Severe coronary spasm in elderly man with respiratory and renal failure

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Case presentation

Male, 78-year-old patient, hypertensive (he couldn't tell about his medication), dyspnea, productive cough and fever not measured for 15 days, with worsening the day he was admitted. He had been taking Ceftriaxone (a cephalosporin antibiotic) with no improvement.

Clinical history: social drinker; former smoker (he quitted 20 years before).

Admission: General regular state, agitated, tachypneic, cooperative, oriented. BP = 150 x 70 mmHg

Cardiac examination: regular cardiac rhythm, normal heart sounds and no murmurs, HR: 76 bpm.

Pulmonary examination: globally decreased gross vesicular murmurs with crepitations at the bases. Respiratory rate: 32.

Limbs: cold

He evolved into respiratory failure.

Associated to symptoms of kidney insufficiency

New regimen is started: antibiotics + mechanical ventilation + hemodialysis

Chest X-ray: compatible with pneumonia.

5 days after the admission he developed mixed shock with renal function worsening associated with metabolic acidosis and hyperkalemia, all refractory in spite of therapeutic measures (K=10.2mEq/L). High doses of noradrenaline were applied.

ECG was performed, revealing ST segment elevation, so he was referred to the hemodynamic lab.

Coronary angiography revealed significant obstructive lesions; however it showed diffuse coronary artery spasm (RCA + left main coronary artery) that was reverted with intracoronary isosorbide mononitrate.

After the result of left heart catheterization, a therapeutic dilemma arose: reducing the dose of noradrenaline (because of the spasm) or keep the high dose to increase BP and allow the hemodialysis.

Hemodialysis was contraindicated by the nephrologist due to refractory hypotension.

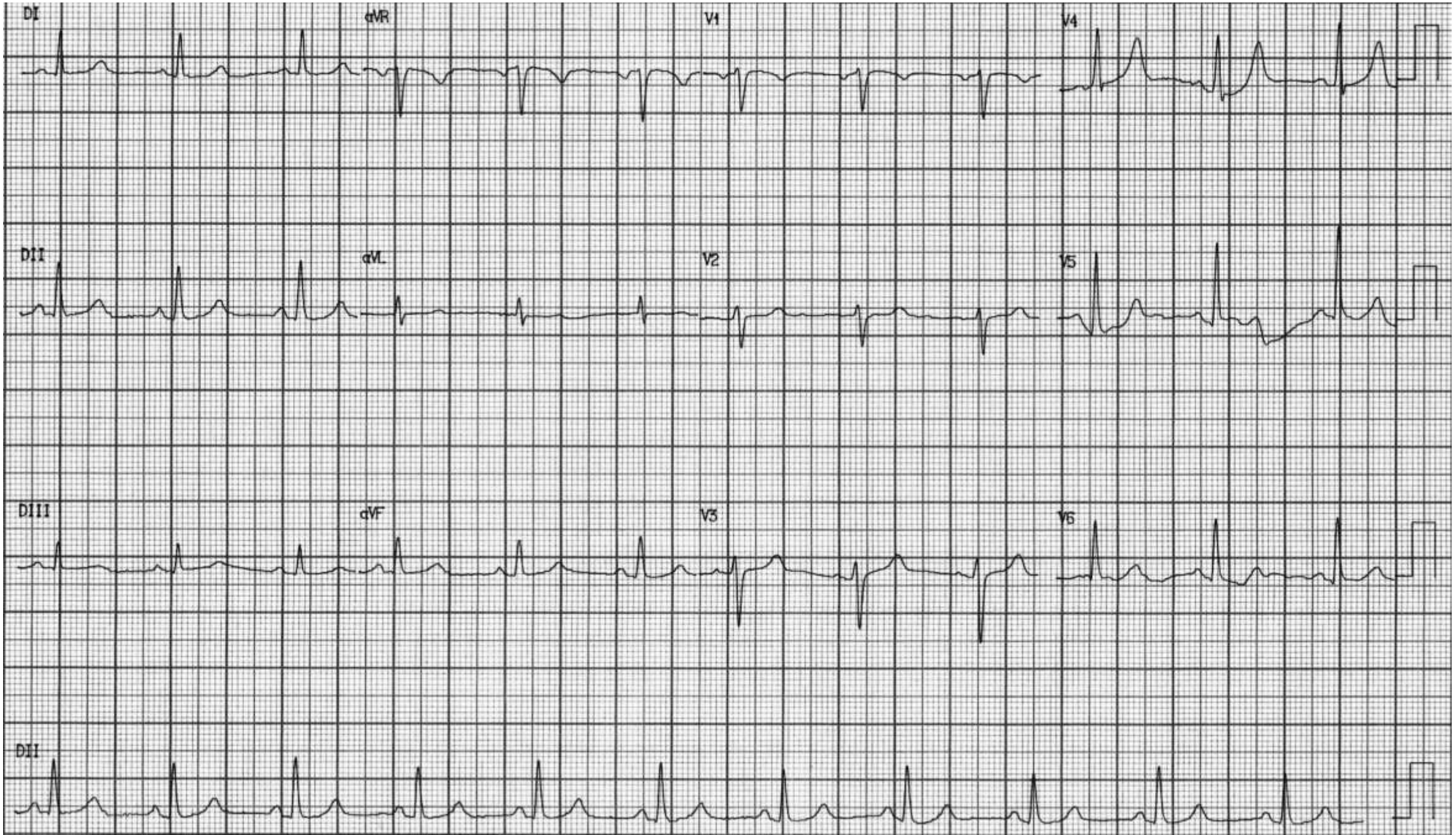
After the catheterization, he died in asystole/pulseless electrical activity.

Questions:

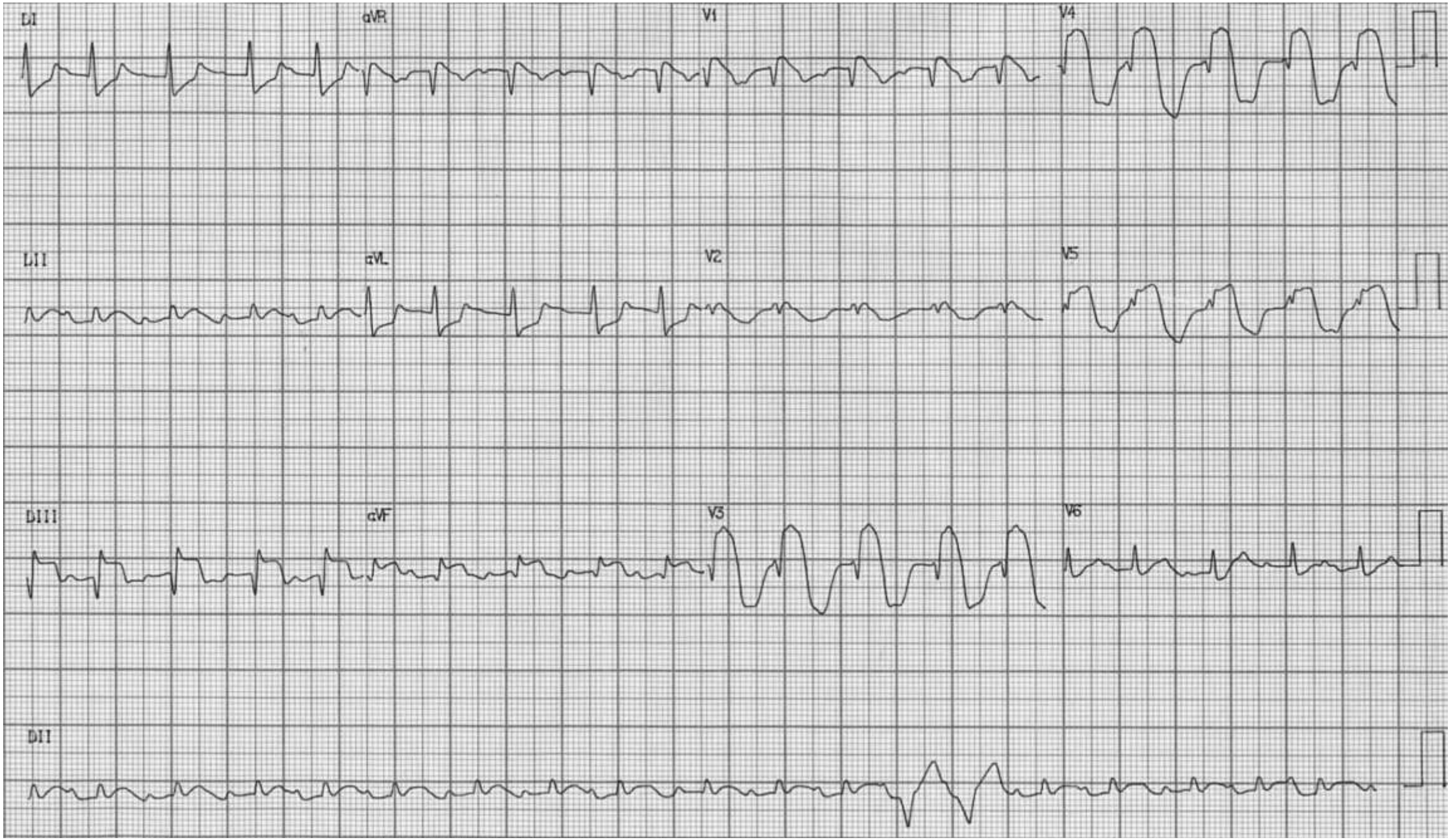
Which are the diagnosis of the ECGs?

Which is/are the responsible mechanism(s) for the ECG-2 and ECG-3 pattern?

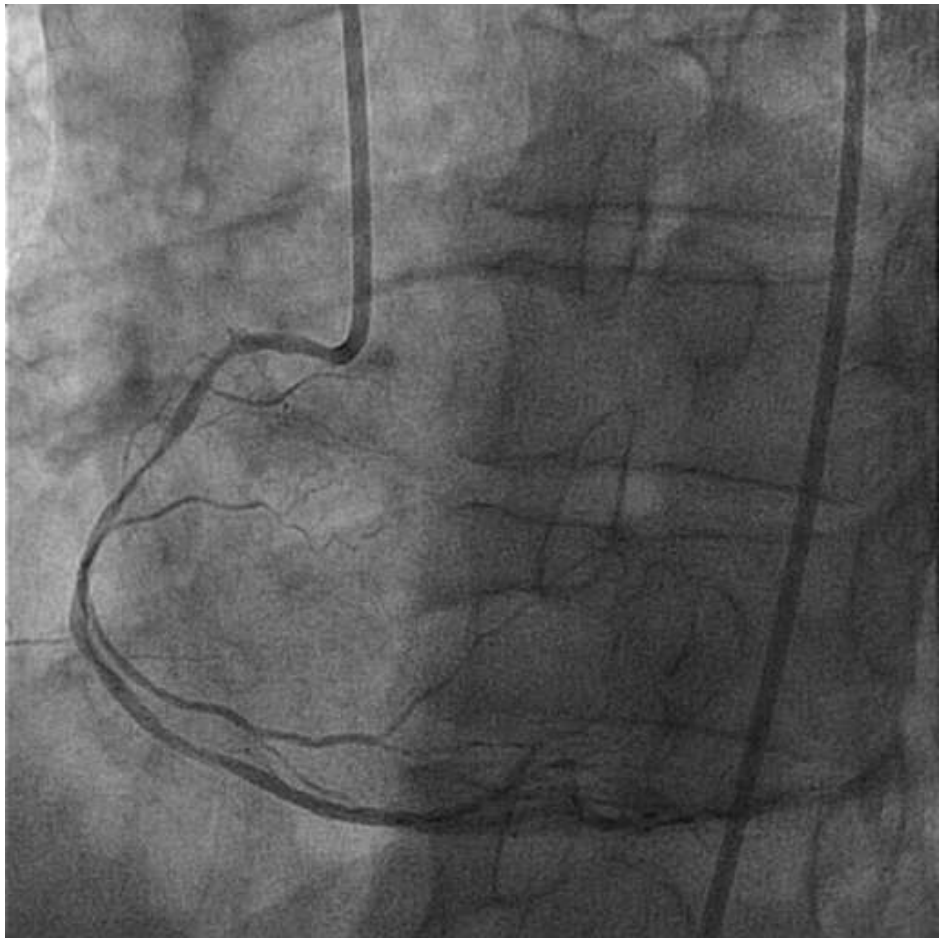
ECG1 - at admission (March 31, 2017)



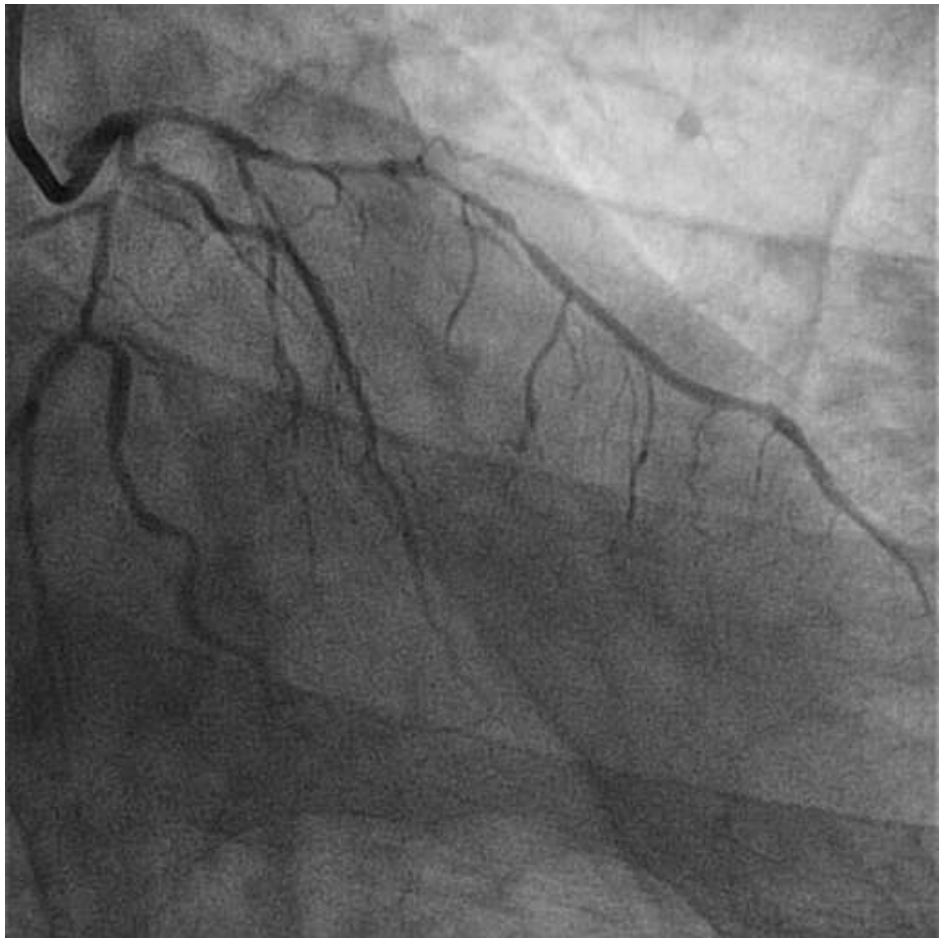
ECG2 - 5th day of admission



Before intracoronary infusion of isosorbide mononitrate - Antes do monocordil intracoronario
Diffuse coronary artery spasm - Espasmo coronario difuso



