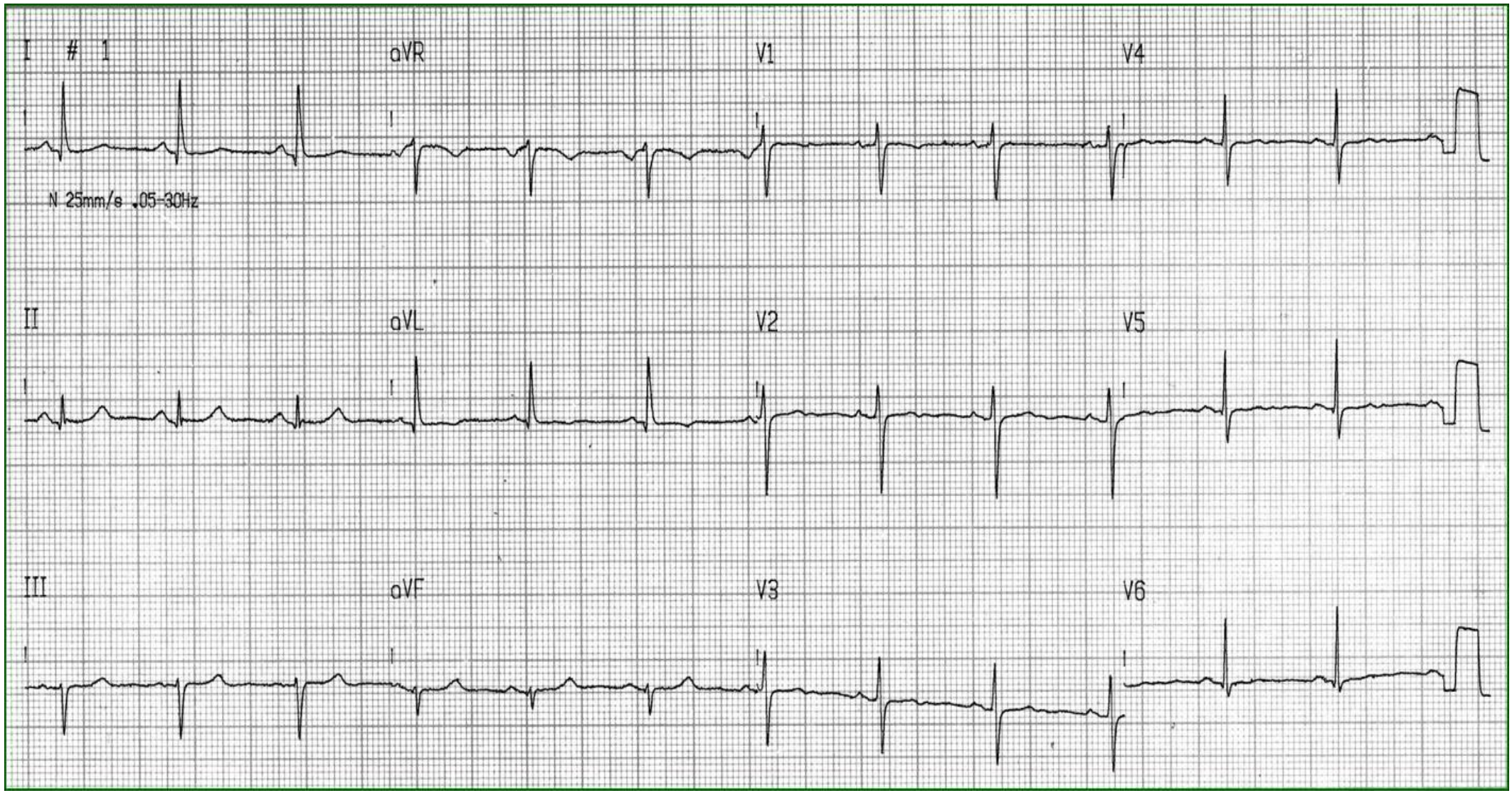
The figure shows the distribution and trajectory of the three fascicles (LSF, LAF, and LPF) of the left intraventricular His system in a longitudinal left sagittal view (A) In these two figures, we can see that the LAF ends in the anterolateral papillary muscle (ALPM), the LPF in the posteromedial papillary muscle (PMPM), and the LSF in the centroseptal and apical region of the interventricular septum (IVS).