RCA - CD

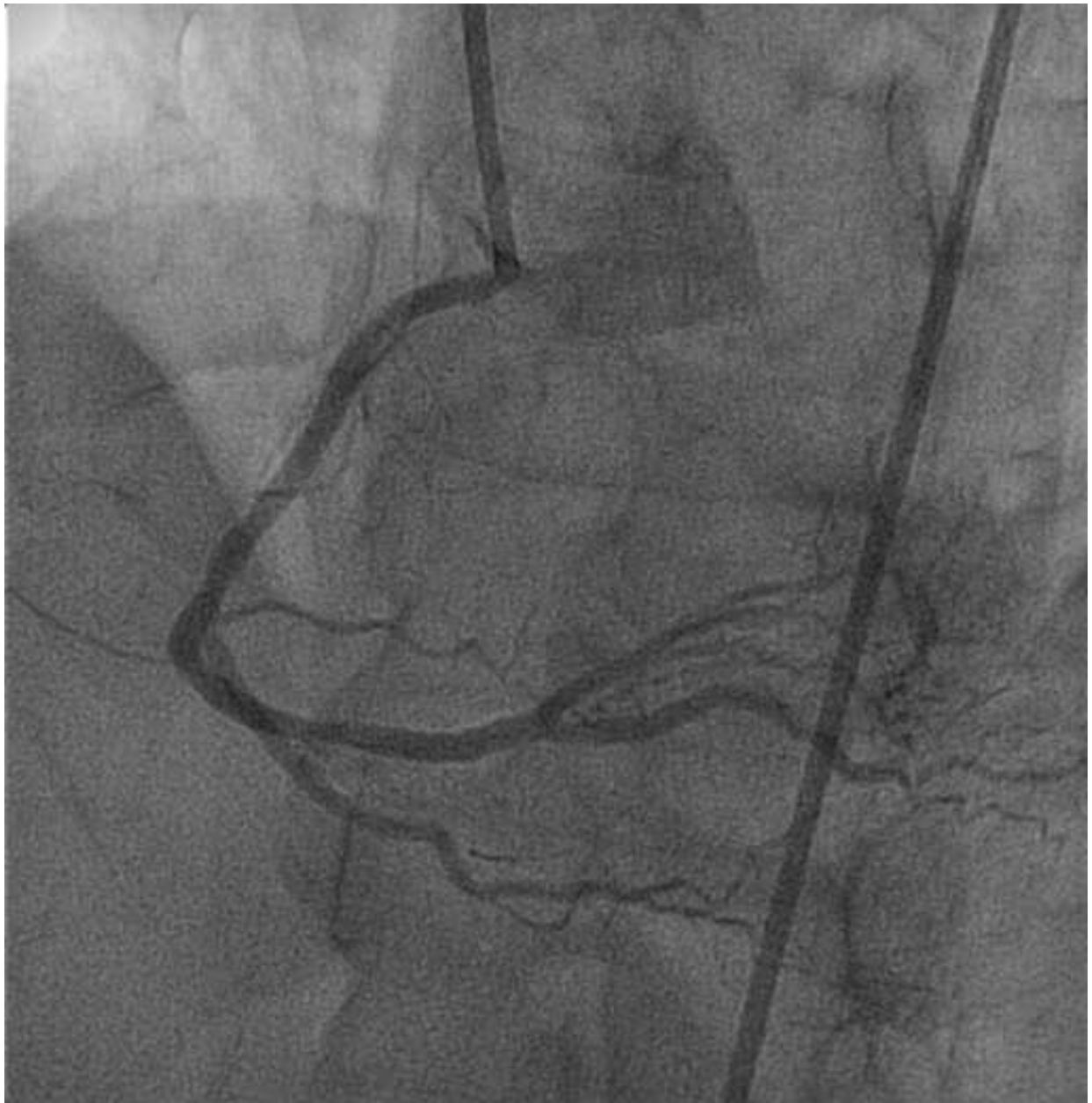


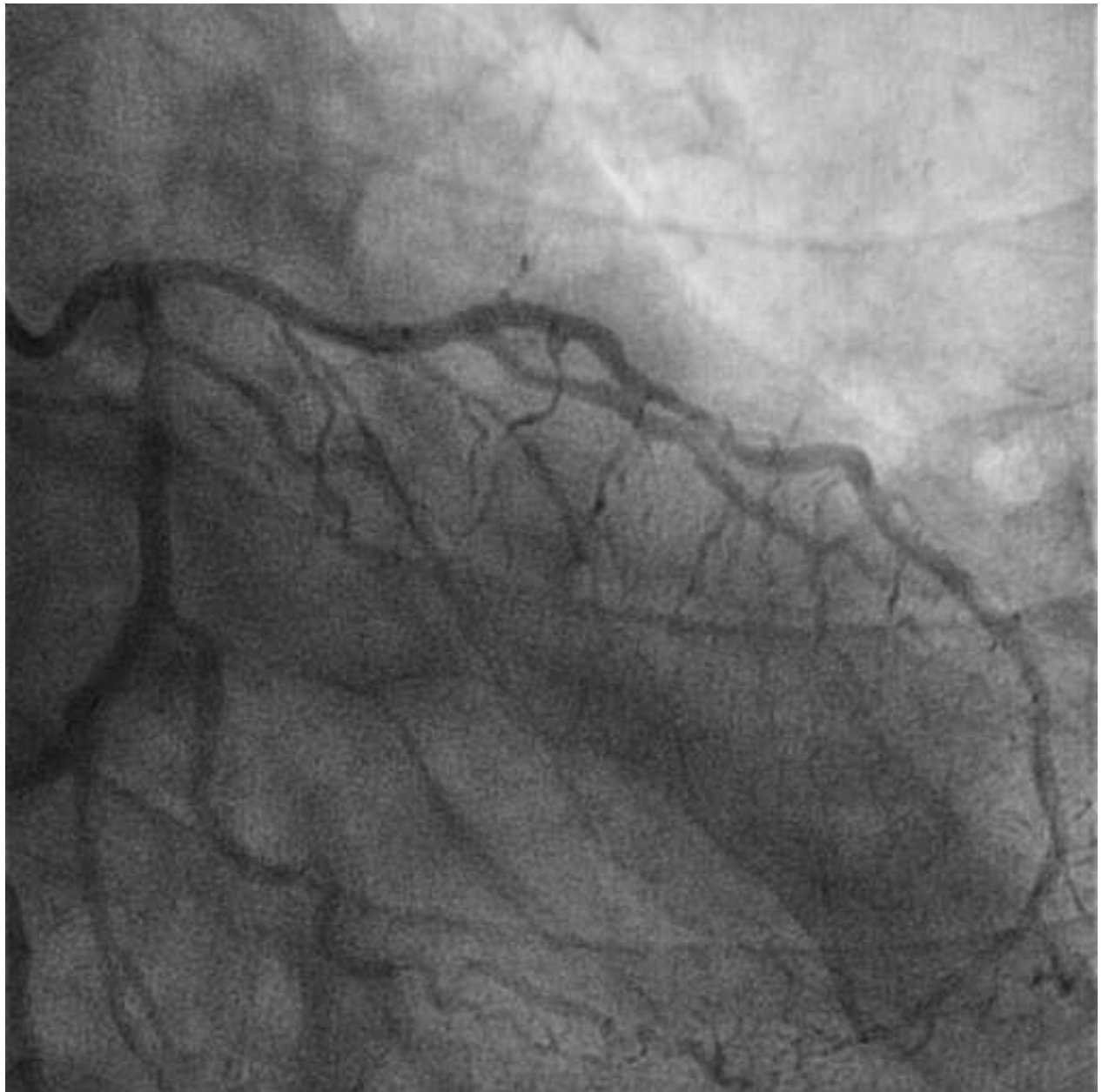
Left coronary artery - Coronaria esquerda

Left heart catheterization made, showing normal coronary arteries, with spasm in left and right coronary arteries. Monocordil was administered during the procedure. Patient died the same day

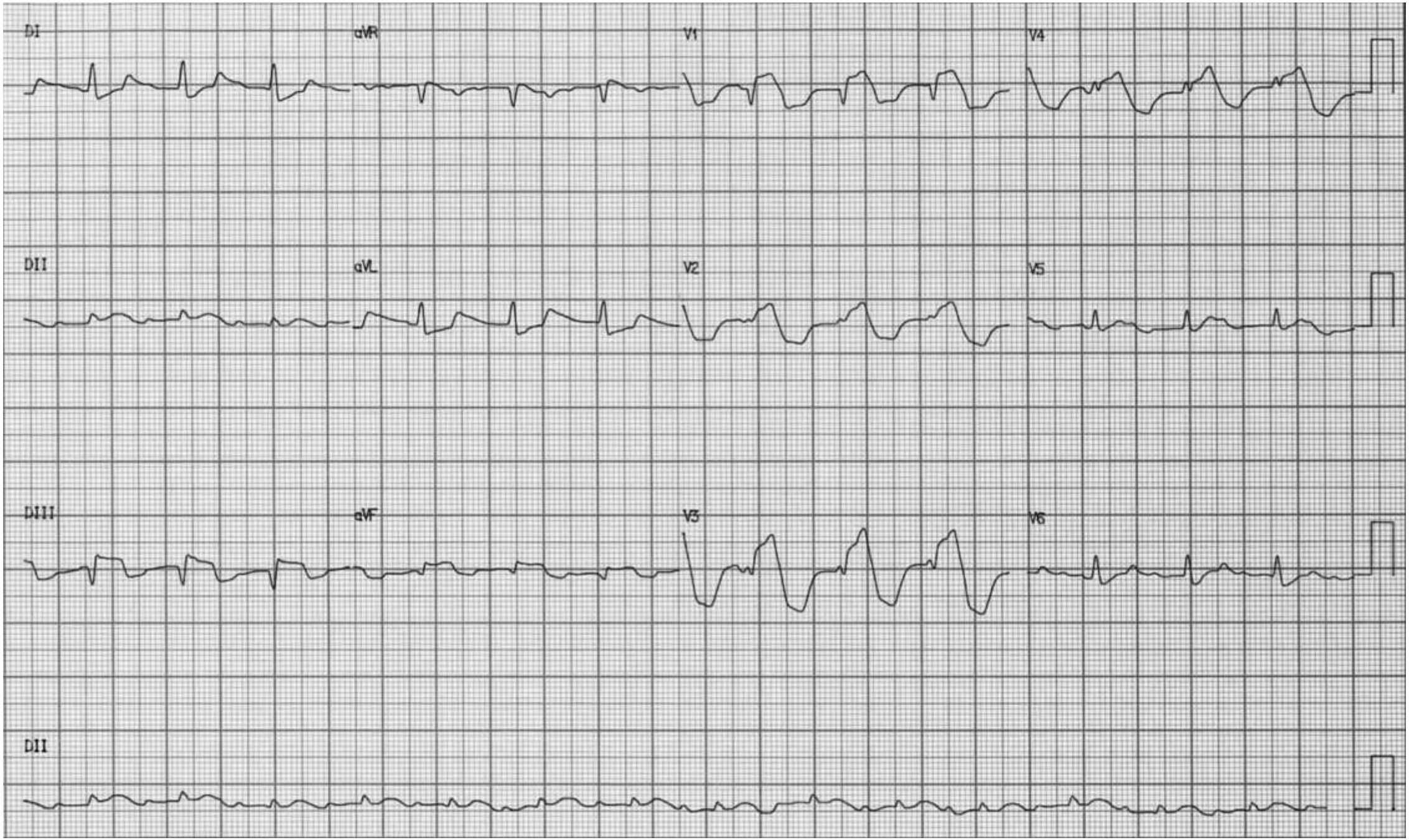
Reversion after intracoronary infusion of isosorbide mononitrate

Reversão após monocordil intracoronário





ECG3 - after intracoronary infusion of isosorbide mononitrate – no improvement



Lab tests

- **Admission**
  - **Leukocytes: 31,640**
  - **Potassium: 5.1 mEq/L**
  - **Calcium: 7.2 mg/dL**
  - **Urea: 336**
  - **Creatinine : 3.18**
  - **Mg: 2.7** mmol/L
  - **Trop: 0.148**
  - **PCR: 25**
  - **PH: 7.31**
- **Fifth day (worsening)**
  - **24,870**
  - **10.16**
  - **0.98 mmol/L**
  - **239**
  - **1.94**
  - **2.4**
  - **7.07**

Echocardiogram

LV with normal dimensions
LVEF = 68%
Test made in bed, with technical difficulties

Colleagues opinions

A great case.

ECG1 is normal
ECG 2 shows sinus tachycardia with PACs. The QRS is a bit wider. There is a Brugada pattern in V1-V2, marked ST elevation inferior leads with reciprocal ST depression in I and aVL and ST elevation in V3-V5. Fever may induce Brugada's pattern. However, I think hyperkalemia and acidosis is the answer with superimposed ischemia.
ECG3 shows further prolongation of the QRS, less ST elevation inferior leads I think it is a sign of reperfusion of the inferior ischemia + severe hyperkalemia
Regards
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Spanish

Hola Andrés y Raimundo:

ECG-1 ritmo sinusal com frecuencia cardíaca de 70 latidos por min eje eléctrico del QRS normal, sin cambios patológicos. Solo microvoltajes que puede sospecharse por al habito físico del paciente o por su patología respiratoria de base.

ECG-2 al 5to día de admisión: Taquicardia sinusal (140 latidos por min), bloqueo atrioventricular de primer grado sin cambio del eje eléctrico y trastorno de la conducción intraventricular por el aumento de la duración del QRS (trastorno de despolarización) asociado a trastorno de repolarización y QT prolongado. Presenta una fenocopia Brugada en V1 y V2, atribuible a hiperkalemia y no descartaria que el estado de acidosis metabólica asociado tenga un rol importante en la aparición del vasoespasmo coronario.

Clinicamente presenta critérios de sepsis (síndrome de respuesta inflamatória sistémica consecuencia del processo infeccioso pulmonar (SRIS)) por el cuadro clínico por la presencia de ≥2 de los siguientes critérios:1) temperatura corporal >38 °C o <36 °C; 2) frecuencia cardíaca >90/min (puede no observarse en pacientes em uso de β-bloqueantes); 3) frecuencia respiratória >20/min o PaCO2<32 mm Hg, 4) leucocitos >12 000/µl o <4000/µl o >10 % de neutrófilos inmaduros. Se trata de una sepsis grave cuyo tratamiento consiste en la administración de fluidos por la hipotensión y aminas vasopresoras (dopamina, dobutamina). Esta suelen indicarse frente a la falta de respuesta. Usaria adrenalina en goteo continuo. Presenta concomitantemente falla renal (falla multiorgánica) frecuente en los estados de acidosis metabólica, vasodilatación periferica por la acidosis láctica y otros factores inflamatorios**.**

No presenta disfunción ventricular porque no tiene aún afectación de las arterias coronárias. Frente a altas dosis de adrenalina o noradrenalina puede provocarse vasoespasmo, más aún al realizar la cinecoronariografía. pero no me impresiona que lo presentara previo a la cinecoronariografia sino que fue inducida en el contexto de la cinecoronariografia y no es responsable de los cambios ECG.

ECG-3 evidencia luego de la infusión intracoronaria que los cambios ECG descritos no ceden luego de la nitroglicerina intracoronária, persistiendo el trastorno de conducción intraventricular y los microvoltajes atribuibles a la hiperkalemia ya la acidosis metabólica.

Un abrazo

Martín Ibarrola Buenos Aires Argentina

English

Hello Potro Andrés and Raimundo,
In admission the patient presented SR 70 bpm, normal electrical axis, no changes of pathological value. Only microvoltages that we may suspect are due to the physical complexion of the patient or to his base respiratory pathology.
In the 2nd ECG, at the 5th day of admission, the following is observed:
Sinus tachycardia 140 bpm. 1st degree AV block with no electrical axis change and intraventricular conduction disorder with increase in QRS duration (depolarization disorder) associated to repolarization disorder and long QT, presenting Brugada phenocopy in V1 and V2, attributable to hyperkalemia and I would not rule out the associated state of metabolic acidosis having quite a significance for the appearance of coronary artery vasospasm. The patient presented sepsis criteria.
Sepsis: systemic inflammatory response syndrome because of infection Systemic inflammatory response syndrome (SIRS): consistent clinical symptoms in ≥2 of the following:
1) Body temperature >38°C or <36°C
2) Heart rate >90 bpm (it may not happen in patients taking β-blockers)
3) Respiratory rate >20 bpm or PaCO2 <32 mmHg
4) Leukocytes >12,000/µl or >10% of immature neutrophils.

In this case, this is a severe sepsis in which the treatment is the administration of fluids, and when the patient presents hypotension, vasopressor amines are administered (dopamine, dobutamine) and adrenaline in continuous drip is usually indicated when there is no response.
This patient presented renal failure (multiorgan failure). Because of the state of metabolic acidosis, peripheral vasodilation is quite common due to lactic acidosis and other inflammatory cases. He did not present ventricular dysfunction, so there was still no involvement of the coronary arteries. Before the high doses of adrenaline or noradrenaline vasospasm may occur, and even more when performing coronary angiography. But it doesn't seem to me that he presented it before the angiography, but rather that it was induced in the context of the angiography and is not responsible for the ECG changes.
The third ECG shows this, as after the intracoronary infusion, the ECG changes described did not yield after intracoronary NTG, with the intraventricular conduction disorder persisting, as well as the microvoltages that could be attributed to hyperkalemia and the metabolic acidosis the patient presented.
Warm regards
Martín Ibarrola MD Provincia de Buenos Aires Argentina

Thank you Raimundo and Andrés for sharing this rare case with hyperkalemia and multivessel coronary spasm. I assume that the spasm was provoked by noradrenaline. ST elevations could be generated by multivessel spasm and hyperkalemia (Patterns of acute inferior wall myocardial infarction caused by hyperkalemia. Pastor JA, Castellanos A, Moleiro F, Myerburg RJ. J Electrocardiol. 2001 Jan;34(1):53-8.)

ECG 2 shows I degree AV block. Inferior transmural ischemia (RCA spasm). RBBB. Anterior ST elevations with peculiar T-wave changes – this is probably due to hyperkalemia.

ECG 3: still signs of hyperkalemia, reduction of inferior ST elevations (spasm is resolving).

Therapeutically there was not much to do in this patient with multiorgan failure.

Best regards
Kjell Nikus, Tampere, Finland

Portuguese

Estranho não haver alterações no ECG da severa hipocalcemia (3,92mg/L) tais como bradicardia e QT longo mas certamente contribuiu para a assistolia

Abraços

Adail Paixão **Almeida MD** Vitoria da Conquista Bahia Brasil

English

It seems strange to me that with severe hypocalcemia (3,92mg/l) the ECG does not show bradycardia associated with prolonged QT interval. Nevertheless, it certainly contributed to asystole death.

Hug

Adail Paixão **Almeida MD** Vitoria da Conquista Bahia Brazil

Answer

Dear friend Adail: The reference range of ionized calcium is 4.4-5.4 mg/dL (1.1-1.35 mmol/L). In the present case ionized calcium is 3,92mg/L

Less than 2 mg/dL (< 0.5 mmol/L) may produce tetany or life-threatening complications.

In patients with multiple blood transfusions, 2-3 mg/dL (< 0.5-0.75 mmol/L) may require calcium administration.

Concerning the ECG manifestations of severe hypocalcemia eventually cause injury current mimicking acute myocardial infarction and dramatic ECG abnormalities as being due to coronary vasospasm.(**Ilveskoski 2012**) Hypocalcemia is mainly the consequence of hypoalbuminemia, advanced renal impairment, cirrhosis, malnutrition, or sepsis such as the present case. (**Kukla 207**)

Final diagnosis/comments

1) Resistant Bronchopneumonia

2) Sepsis: It is a complex condition characterized by the simultaneous activation of inflammation and coagulation in response to microbial insult. These events manifest as systemic inflammatory response syndrome or sepsis symptoms through the release of proinflammatory cytokines, procoagulants, and adhesion molecules from immune cells and/or damaged endothelium. Today, sepsis is a severe multisystem disease with difficult treatments for its manifestations and high mortality rates. To be diagnosed with sepsis, it is necessary exhibit at least two of the following symptoms, plus a probable or confirmed infection: Body temperature above 101 F (38.3 C) or below 96.8 F (36 C), heart rate higher than 90 bpm, respiratory rate higher than 20 breaths a minute. The diagnosis will be upgraded to severe sepsis because exhibit at least one of the following signs and symptoms, which indicate an organ may be failing: Significantly decreased urine output(the present case), abrupt change in mental status, decrease in platelet count, difficulty breathing, abnormal heart pumping function and abdominal pain. **Severe sepsis is a systemic inflammatory response syndrome (**SIRS) is nonspecific and can be caused by ischemia, inflammation, trauma, infection, or several insults combined. Thus, SIRS is not always related to infection. Sepsis can result from bacteria, viruses, fungi, or parasites, or it can develop in noninfectious intraabdominal incidents such as severe trauma, pneumonia, pancreatitis, and other incidents such as urinary system infection.

Clinical Phases of Sepsis

I. Infection having clinical symptoms
II. SIRS (having two or more of the following)
    - Body temperature of >38°C or <36°C,
    - Tachycardia: heart rate more than >90/min,
    - Tachypnea (respiratory frequency of >20/min) or mechanical respiratory requirement
    - White blood cell count of $>12\times10^9$/L or $<4\times10^9$/L
III. Severe sepsis Sepsis-induced organ dysfunction or hypotension along with sepsis
IV. Sepsis shock Severe sepsis along with arterial hypotension (systolic arterial pressure of <90 mmHg or mean arterial blood pressure of <65 mmHg)
V. MODS >2 organs affected

L: liters; mmHg: millimeters of mercury; °C: degrees Celsius; SIRS: systemic inflammatory response syndrome. Mertens K. Applied Biology. University of Aberdeen.; 2014. Zinc in inflammation and sepsis. Available From: URL: http://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.600115.

3) Acute renal failure

4) Diffuse iatrogenic Coronary Artery Spasm (RCA + LMCA)

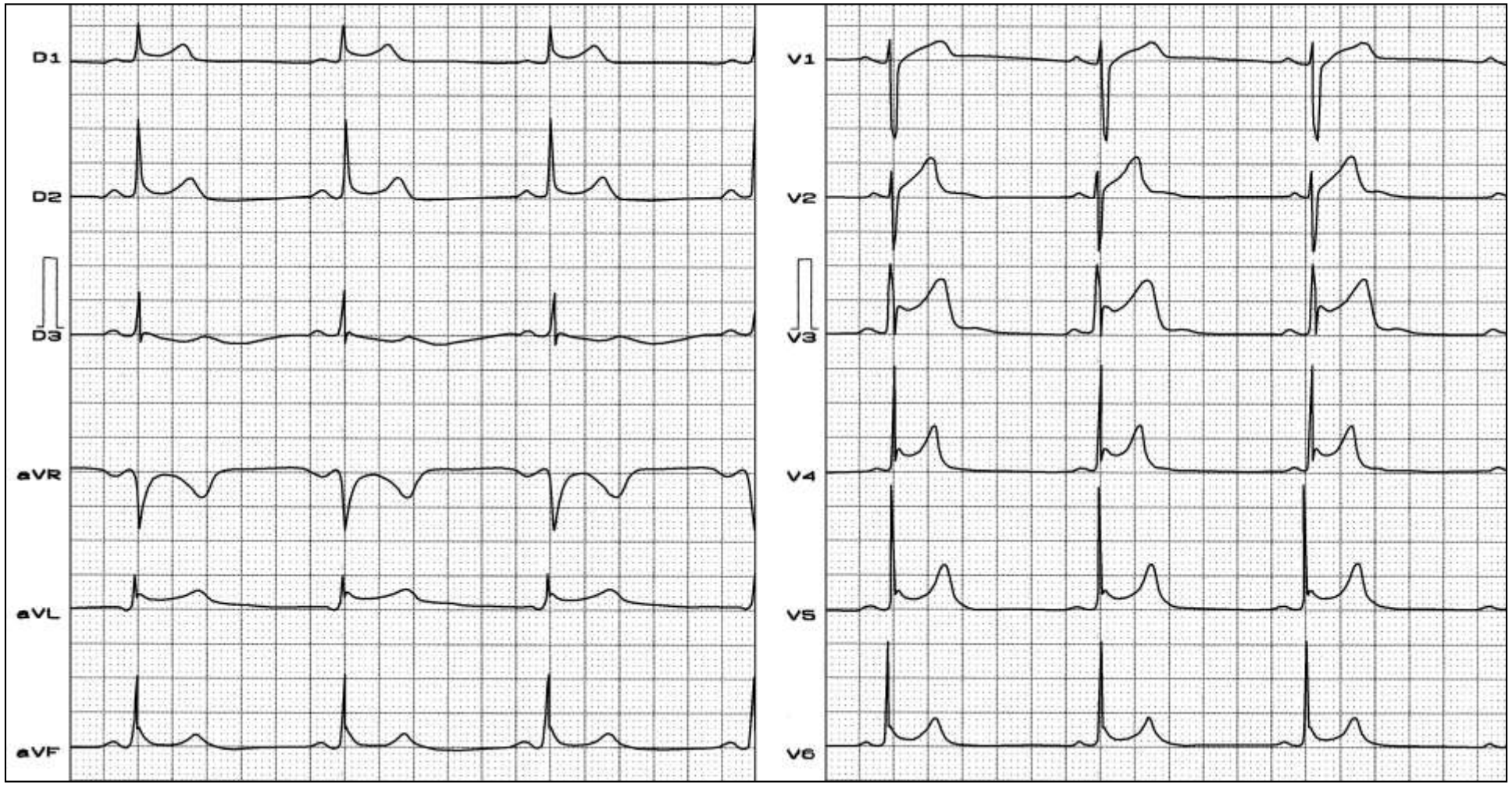
5) Severe hyperpotassemia: pseudo acute inferior myocardial infarction(AIMI) with reciprocal or mirror image in lateral wall. The high lateral leads, especially lead aVL, are reciprocal to the inferior leads, especially lead III, and, as in this case, ST-segment depression in lead aVL has often been used to aid in the diagnosis of acute IMI.(**Birnbaum 1993**) + non-specific intraventricular conduction disturbance + type 1 Brugada pattern (Brugada phenocopy ?) For the diagnosis of Brugada phenocopy it is necessary the presence of the following conditions (**Baranchuk 2012; Anselm 2014; Anselm 2013**): I) An ECG pattern that has a type-1 or type-2 pattern.; II) Identifiable underlying condition. III) The ECG pattern resolves upon resolution of the underlying condition IV) Negative provocative testing with a sodium channel blocker. Provocative testing is not mandatory if surgical RVOT manipulation has occurred within the last 96 hours).(**Rambod 2014**); V) Negative results of genetic testing (desirable but not mandatory because the SCN5A mutation is identifiable in 25% of probands affected by true BrS. VI) Correction of the hypokalemia.

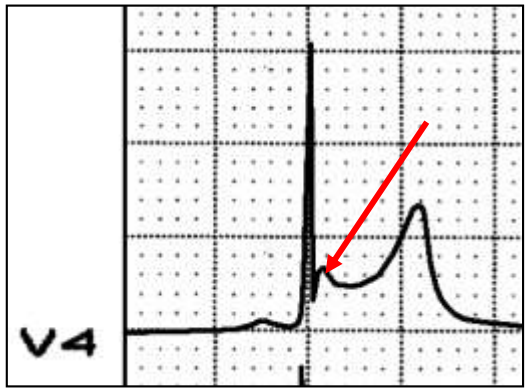
The ECG remains the cornerstone of prompt diagnosis of STEMI; Furthermore, the ECG provides the primary indication for emergent reperfusion therapy in the STEMI patient. STE ≥1 mm in the limb leads and ≥2 mm in the precordial leads in at least two anatomically contiguous leads. However, not all ECGs with STE necessarily reflect transmural infarction from acute thrombotic occlusion of an epicardial coronary artery. A significant percentage of patients met STEMI ECG criteria. A large number of patients with STD in V_1-V_6 had angiographic evidence compatible with inferolateral STEMI equivalent.(**Wei 2013**) In certain cases, a patient's ECG can resemble STEMI yet manifest STE from a non-coronary-based syndrome("benign nonischemic STE (NISTE)") and they mimics and include (**Huang 2011**).

1. **"Benign" early repolarization pattern: Electrocardiographic criteria that suggest benign early repolarization (BER),** electrically characterized by:
   - Sinus bradycardia and phasic sinus arrhythmia are often present
   - The frontal plane QRS axis and ST segment axis and T wave axis are all in the same direction
   - Notching or slurring of the terminal portion of the QRS complex (R wave) and beginning of the ST-segment, J point/J (red wave arrows)
   - Reciprocal or mirror image only in aVR lead
   - Prominent, relatively deep but narrow, q waves may appear in the left precordial leads
   - A rapid transition may occur from right oriented complexes to left oriented complexes in the precordial leads
   - Minimally elevated J point <2mm in precordial leads(but can rarely be > 5mm) and <1mm in inferior leads with upward concavity of the ST segment. Elevated st segments are most commonly seen in the mid-to-left precordial leads, and they are also sometimes seen in both the limb leads (I, II, III, aVF and aVL) + chest leads (V2 - V6) with the degree of precordial lead STE >> limb lead STE followed by pseudo symmetric, concordant T waves of large amplitude - the T waves may appear "peaked" or pointed

- Reduction in ST segment elevation may occur secondary to sympathomimetic influences
- Relative temporal stability of the ST segment and T wave pattern (**Pérez-Riera 2012**)

Name: DAS; **Age:** 24years of age; **Sex:** Male; **Ethnic group:** Afro-descendant; **Weight:** 82 kg; **Height:** 1.91 m**; Biotype:** Athletic**; Occupation:** professional basketball player

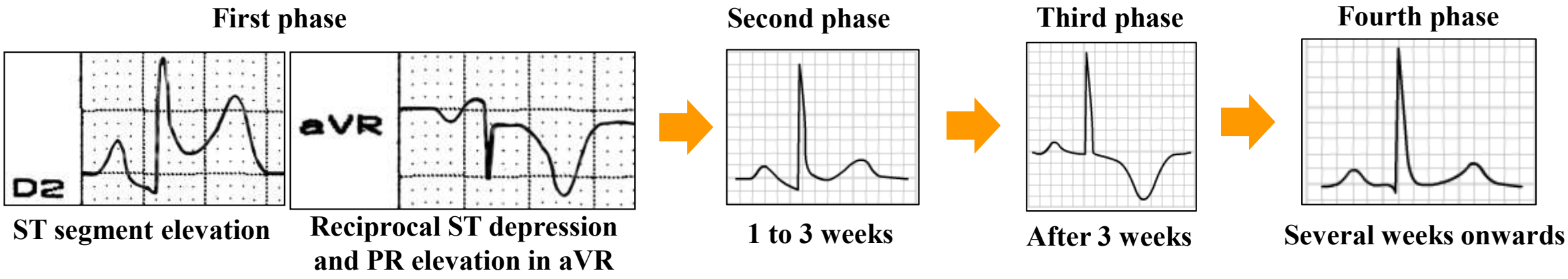




ECG Diagnosis: sinus bradycardia, (HR 50 bpm). “Notching" and "slurring" of the terminal portion of the R wave and beginning of the ST-segment,(J point/J wave arrows) and ST-segment elevation (> 4 mm) in precordial leads from V3-V5 of concave upward. Above the isoelectric line(relative to the subsequent TP interval). **Conclusion:** sinus bradycardia, early repolarization pattern.