Seven years ago we presented for the first time in the literature a case of Wellens syndrome associated with LSFB (**Riera 2008**). This is a clinical-electrocardiographic entity with symptoms and signals indicating the existence of an undesirable condition, secondary to critical high-grade proximal stenosis of the LAD artery, characterized by the association of prior history of ACS, little or no elevation of markers of myocardial damage (unstable angina), characteristic ECG changes consistent with anterior ischemic pattern in the LAD territory ($V_1$ through $V_5$ or $V_6$) (**de Zwaan 1982**): Plus-minus T waves with inversion of the terminal portion or persistently symmetrical, deep negative and broad-based T-waves (type 2). Sensitivity and specificity for significant (≥ 70%) stenosis of the LAD artery was found to be 69% and 89% respectively with positive predictive value at 86% (**Haines 1983**).

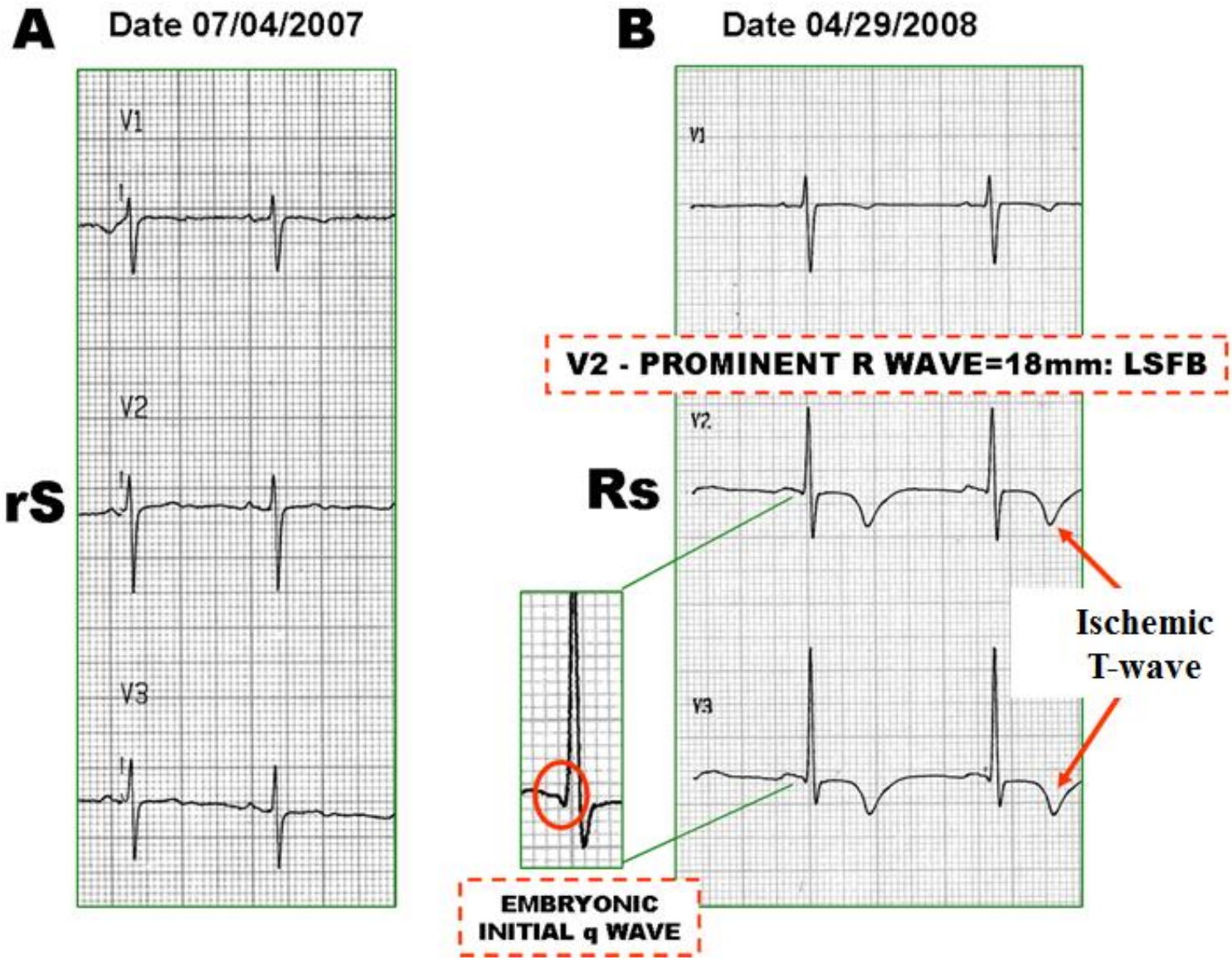
ECG performed upon arrival to the ED (04/29/2008), and while having chest pain. Deep negative and broad-based T-wave inversions in precordial leads from $V_2$ through $V_6$, with high voltage R wave in $V_2$ (R = 18 mm). Initial small q waves were observed in $V_2$-$V_3$. Left septal initial q waves in left leads are absent. R/S ratio in $V_2$ > 2 + S wave depth in $V_2$ < 5 mm.