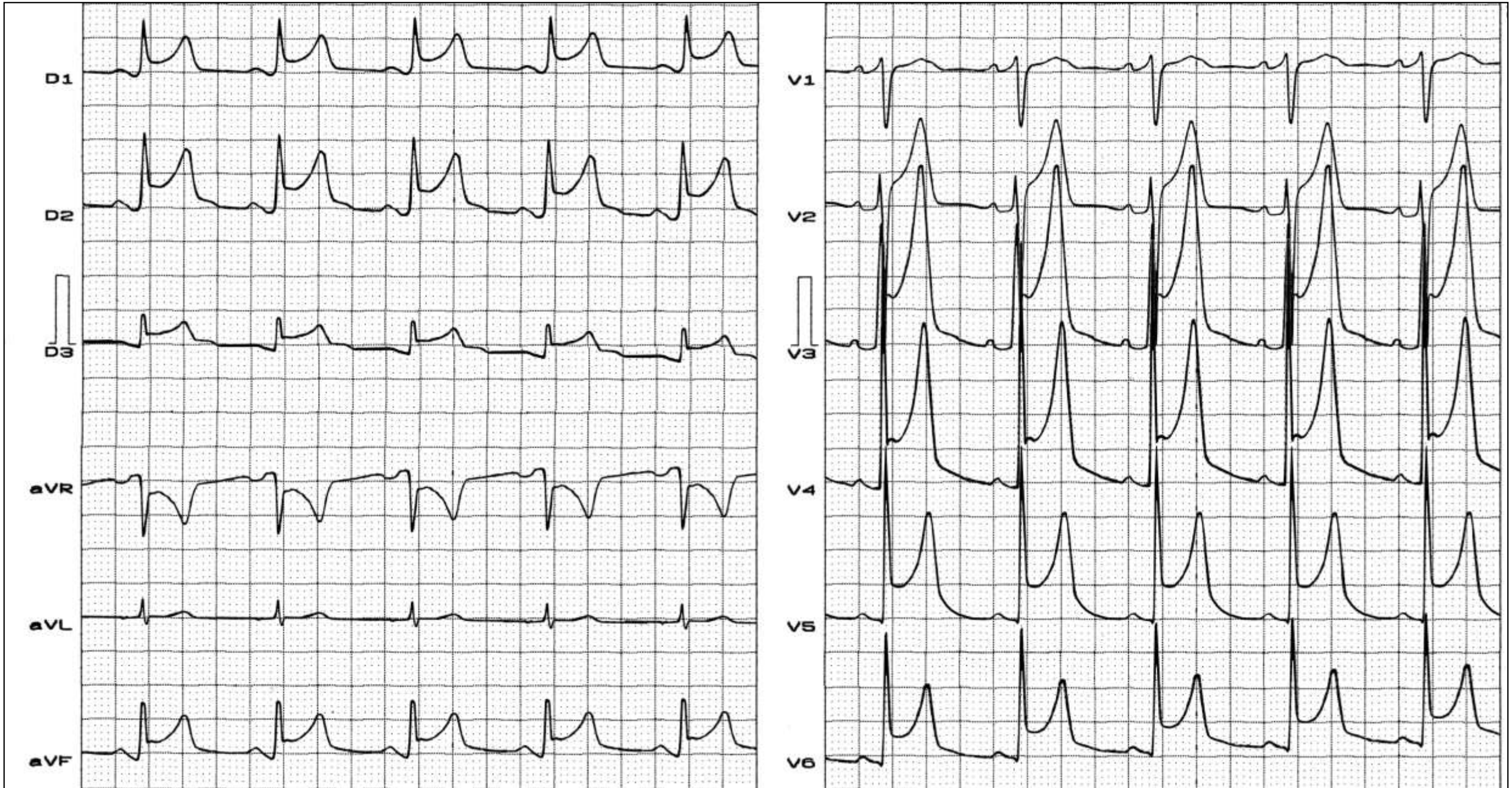
2. **Acute pericarditis:** syndrome caused by inflammation of the pericardium, a sack made up by two sheets (parietal and visceral) that wrap the heart and the great vessels. Electrocardiographically characterized by frequent sinus tachycardia, difuse concave STE, PR depression throughout most of the limb leads (I, II, III, aVL, aVF) and precordial leads (V2-6), reciprocal ST depression and PR elevation in lead aVR (± V1) (**Kasasbeh 2009**). Additionally, acute STEMI, but not acute pericarditis, show prolongation of QRS complex and shortening of QT interval in ECG leads with STE. (**Rossello 2014**). Acute pericarditis is classified in four phases:

- **First phase:** Frequent sinus tachycardia in acute pericarditis due to pain and/or pericardial effusion. Widespread concave ST segment elevation (<5 mm) of superior concavity. It is observed only two hours before chest pain and it lasts for several days. ST segment changes are extensive and not too intense, normally noticeable in several leads simultaneously, excluding V1. Occasionally, reciprocal alterations are observed in aVR. PR depression throughout most of the limb leads (I, II, III, aVL, aVF) and precordial leads (V2-6).
- **Second phase:** ST segment returns to baseline and generalized flat T wave in 7 to 21 days (pseudo normalisation: transition).
- **Third phase:** inversion of T wave, with no formation of Q wave after 3 weeks.
- **Fourth phase:** ECG normalization with gradual reversion of T wave inversion.



Observation: Less than 50% of patients progress through all 4 classical stages and evolution of changes may not follow this typical pattern.

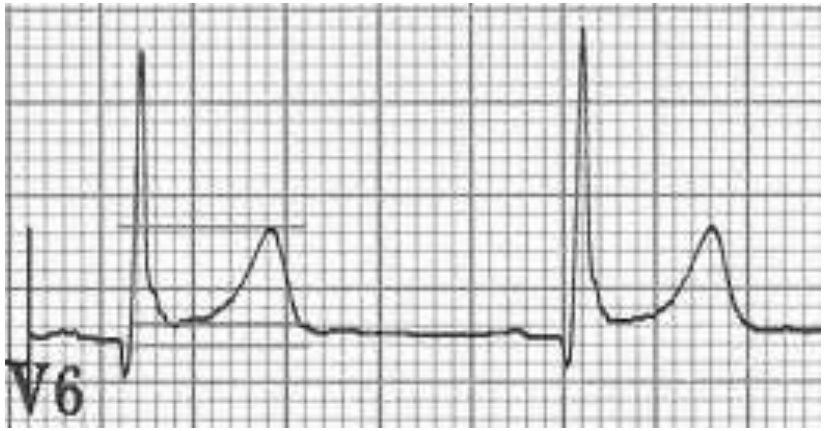
Typical ECG of acute pericarditis in the first phase with diffuse elevation of upwardly concave STSE followed by tall T waves



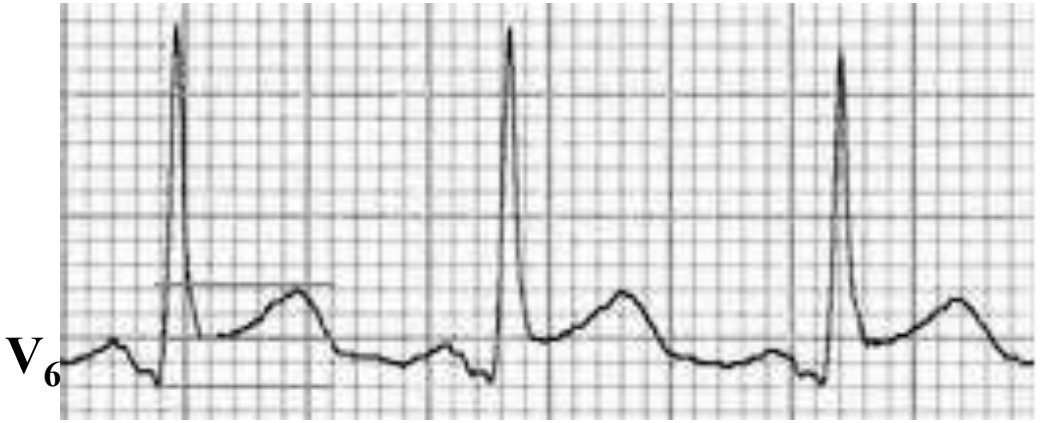
Benign Early Repolarization	Pericarditis
ST segment height = 1 mm	Generalized ST segment elevation. Height = 2 mm
T wave height = 6 mm	T wave height = 4 mm
ST / T wave ratio = 0.16	ST / T wave ratio = 0.5
The ST / T wave ratio < 0.25 followed by prominent T waves	Universal elevation (all of them). There may be reciprocal depression in opposite leads.
The presence of a notched or irregular J point: the so-called “fish hook” pattern. This is often best seen in lead V4.	Absence of “fish hook” appearance in V4
ST elevation limited to the precordial leads. Reciprocal depression only in aVR.	Normal T wave amplitude. It decreases amplitude in hours. Lower voltage. Only increased in early phase.
Absence of PR depression	Presence of PR depression
ECG changes usually stable over time (i.e. non-progressive)	ECG changes evolve slowly over time
Response to strain: Frequent return of ST to baseline. T wave may normalize.	ST segment elevation is not modified.
Hyperventilation: T polarity may be modified.	T polarity is not modified.
Frequent bradycardia.	Frequent tachycardia.
Presentation: Stable.	Transitory.
Clinic: Asymptomatic.	Marked alteration.
Age range: 20 to 40 years old.	40 or more.

Differential diagnosis between pericarditis and benign early repolarization

Pericarditis can be difficult to differentiate from benign early repolarization (BER) as both conditions are associated with concave ST elevation. One useful trick to distinguish between these two entities is to look at the **ST segment / T wave ratio:** The vertical height of the ST segment elevation (from the end of the PR segment to the J point) is measured and compared to the amplitude of the T wave in V6; a ratio of >0.25 suggests pericarditis; a ratio of <0.25 suggests BER.



Benign Early Repolarization



Pericarditis

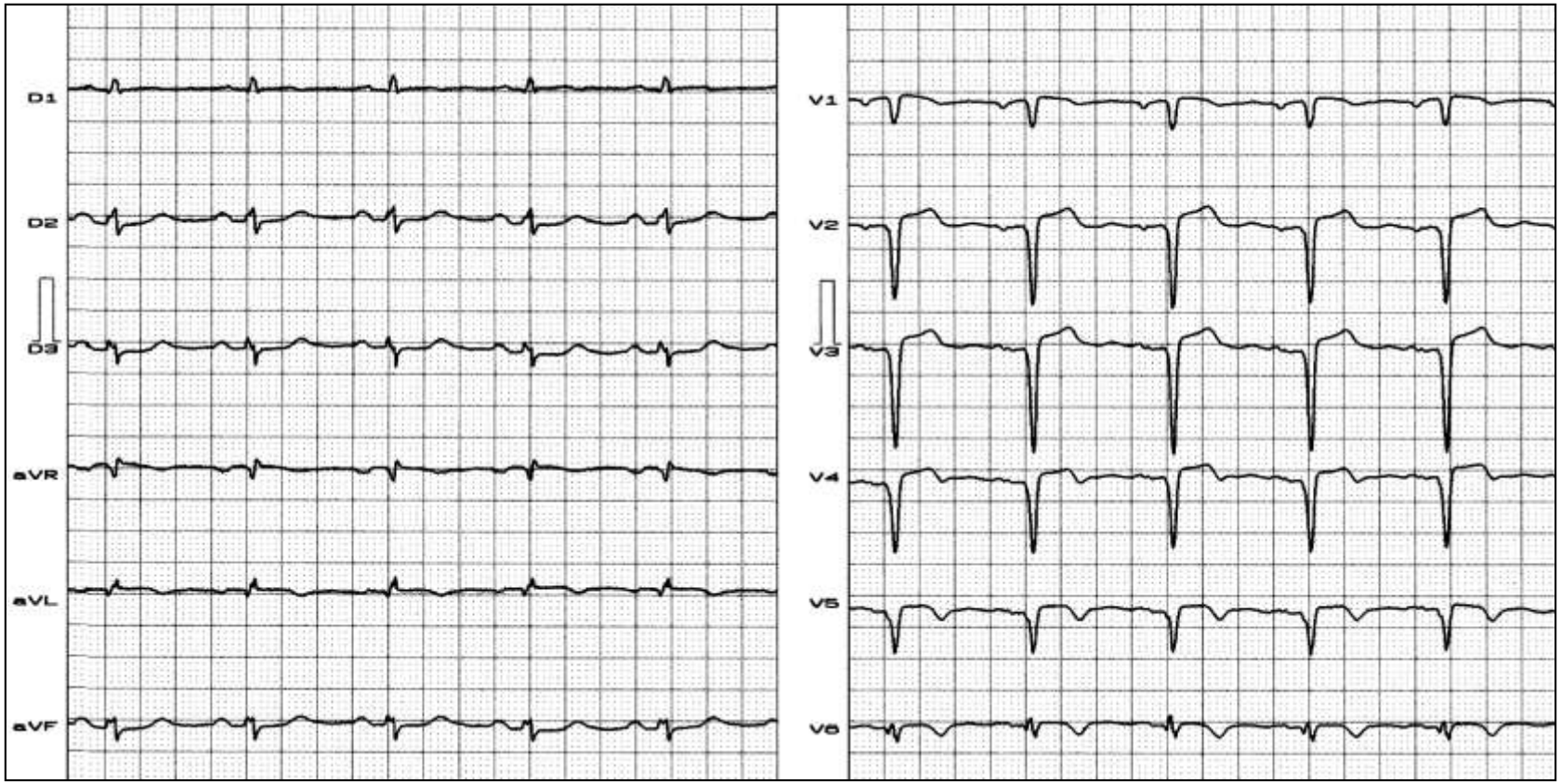
Differential diagnosis between acute MI with STEMI and pericarditis

	STEMI	Pericarditis
Number of involved leads	Less (segmentary)	Major (diffuse) and extensive
Intensity of the phenomena	Major	Lesser
Reciprocal effect or mirror image	Frequently present	Absent, except aVR
ST segment elevation convex upward or horizontal	Frequently. In the initial phases is possibly concave upward.	Absent, always concave to the top
PR segment depression	Possible if atrial infarction	Only in viral pericarditis
STSE III > II	Characteristic when present	Absent
Pleuritic positional pain	Rare, but possible	Characteristic

Steps to distinguish pericarditis from STEMI:

1. Is there ST depression in a lead other than AVR or V1? *This is STEMI*
2. Is there convex up or horizontal ST elevation? *This is STEMI*
3. Is there ST elevation greater in III than II? *This is STEMI*
4. Now look for PR depression in multiple leads… this suggests pericarditis (especially if there is a friction rub!)

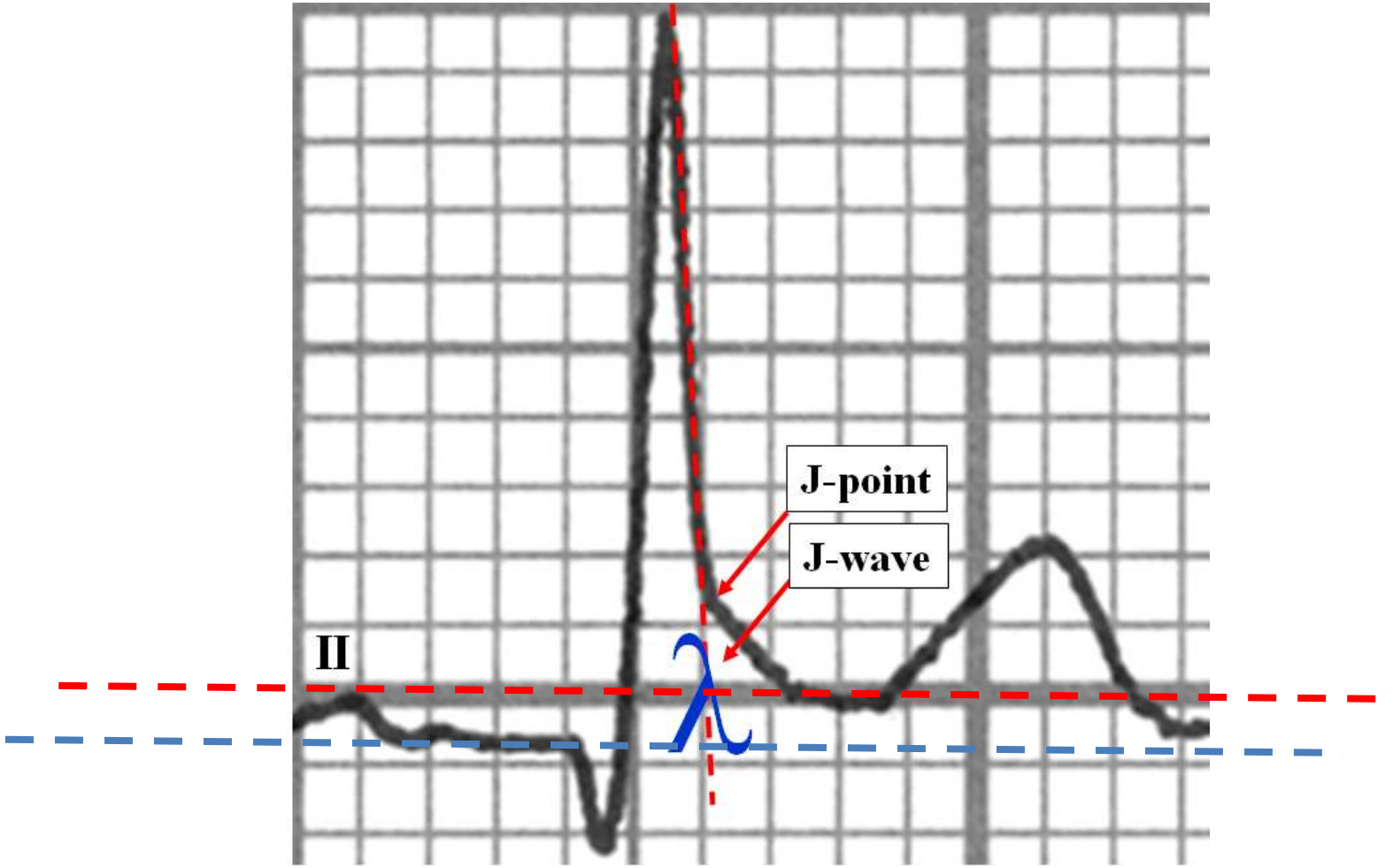
3. **Myopericarditis** (Patel 2016)
4. **LV aneurysm consequence of old myocardial infarction(MI) or dyskinetic LV segment** (Engel2002): It is defined as a localized area of infarcted myocardium that bulges outward during both systole and diastole. LVAs most often are noted after large anterior wall events but may be observed after inferior or lateral MI. Electrocardiographically it is characterized by persistent STE over a period of two weeks following an acute MI. The mechanism is thought to be related to incomplete reperfusion and transmural scar formation following an acute MI. This ECG pattern is associated with paradoxical movement of the ventricular wall on echocardiography (ventricular aneurysm). ECG characterization: STE seen > 2 weeks following an acute MI; most commonly seen in the precordial leads; may exhibit concave or convex shape; usually associated with well-formed Q- or QS waves; T-waves have a relatively small amplitude in comparison to the QRS complex (unlike the hyperacute T-waves of acute STEMI).



QS from V_1 to V_6, QS across precordial leads: transmural extensive anterior MI; STE from V_2 through V_4 that suggests anterior aneurysm. Negative T wave in the lateral leads.

5. **Spontaneously reperfusion in STE MI**: Whereas the frequency of spontaneously reperfusion is comparable using either ECG or angiographic criteria, clinical outcomes were best aligned with ECG SR. The ECG in assessing reperfusion and likely reflect the overall impact of myocardial perfusion versus infarct-related artery epicardial patency alone. (**Zalewski 2011**)
6. **Takotsubo cardiomyopathy(TC) or apical ballooning syndrome:** Given the consequences of missing the diagnosis of an acute anterior STEMI the diagnostic accuracy of the ECG criteria investigated in a retrospective study were insufficient to reliably distinguish patients with TC 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. (**Vervaat 2015**) A number of hypotheses have been proposed to explain the pathogenesis of TC, which include (1) catecholamine cardiac toxicity, (2) myocardial sympathetic innervation disruption, (3) coronary vasospasm, (4) myocardial microvascular dysfunction, and (5) aborted myocardial infarction. These proposals are primarily derived from findings of nuclear myocardial perfusion, metabolism, and cardiac sympathetic innervation imaging. Although data in the literature are not necessarily uniform, the two most plausible working postulates for explaining the phenomenon are: Regional myocardial stunning (due to coronary vasospasm, microvascular dysfunction, or aborted myocardial infarction) and Cardiac sympathetic innervation disruption or toxicity. Current data suggest that disturbances of both coronary circulation and neural innervation are associated with the TC: myocardial stunning from transient ischemic attack and sympathetic innervation disruption. It remains to be determined, however, whether the observed leading mechanistic explanations that have gained momentum are merely the sequelae of the disease rather than its primary etiology. Recently Giusca et al presented a case of Takotsubo-like cardiomyopathy with aborted sudden cardiac death in a female patient presenting with Takotsubo-like cardiomyopathy due to epicardial coronary vasospasm. Coronary angiography revealed epicardial spasm of the left anterior ascending, which resolved after intracoronary injection of 0.2 mg nitroglycerine. Cardiac magnetic resonance exhibited subendocardial late enhancement and echocardiography showed normalization of LV dysfunction during follow-up. The patient was put on conservative treatment with nitrates and calcium inhibitors and ICD implantation were deferred. (**Giusca 2017**)
7. **STE secondary to left ventricular hypertrophy (LVH):** on right precordial leads (**Deshpande 2014**)
8. **Transient STE during hypertensive crisis in a patient with LVH** (**Cappelletti 2012**)
9. **False positive STE during dobutamine stress echocardiography due to LVH**.(**Burger 2002**)
10. **STE secondary to - "Non-specific" intraventricular Conduction Delay (IVCD)** (**Deshpande 2014**)
11. **Inferolateral Early Repolarization (ER): with J-point elevation of ≥ 1mm or 0.1 mV in two contiguous inferior and/or lateral leads**
12. **Idiopathic Ventricular Fibrillation(IVF)** (**Shu 2005**)

13. **Early Repolarization syndrome (ERS) (Shu 2005: Tam 2016)**
14. **Brugada syndrome (BrS) (Shu 2005)**
15. **Congenital Short QT Syndrome(SQTS) (Pérez-Riera 2013)**



Lead II of a patient carrier congenital SQTS The first point of inflection of the R wave descendent ramp is considered the real J point. In these cases the "tangent line" method is ideal. ST-segment elevation = 0.8 mm. We considered it an atypical C type variant of early repolarization pattern. The lambda-like aspect is a marker of fatal arrhythmias.

16. J wave syndromes

J wave syndromes are a spectrum of variable phenotypes characterized by the appearance of prominent electrocardiographic J waves (or Osborn waves) with a risk of ventricular fibrillation (VF), including the inherited Brugada syndrome (BrS), traditional early repolarization syndrome (ERS), idiopathic ventricular fibrillation (IVF) with J wave in inferior leads as well as acquired arrhythmias linked to the acute ST-segment elevation myocardial infarction (MI) and hypothermia. Although they may bear differences with regard to the ECG lead location, amplitude, and underlying causes of J wave, these disease entities share a similar ionic and cellular basis, risk factors, and similar clinical outcomes.

J wave syndromes were first defined by Yan et al., in a Chinese journal in 2004 (**Yan 2004**) and has gained worldwide recognition.

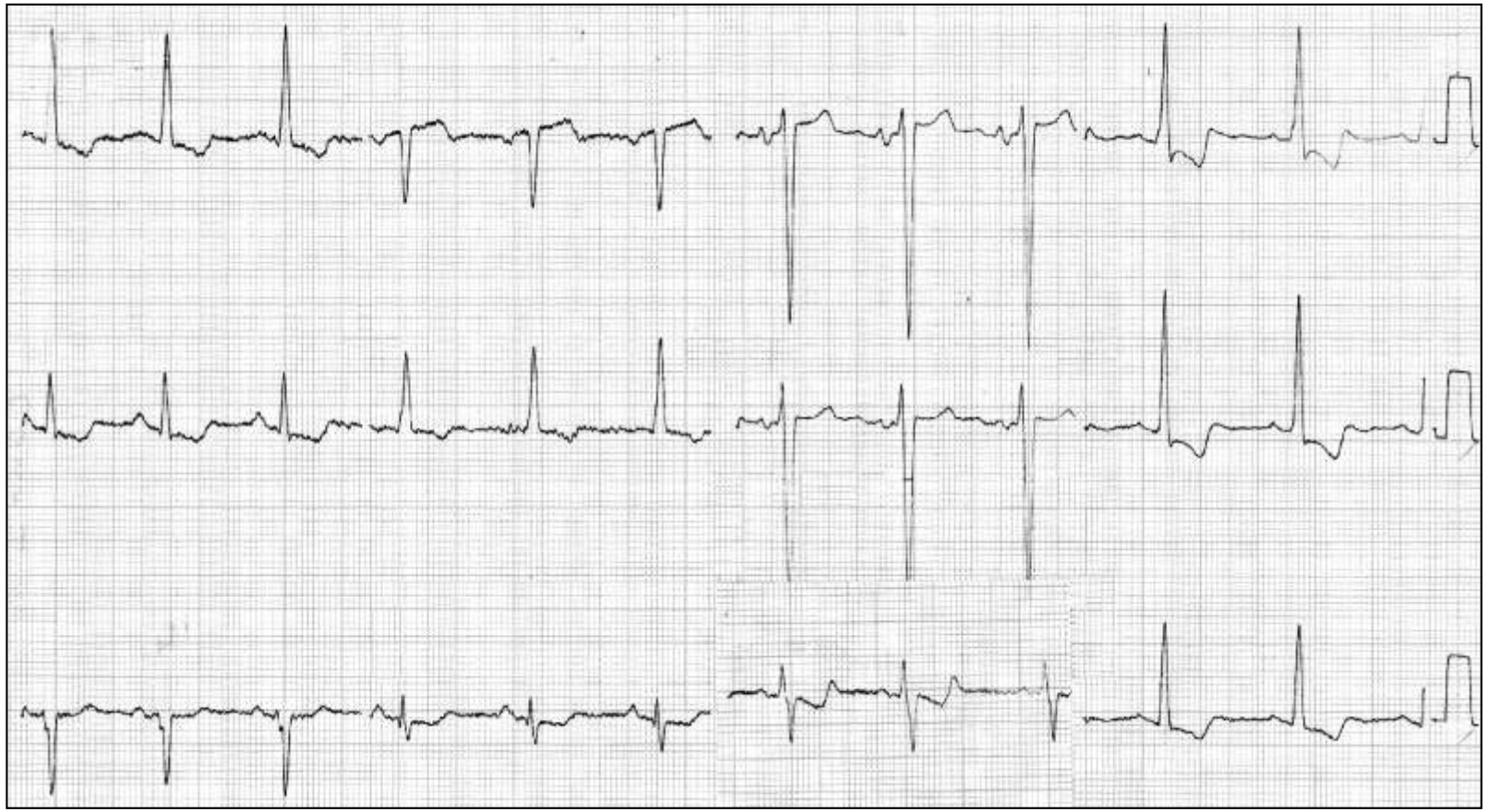
The J wave is a positive deflection immediately following the QRS complex of surface ECG or is in part buried inside of the QRS as notching or slurring. The J wave may be accompanied by an ST segment elevation, traditionally referred to as an early repolarization (ER) pattern (**Antzelevitch 2011**).

J wave was demonstrated as early as in the last century. J wave (QRS slurring or notching) was first reported in an experimental model of hypercalcemia (**Kraus 1920**), followed by hypothermia-induced J waves in an accidentally frozen man by Tomaszewski, who described the wave as a very slowly inscribed deflection between the QRS complex and the ST segment of the ECG (**Tomaszewski 1938**). Shipley and Hallaran described J wave in healthy young individuals shortly afterward (**Shipley 1936**). J wave was later named as Osborn wave after being highlighted by a landmark study in which Osborn described hypothermia-induced J wave in hypothermic dogs and its accentuation prior to VF (**Osborn 1953**). Over the past decades, J waves have been increasingly recognized in subjects with central nervous system disorders (**Hersch 1961**), clinical hypercalcemia (**Sridharan 1984**), BrS (**Brugada 1992; Yan 1996**), IVF (**Kalla 2000; Haïssaguerre 2008**), and myocardial ischemia (**Yan 2004; Jastrzebski 2009**). Especially, J wave has gained a great deal of attention after determining it as a sign of a substrate capable of generating fatal VT/VF. Underlying ionic and cellular basis of Ito-mediated J wave was elucidated in the days when the arterially perfused ventricular wedge preparation was first developed in 1996 (**Yan 1996**). Ito is the main current contributing to the repolarizing phase 1 of the AP.