**Conclusion**: Type 2 Wellens' pattern associated with prominent anterior forces: several LSFB criteria are present.




ECGs performed one year before clinical manifestation (07/04/2007). There is no ischemic T wave pattern and QRS complexes of the rS type in $V_2$. Initial q waves are observed in left leads I, aVL, $V_5$ and $V_6$.




A) Basal anteroseptal precordial leads performed approximately one year before the onset of the clinical picture.

B) The same leads performed during the clinical manifestation. A transient form of LSFB; observed in an ACS scenario in a 72-year-old male, admitted in the ED with typical precordial pain that yielded after the administration of IV nitroglycerin. The coronary angiography revealed LMCA spasm and proximal critical lesions of the LAD. **Management:** The patient was urgently revascularized, successfully (Coronary Artery Bypass Graft).

## Risk factors

A significant emotional or physical stressor typically precedes the development of the TCM. Stressors include learning of a death of a loved one; bad financial news; legal problems; natural disasters; motor vehicle collisions; exacerbation of a chronic medical illness; a newly diagnosed, significant medical condition; surgery; an intensive care unit stay; and the use of or withdrawal from illicit drugs. TCM has also been reported after near-drowning episodes.(**Buchholz2007**)

Epidemiology: Studies reported that 1.7-2.2% of patients who had suspected acute coronary syndrome (ACS) were subsequently diagnosed with TCM. ( **Citro 2008; Bybee 2004**)Patients are typically Asian or Caucasian. In a literature review of cases in which race was reported 57.2% were Asian, 40% were Caucasian, and 2.8% were other races. (**Ito 2003**)

Literature reviews report a mean patient age of 67 years, although cases of TCM have occurred in children and young adults (**Lindsay 2010, Dhoble 2008**). Nearly 90% of reported cases involve postmenopausal women (**Pilgrim 2008**).

The prognosis in TCM is excellent, with nearly 95% of patients experiencing complete recovery within 4-8 weeks (**Gianni 2006; Pilgrim 2008**). A study by Singh et al (**Singh 2014**) indicated that the annual recurrence rate is approximately 1.5% but that the frequency of ongoing symptoms is greater (**Prasad 2008**). Estimates of mortality rates have ranged from 1-3.2% (**Gianni 2006; Pilgrim 2008**).

## Complications (present in ≈20% of cases)

- Left heart failure with and without pulmonary edema
- Cardiogenic shock
- LV outflow obstruction
- Mitral regurgitation
- Ventricular arrhythmias
- LV mural thrombus formation
- LV free-wall rupture (**Aoki 2015**)
- Death (**Singh 2014; Bybee 2004**)

The clinical presentation of patients ultimately diagnosed with TCM is usually indistinguishable from that of ACS. The most common presenting symptoms are chest pain and dyspnea, although palpitations, nausea, vomiting, syncope, and rarely, cardiogenic shock have been reported. 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. Unlike ACS, in which peak occurrence is during the morning hours, TCM events are most prevalent in the afternoon, when stressful triggers are more likely to take place (**Merchant 2008**). A large systematic review found 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. (**Gianni 2006**).

Physical examination findings are nonspecific and often normal, but the patient may have the clinical appearance of having ACS or acute CHF. Patients may appear anxious and diaphoretic. Tachydysrhythmias and bradydysrhythmias have been reported, but the average heart rate in one review was 102 bpm (**Khallafi 2008**).