17. **Hypothermic J wave:** The Osborn wave is a deflection with a dome-shaped configuration at the R-ST junction of the ECG. It is mainly encountered in hypothermic states but is also recognized in other nonhypothermic conditions.**(Omar 2016)**
18. **Hypercalcemia (Durant 2017)**
19. **Hipocalcemia (Kukla 2017):** QT interval prolongation at the expense of ST segment, and normal T wave.
20. **Neurocardiogenic injury in acute cerebral hemorrhage:** transient cardiac dysfunction with STE, QT interval prolongation and T wave inversion with simultaneous release of cardiac troponin **(Wybraniec 2014),** acute ischemic stroke, or a severe acute head injury.
21. **Cardiac arrest (Kim 2017)**
22. **Dysfunction of the cervical sympathetic system,(Carrillo-Esper 2004)**
23. **STE secondary to Left Bundle Branch Block** ST segment elevation upwardly convex in V_1 and V_2 because the ST segment and T wave vector are directed rightward and anteriorly (opposite to QRS-loop) Abnormalities in the ST segment and T wave changes are consequence of the sequence and/or duration of ventricular depolarization(secondary repolarization abnormality).
24. **STE secondary to IVCD(the present case) (Deshpande 2014)**
25. **STE secondary to pre-excitation (Deshpande 2014)**
26. **Bonsai abuse:** it is a synthetically-derived illicit drug which mimics the effects of cannabis and is known as "spice" in European countries. **(Yalçın 2017)**
27. **Cannabis abuse: smoking could be a potential risk factor for the development of cardiac ischemia.(Draz 2016)**
28. **Coronary arteritis/aneurysm (Patel 2016)**
29. **Coronary vasospasm, Prinzmetal's angina, variant angina, or inverse angina (Patel 2016) The presente case.**
30. **STE secondary to pre-excitation (Deshpande 2014)**
31. **'STEMI-like' acute pulmonary embolism (Abdalla 2014)**
32. **Arrhytmogenic Right Ventricular Cardiomyopathy/Dysplasia(ARVC/D) (Kataoka 2016)**
33. **STE post-electrical cardioversion (Ben-Dov 2006)**
34. **Ventricular paced rhythm (Madias 2004)**
35. **Hypertrophic cardiomyopathy (HCM) patients with early repolarization (ER) pattern:** These patients are at higher risk of ventricular arrhythmia,
36. **Hypertrophic cardiomyopathy with early repolarization and short QT syndrome (Chen 2017)** this is a new novel CACNA1C mutation underlying the unique ER pattern ECGs with SQTS. It also shows the rare trigenic mutations are the pathogenic substrates for the complicated clinical manifestation in HCM patients.

37. **After percutaneous transluminal septal ablation for hypertrophic obstructive cardiomyopathy:** this procedure is an emerging as an alternative to surgical myectomy in the management of class III or IV NYHA symptomatic cases of hypertrophic obstructive cardiomyopathy (HOCM). This involves injection of absolute alcohol into the first septal perforator branch of the left anterior descending artery(LAD) thereby producing minimal myocardial necrosis with resultant septal remodeling. This results in reduction of septal thickness and LV outflow track gradients with improvement in symptoms.

Name: AV; **Age:** 69 y/o; **Sex:** M; **Ethnic group:** Caucasian; **Weight:** 72 Kg; **Height:** 1.72 m; **Date:** 10/28/1998

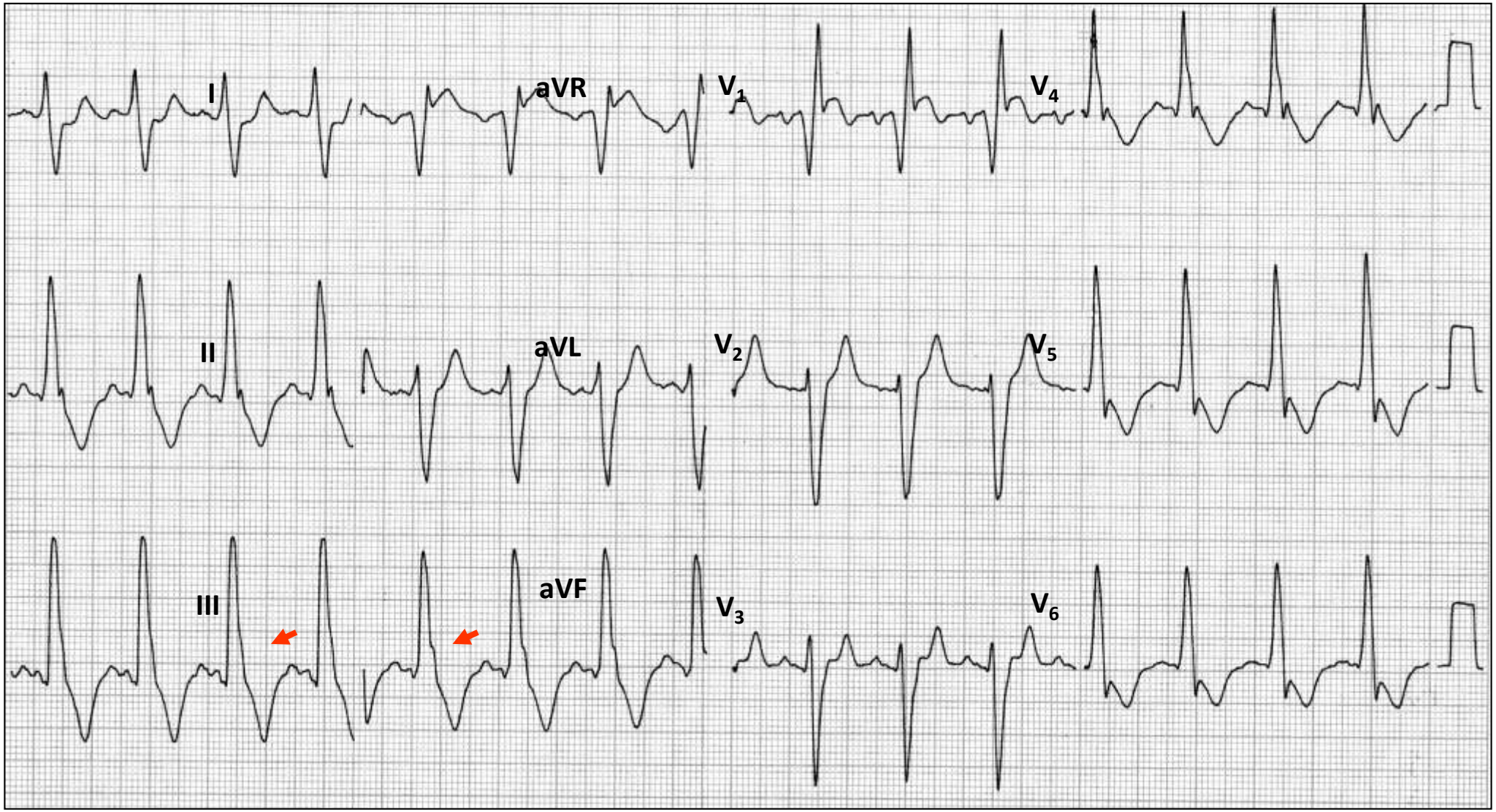


Clinical diagnosis: OHCM with gradient in LV outflow tract of 80 mmHg and clinically in functional group IV (dyspnea in rest), even with medication.

ECG diagnosis: left chamber enlargement: LAE+LVH with strain or systolic pattern.

Approach: Reduction of hypertrophic septum is chosen, by absolute alcohol injection in the first perforating artery of LAD.

Name: AV; Age: 69 y/o; Sex: M; Ethnic group: Caucasian; Weight: 72 Kg; Height: 1.72 m;Date: 10/29/1998; Drugs in use: Propanolol 360 mg/day



Clinical data: the same patient immediately after percutaneous septal ablation with absolute alcohol injection in the first perforating branch of the LAD.

ECG: STE in V1 and aVR + LAE + LVH + CRBBB + LPFB + septal MI: QR in V_1 and STSE in V1-aVR+ left septal fascicular block (LPFB): I and aVL rS, qR in III, RIII>RII, notch in descending limb of R wave of III and aVF (red arrows) and AQRS shifted to the right (+110º).

38. **Kounis syndrome: (KS)** It is a hypersensitivity coronary disorder induced by exposure to drugs, food, environmental and other triggers. Vasospastic allergic angina, allergic myocardial infarction and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells constitute the three main variants of this syndrome. The association between acute coronary events and acute allergic reactions has been recognized for several years. The first reported case occurred in 1950, during an allergic reaction to penicillin. In 1991, Kounis and Zavras described the syndrome of allergic angina and allergic myocardial infarction, currently known as Kounis syndrome. Two subtypes have been described: type I, which occurs in patients without predisposing factors for CAD and is caused by coronary artery spasm (**Keber 2017**), and type II, which occurs in patients with angiographic evidence of CAD when the allergic events induce plaque erosion or rupture. This syndrome has been reported in association with a variety of medical conditions, environmental exposures, and medication exposures. Entities such as Takotsubo cardiomyopathy, drug-eluted stent thrombosis, and coronary allograft vasculopathy appear to be associated with this syndrome. In this review, we discuss the pathobiology, clinical features, associated entities, and management of Kounis syndrome.

39. **Severe hyperkalemia: (**The present case). Can even cause life threatening ventricular arrhythmias and cardiac conduction abnormalities. Most common ECG findings include peaked tall symmetric T waves, prolonged PR interval, wide QRS complex and sine wave pattern. Since it is very commonly encountered disorder, physicians need to be aware of even its rare ECG manifestations, which include P wave absence, ST segment elevation and Brugada pattern ECG (BrP) (**Ameen 2017**). It is predicted that with increasing level of potassium concentration, progressive can show ECG pattern suggesting an acute STEMI. Emergent coronary angiography show no evidence of acute thrombotic occlusion of an epicardial coronary artery. Bhagwat et al presented two cases of pseudo Inferior MI consequence of sever hyperkalemia (**Bhagwat 2016**).

The typical progressive ECG changes of hyperkalemia

Serum K^+ level mEq/L	ECG changes
Light hyperkalemia 5.5-6.5	T-waves become abnormally tall, peaked/pointed, symmetrical, with narrow base: “Eiffel tower T waves” or “desert tent T waves”
Moderate hyperkalemia 6.5-7.0	P wave becomes broader and flatter (slow interatrial conduction): reduction in P wave amplitude, prolonged PR interval (first degree AV block) R wave height decreases, QRS complexes become wider and ST segments present elevation in some leads and depression in others.; ST-segment deviation simulates “acute injury” pattern or “dialyzable injury current”. Brugada phenocopy.
Severe hyperkalemia 7.0-7.5	Further widening and distortion of QRS occurs Non specific intraventricular conduction pattern, prolonged QT interval, and premature ventricular beats become frequent.
Extreme hyperkalemia >7.6	Absent P waves, frequent escape beats. Sinoventricular rhythm. Combination of an irregular rhythm. The stimulus originates in the SA node, it is conducted to the AV node through internodal bundles and reaches the junction without depolarizing the atrial muscle (P wave is not recorded). Absent P weave may simulate atrial fibrillation. atrioventricular block, very broad and bizarre QRS complexes. Ventricular tachycardia. Ventricular fibrillation or ventricular asystole with potassium concentration above 12 to 14 mEq/L

ECG characteristics of serum potassium values between 8 to 9 mEq/L

QRS is described:

- Decrease of R wave voltage;
- Prominent S waves;
- Diffuse QRS complexes widening, similar to left or right bundle branch block, associated to anterior or posterior fascicular block by extreme shift of SÂQRS in the FP to left or right. This QRS complex widening is differentiated from genuine bundle branch blocks and WPW pattern because in them, the delay is final or middle-final, or initial, while in hyperpotassemia is always global or diffuse.

In brief:

Right Bundle Branch Block: final QRS delay.

Left Bundle Branch Block: middle-final QRS delay.

WPW pattern: initial QRS delay (delta wave)

Hyperpotassemia: global delay.

In the late phase, a possible convergence of the QRS complex with the T wave is described, outlining a smooth diphasic wave or sine curve associated to concomitant QT interval prolongation.

ST segment depression or elevation may be observed, known as “dialyzable injury current” that may possibly resemble electrocardiographic Brugada-like pattern or ST Segment Elevation Myocardial Infarction (STEMI). Rare cases are described, which resemble acute anteroseptal infarction by absence of R wave from V1 to V4 associated to ST segment elevation of the subepicardial injury current.

Main causes of hyperpotassemia

A) Deficiency in renal elimination

- Acute and chronic renal insufficiency (CRI).
- Addison's disease.
- Diuretics that produce potassium reduction: spironolactone, amiloride, and triamterene.
- Hyporeninemic hypoaldosteronism: associated to moderate CRI: E.g.: diabetic nephropathy.
- Chronic interstitial nephropathies and use of nonhormonal anti-inflammatory agents.
- Captopril: by inhibition of aldosterone synthesis.
- Heparin: by inhibition of aldosterone synthesis.
- Cyclosporine.
- Renal transplantation.
- Systemic lupus erythematosus.
- Drepanocytosis.
- Amyloidosis.
- Multiple myeloma.
- **Severe sepsis**

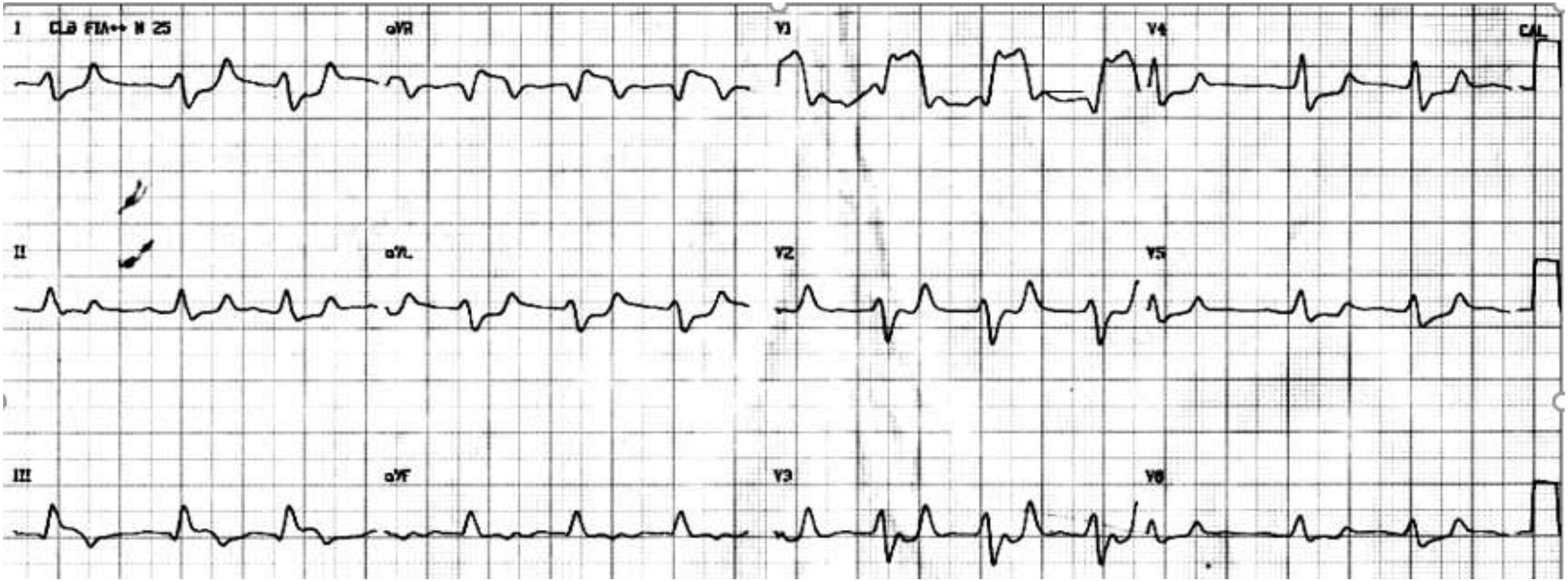
B) Passage of cation from the intracellular to the extracellular medium

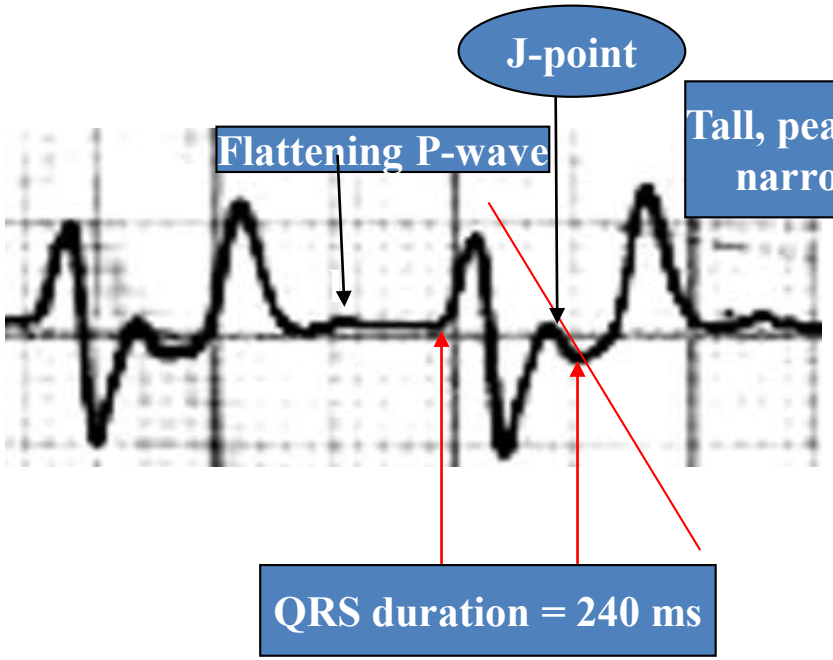
- Acidosis: passage to the extracellular compartment.
- Mass cell destruction: E.g. Extensive trauma, burns, rhabdomyolysis, hemolysis, cell lysis in chemotherapy.
- Hyperpotassemia periodic paralysis: dominant autosomal.
- Severe hyperglycemia with hyperosmolarity.
- Beta 2 adrenergic receptor blockers.
- Propranolol.
- Massive digitalis intoxication.
- Use of the anesthetic agent succinylcholine.
- Perfusion of the amino acid arginine.