Hypotension can occur from a reduction in stroke volume because of acute LV systolic dysfunction or outflow tract obstruction. Murmurs and rales may be present on auscultation in the setting of acute pulmonary edema.

## Diagnoses

Physicians should be aware of the presentation of TCM, because chest pain after a recent stressor is not necessarily due to anxiety. The chest pain may be more complicated and deteriorate into dysrhythmias and/or shock. Patients with TCM do not usually have cardiac risk factors, but their pain should be taken seriously. Also, patients may present to the ED after a natural disaster, and providers should be aware that the incidence of TCM might increase soon afterward. These patients should be treated in the ED as having ACS, given supportive treatment, and undergo subsequent cardiology evaluation. (**Sharkey 2012**).

Atypical forms of TCM have been described with varying wall-motion abnormalities, including right ventricular and basal/midventricular akinesia. Clinically, these patients tend to present similarly to the classic form (**Gianini 2006**).

# Differential diagnosis

- Esophageal spasm
- ACS
- Gastroesophageal reflux disease
- Myocardial ischemia
- Myocarditis
- Acute pericarditis
- Pneumothorax
- Cardiogenic pulmonary edema
- Pulmonary embolism
- Unstable angina
- Aortic dissection
- Boerhaave syndrome (transmural perforation of the esophagus)
- Cardiac tamponade
- Cardiogenic shock
- Cocaine related
- Cardiomyopathy
- Coronary artery vasospasm
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy.

Cardiac markers, specifically troponin I and T, are elevated in 90% of patients with TCM, although to a lesser magnitude than is seen in STEMI. The brain natriuretic peptide level is also frequently elevated. As with any patient in whom ACS is suspected, electrocardiography should be the initial test obtained soon after presentation to the ED. Transthoracic echocardiography provides a quick method of diagnosing wall motion abnormalities typically seen in TCM, specifically hypokinesis or akinesis of the midsegment and apical segment of the LV. The diagnosis of TCM is typically confirmed with cardiac angiography.

**Laboratory:** At the time of admission, the mean troponin T level has been found to be 0.49 ng/mL (normal < 0.01) and the mean troponin I level has been reported as 4.2 ng/mL (normal < 0.04), in patients with TCM, while mean peak values during hospitalization for troponin T and troponin I have been demonstrated to be 0.64 and 8.6 ng/mL, respectively.

The brain natriuretic peptide level is frequently elevated, especially in those patients demonstrating left heart failure, as it is an indicator of increased LV end-diastolic pressures that result from the stunned myocardium.

Several studies looked at levels of circulating catecholamines in the acute phase and found that nearly 75% of patients had elevations markedly higher than did patients with STEMI (**Scantlebury 2014; Sharkey 2008** ).

As with any patient in whom ACS is suspected, ECG should be the initial test obtained soon after presentation to the ED. ST-segment elevation (67-75%) and T-wave inversion (61%) are the most common abnormalities seen on the initial ECG. 95% of ST-SE have been found to involve the precordial leads and to be maximal in leads $V_2$ -$V_3$. When compared with patients with STEMI from LAD artery occlusion, the amplitude of ST-SE in patients with TCM was significantly less.

**Transthoracic echocardiography** provides a quick method of diagnosing wall-motion abnormalities typically seen in TCM (**Kolkebeck. 2007**), specifically hypo kinesis or akinesis of the midsegment and apical segment of the LV. Perhaps most importantly, these wall motion abnormalities extend beyond the distribution of any single coronary artery.

**Electrocardiography** As with any patient in whom ACS is suspected, ECG should be the initial test obtained soon after presentation to the ED. ST-SE(67-75%) and T-wave inversion (61%) are the most common abnormalities seen on the initial ECG. 95% of ST-SE have been found to involve the precordial leads and to be maximal in leads $V_2$ -$V_3$. When compared with patients with STEMI from LAD artery occlusion, the amplitude of ST-SE in patients with TCM was significantly less. An initially normal or nonspecific ECG finding is seen in 15% of patients with TCM. Diffuse T-wave inversions tend to occur in the days and weeks following presentation as the ST-segments normalize. T-wave inversion is more common than ST-SE (**Yayehd 2015**). No reliable way to differentiate TCM from STEMI is possible based solely on ECG findings (**Bybee 2004**). In a retrospective study of 33 patients with TCM, the authors proposed ECG criteria to distinguish TCM from anterior AMI in those who presented within 6 hours of symptom onset.