Simulation of ECG manifestation of ST Segment Elevation Myocardial Infarction (STEMI): Severe hyperkalemia key for diagnosis

65-year-old man, white, businessman, suffers from hypertension and long-standing type 2 diabetes. He was admitted to our emergency room complaining of chest discomfort that started an hour ago. The admission ECG is shown attached. The strategy was primary percutaneous coronary intervention for ST-segment elevation myocardial infarction because patients with ST-segment elevation myocardial infarction benefit from prompt reperfusion therapy. Additionally, the patient had testicular seminoma, widespread metastasis, and renal failure exacerbated by cardiac catheterization, and probably by high blood pressure and diabetes mellitus. There was some initial improvement after dialysis but unfortunately as a consequence of the underlying disease he died. Serum $K^+ = 7.9$ mEq/L

Questions: What is the electrocardiographic diagnosis? Culprit artery? What would you expect to find in the catheterization?

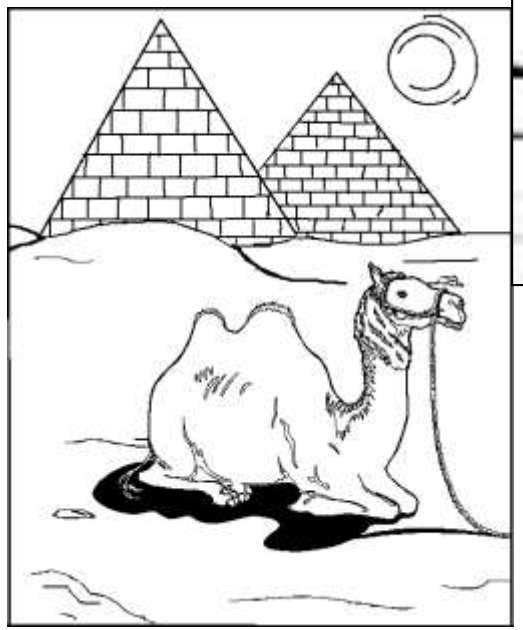


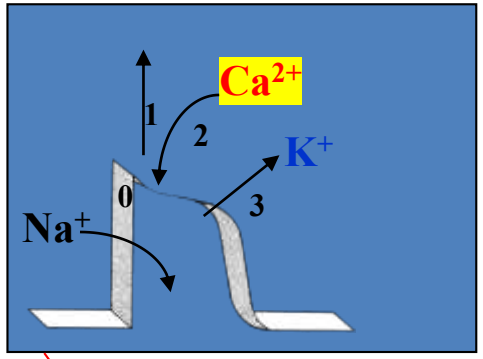


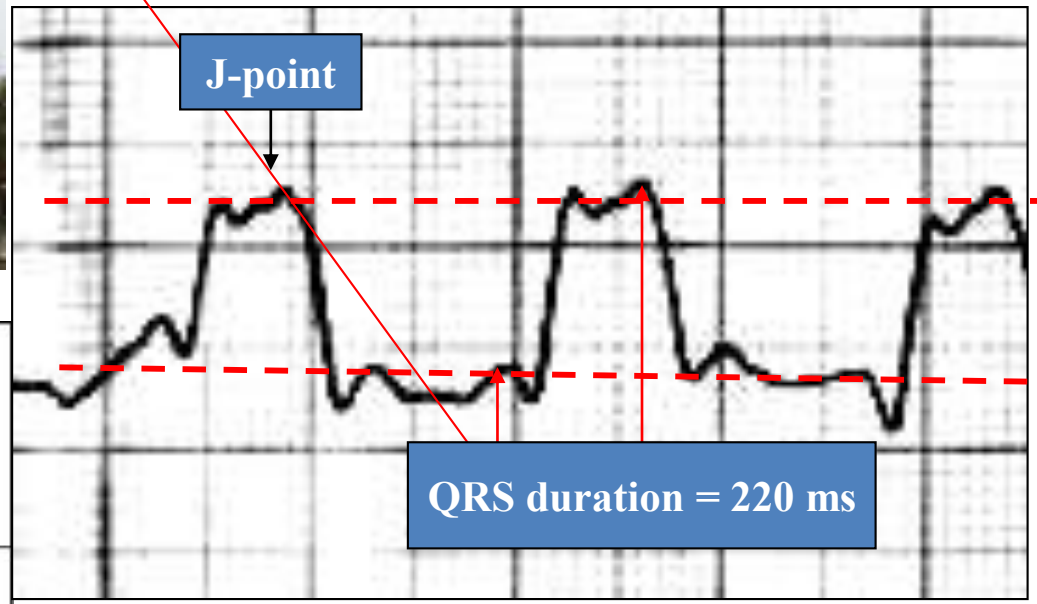
Tall, peaked/pointed, narrow T waves

Eiffel tower T-wave

or "desert-tent" T-wave





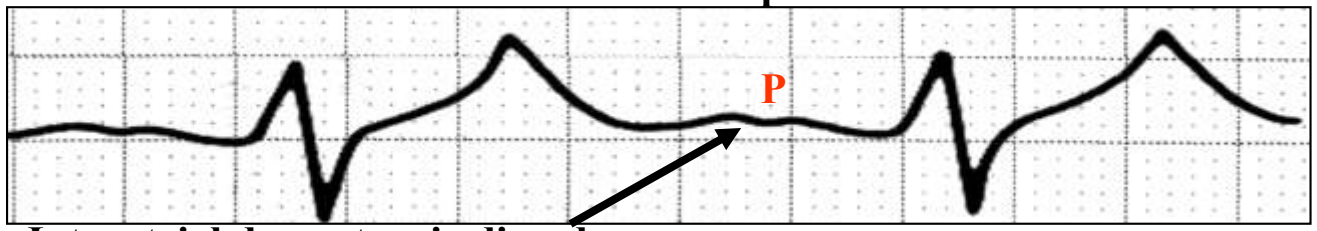


Widening of QRS at the initial, middle and terminal portions when K^+ concentration exceeds 6.5 mEq/L.

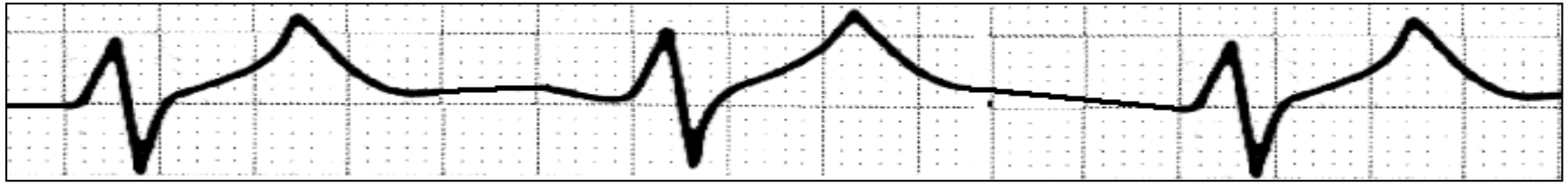
ECG characteristics with serum potassium values around 7 mEq/L and 8.4 mEq/L

Serum potassium: 7 mEq/l

Reduction of P wave amplitude



Serum potassium: 8.4 mEq/l



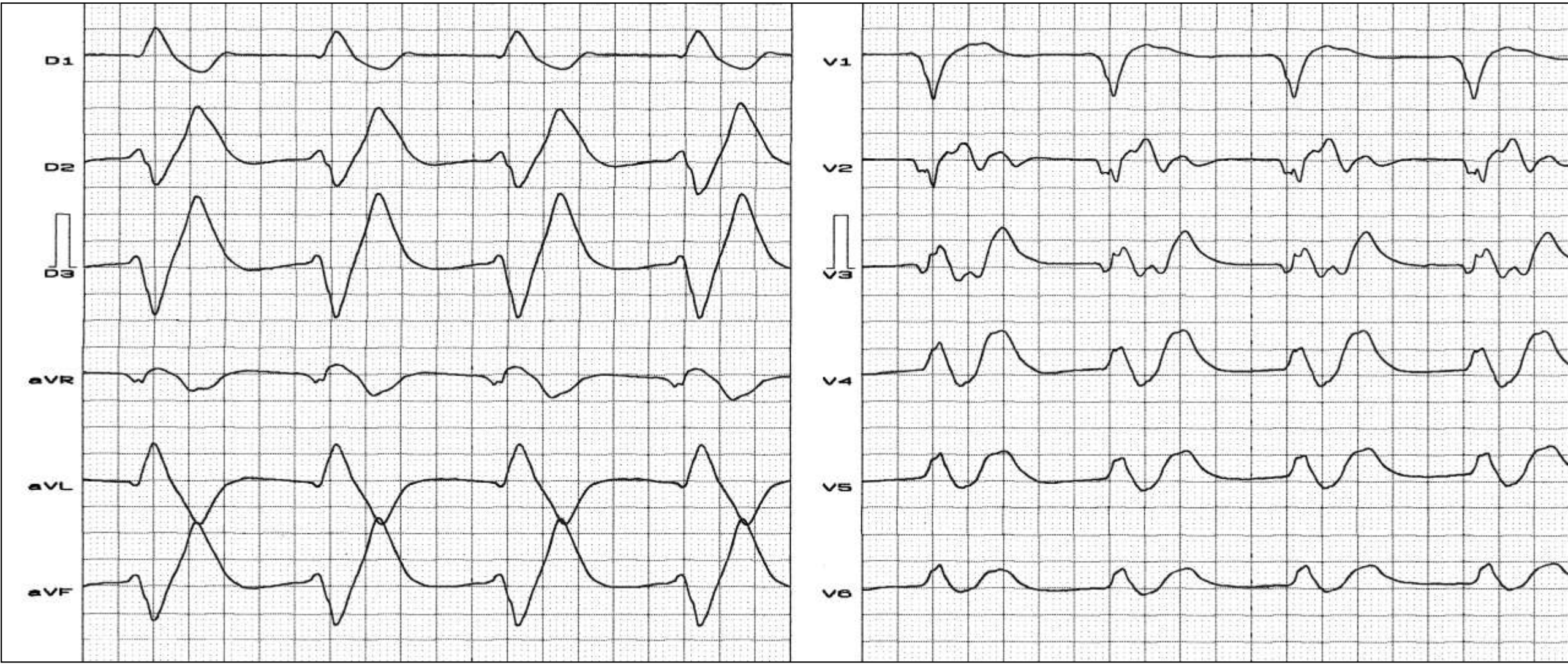
Sinoventricular rhythm: absence of P wave. The stimulus originates in the SA node, it is conducted to the AV node through internodal bundles and reaches the junction without depolarizing the atrial muscle (P wave is not recorded).

Normal serum potassium levels are between 3.5 and 5.3 mEq/L. Hyperkalemia is defined as a condition in which serum potassium is greater than 5.3 mEq/L. At least 95% of the body's potassium is found inside cells, with the remainder in the blood. Membrane potential is maintained specially by the concentration gradient and membrane permeability to potassium with some contribution from the Na^+/K^+ pump.

ECG is vital to assess the physiologic significance of the hyperkalemia. However, ECG changes often do not correlate with the degree of hyperkalemia. ECG changes suggestive of an effect of hyperkalemia on cardiac conduction include the following in order of appearance (**Diercks 2004**):

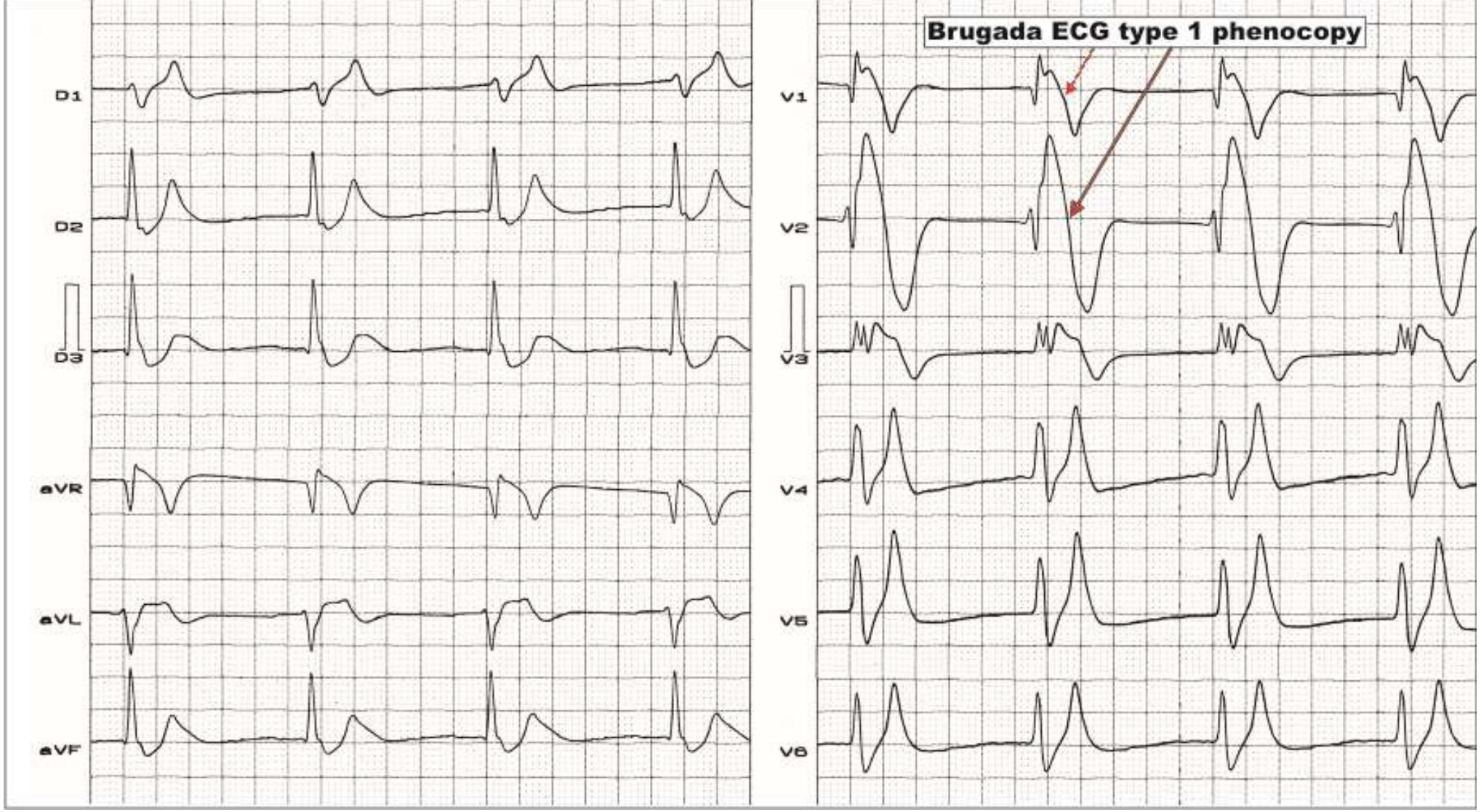
- Tall, peaked/pointed, symmetric and narrow base T waves called tended T-wave or Eiffel tower T-wave.
- Prolongation of the PR interval.
- Widening of the QRS at the initial, middle and terminal portion: when K^+ concentrations exceed 6.5 mEq/L.
- The P wave amplitude decreases and the duration increases (7 mEq/L), flattening or absence of the P wave because of sinoventricular rhythm.
- A "sine wave" appearance at severely elevated levels.
- ST-segment deviation simulates "acute injury" pattern or "dialyzable injury current". Brugada phenocopy.
- Sinus arrest.
- Ventricular asystole or ventricular fibrillation with serum K^+ above 12 to 14 mEq/L.
- In patients with organic heart disease and abnormal baseline ECG, bradycardia may be the only new ECG abnormality.