The combination of absent abnormal Q-waves, absent reciprocal changes, lack of ST-SE in lead $V_1$, and presence of ST-SE in lead aVR had more than 91% sensitivity and 96% specificity for TCM (**Citro 2014**).

The LVEF can be estimated by echocardiogram, cardiac magnetic resonance imaging (MRI), or left ventriculography. Mean LVEF on admission has been found to range from 20-49%.

Echocardiography is commonly used in following the resolution of the cardiomyopathy and impaired LV function, with LVEF improving to 59-76% on average, by day 18.

**Cardiac angiography:** The diagnosis of TCM is typically confirmed in the cardiac catheterization laboratory. In a review of 240 patients diagnosed with TCM, 211 were found to have completely normal coronary arteries, whereas the remainder had noncritical stenosis. The prevalence of normal coronary arteries by angiography in patients presenting with STEMI ranges from 1-12%. Aside from TCM, this phenomenon may be explained by transient vessel occlusion with spontaneous thrombolysis, by vasospasm, or it may be drug related. Left ventriculography is perhaps the best imaging modality to demonstrate the pathognomonic wall motion and to evaluate LVEF (**Gianni 2006; Pilgrim 2008**).

**Chest radiographs** in TCM are often normal, but they may demonstrate pulmonary edema. CMR imaging may be a diagnostic modality uniquely suited for establishing the diagnosis of TCM by accurately visualizing regional wall motion abnormalities, quantifying LV function, and identifying reversible injury to the myocardium by the presence of edema/inflammation and the absence of necrosis/fibrosis (**Kosuge 2010**).

This technology may give new insight into the pathophysiology of TCM and be of potential use at acute presentation, broadening recognition and improving clinical outcomes (**Kohan 2014**). In addition to evaluating wall-motion abnormalities and LVEF, cardiac MRI has been found to differentiate TCM, characterized by the absence of delayed gadolinium hyper enhancement, from MI and myocarditis, in which the opposite occurs. Although not indicated in the initial evaluation of patients with TCM, reports are emerging of the use of coronary computed tomography (CT) angiography in the subsequent evaluation of patients with the disorder (**Eitel 2011; Scheffel 2008**).

**Exercise stress testing**, which is known to cause increased levels of catecholamines, has resulted in false positives attributable to TCM ( **Lindsay 2010**). 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 (**Dhoble 2008**). The apical portions of the LV have the highest concentration of sympathetic innervation found in the heart and may explain why excess catecholamines seem to selectively affect its function ( **Khallafi 2008**).

## Management

Patients should be treated as having ACS until proven otherwise. Addressing the airway, breathing, and circulation; establishing intravenous access, and providing supplemental oxygen and cardiac monitoring should take precedence. Testing in the ED should include ECG, chest radiography, cardiac biomarker levels, brain natriuretic peptide level, and other appropriate laboratory studies.

If the patient continues to manifest a clinical picture consistent with ACS, especially STEMI, then standard therapies, such as the following, may be indicated: aspirin, β-blockers, nitrates, heparin or enoxaparin, platelet glycogen (GP) IIb/IIIa inhibitors, morphine and clopidogrel.

Patients in acute CHF may require diuresis, and patients with cardiogenic shock may require resuscitation with intravenous fluids and inotropic agents. If available, bedside echocardiography could show the characteristic wall-motion abnormality.

The insertion of an intra-aortic balloon pump has also been reported as being a successful resuscitative intervention, due to LV outflow obstruction that can result from a hyperkinetic basal segment and dyskinetic apex.

Fluids and β- blockers, or calcium channel blockers, are beneficial in this situation, whereas inotropes may exacerbate the problem and should be used with caution.

Dysrhythmias and cardiopulmonary arrest should be treated using current advanced cardiac life support (ACLS) protocols. Although thrombolytic will not benefit patients with TCM, their use should not be withheld when PCI is not available and patients otherwise meet criteria (**Kurisu 2009**; **Bybee 2004**).

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