Typical ECG example of patient with extremely high level of serum potassium



Clinical diagnosis: chronic renal insufficiency and in dialysis. The patient delayed 72 hours the dialysis session. Severe hyperpotassemia of 9 mEq/L.

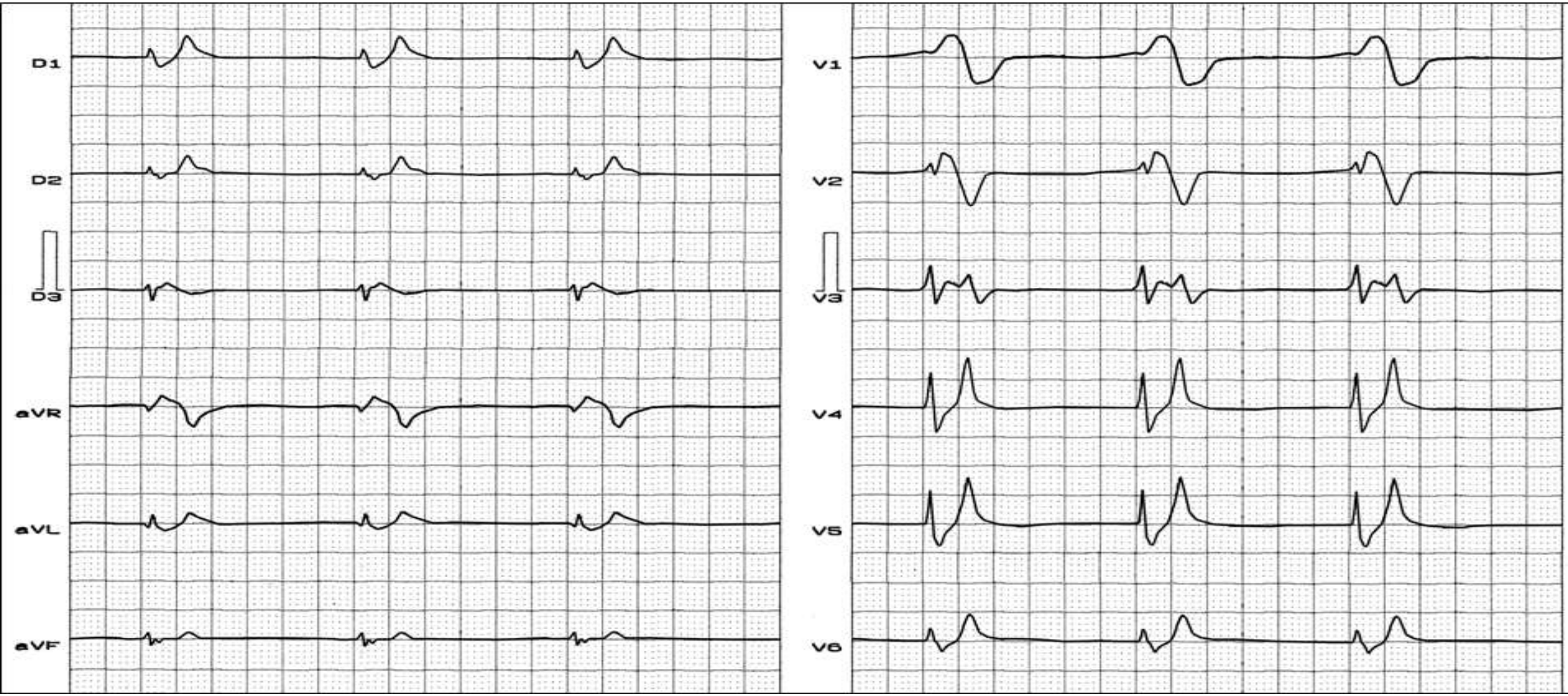
ECG diagnosis: absence of P wave, sinoventricular rhythm, 57 bpm, morphology of bizarre intraventricular severe disorder (QRSd: 240 ms) that is similar to complete LBBB. T waves with polarity matching with QRS from V3 to V6. Convergence of QRS with T wave that outlines smooth diphasic wave or sine curve.



Clinical diagnosis: terminal renal insufficiency. Severe hyperkalemia: K^+ 8.7 mEq/L. This sign is known as "dialyzable injury current". ECG diagnosis: very likely, junctional with P waves near the J point, HR: 54 bpm, QRSd: 160 ms, ST segment elevation from V1 to V3 and I, aVL and aVR. V1 to V3 displays ST segment with upwardly convex pattern, similar to Brugada syndrome or Brugada phenocopy", typical T waves in "tent", pointed, and with a narrow base. Numerous conditions which resemble the type-1 BrS pattern should be ruled out. These are called "acquired forms of BrS", "Brugada-like ECG pattern" or Brugada phenocopies (**Nguyen 2011; Riera 2010**) (an environmental condition that imitates or mimics one produced by a gene).

Typical ECG of hyperpotassemia associated to Brugada-phenocopy pattern

Name: FHM; Sex: M; Age: 56 y/o; Ethnic group: Mulatto; Weight: 65 Kg; Height: 1.62 m; Date: 05/11/2003



P wave is not identified; sinoventricular rhythm. Severe hypercalcemia with electrocardiographic Brugada-like pattern. Chronic renal insufficiency with hypercalcemia has been described transitorily, and reversed with dialysis. Apiculate T waves in “tent” from V4 through V6.

Coronary Artery Spasm

The term coronary artery spasm (CAS) refers to a sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near occlusion. Although CAS may be involved in other coronary syndromes, it represents the usual cause of variant angina. The variant form of angina was first described in 1959 by Prinzmetal et al (**Prinzmetal 1959**), who used this term to indicate that angina attacks, unlike the most common form of effort angina, occurred at rest and were associated with ST-segment elevation, rather than ST-segment depression, on the ECG. Because myocardial ischemia occurred in the absence of any change in myocardial oxygen demand, the authors hypothesized that it was caused by an increased tonus of vessels at the level of coronary stenosis. CAS, or smooth muscle constriction of the coronary artery, is an important cause of chest pain syndromes that can lead to myocardial infarction (MI), ventricular arrhythmias, and sudden death. It also plays a key role in the development of atherosclerotic lesions. Subsequently, Maseri et al described the clinical, ECG, and angiographic features of 138 patients with variant angina and concluded that the syndrome was considerably more polymorphic than was initially inferred by Prinzmetal (**Maseri 1978**).

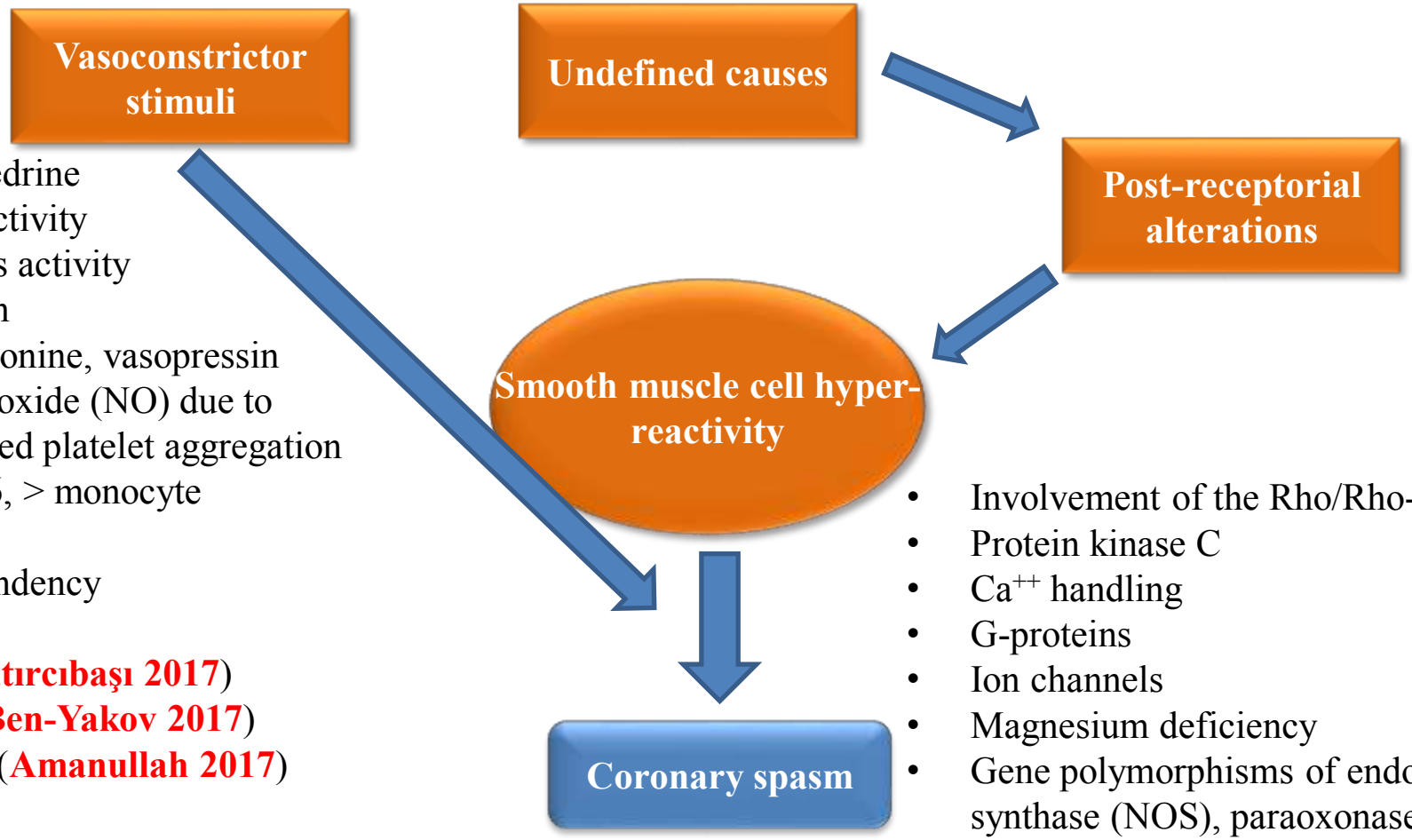
Etiopathophysiology

The pathophysiologic mechanisms leading to CAS are not yet completely understood. Coronary arterial tone varies normally via physiologic mechanisms, but the degree of vasoconstriction can range along a spectrum extending from undetectable constriction to complete arterial occlusion such as the present case. In some patients with partial vasoconstriction, symptoms can arise with activities that exceed a threshold of myocardial demand (**Yasue 2008a**). In other patients, constriction may be so severe that myocardial ischemia develops at rest. Many observers use the presence of constriction-induced ischemia as the threshold for defining clinical coronary artery vasospasm (**Yasue 2008a**), which has also been called vasospastic angina or variant angina. In many cases, CAS can occur spontaneously without an identifiable cause. Known triggers of CAS in susceptible patients include hyperventilation, cocaine or tobacco use, and administration of provocative agents such as acetylcholine, ergonovine, histamine, or serotonin (**Yasue 1979**).

That CAS can be induced through stimulation of α-receptors (**Yasue 1976**) or intracoronary injection of the parasympathetic neurotransmitter acetylcholine indicates that there are different mechanisms of action. Acetylcholine causes coronary vasodilation in healthy coronary arteries through the release of endothelial nitric oxide (NO) (**Yasue 1986**); however, in atherosclerotic arteries, vasoconstriction ensues instead. Patients with coronary artery vasospasm appear to have a heightened vasoconstrictor response to acetylcholine as well as an enhanced response to the vasodilator effects of nitrates, an observation that is consistent with a deficiency of endogenous nitric oxide (NO) activity (**Yasue 1986**). Thus, nitric oxide (NO) deficiency is believed to play an important role in the development of CAS. This may also explain the correlation between coronary artery vasospasm and increased intimal thickening: NO deficiency results in enhanced activity of potent vasoconstrictors and

stimulators of vascular smooth muscle proliferation, such as angiotensin II and endothelin 1.(**Yasue 2008**)
Several genetic polymorphisms that compromise endothelial NO production have been found to be significantly associated with CAS.(**Kaneda 2008**)Some have even been found to have prognostic value, including the -786T/C polymorphism.(**Nishijima 2007**) However, additional studies showing that NO levels are not decreased at the sites of CAS dispute the primacy of the role of NO.(**Egashira 1996**) Alternative (or coexisting) mechanisms of CAS include enhanced phospholipase C activity.(**Nakano 2002**) In addition, CAS is associated with increased markers of oxidative stress and inflammation, including thioredoxin, C-reactive protein (CRP), and monocyte levels.(**Yasue 2008**) Certain behavioral traits (eg, type A personality, panic disorder, and severe anxiety) are also described as being associated with CAS.(**Stern 2009**)

Pathogenetic mechanisms in coronary artery spasm (Lanza 2011)



- Catecholamines: e.i.Pseudoephedrine
- Increase or reduction of vagal activity
- Imbalance in autonomic nervous activity
- Chronic low-grade inflammation
- Histamine, amphetamines, serotonine, vasopressin
- Deficient basal release of nitric oxide (NO) due to endothelial dysfunction, increased platelet aggregation
- Tromboxane A2, > interleukin-6, > monocyte
- Endothelin-1
- Thrombin: strong thrombotic tendency
- Alkalosis
- Gemcitabine chemotherapy (**Katırcıbaşı 2017**)
- 5-fluorouracil chemotherapy (**Ben-Yakov 2017**)
- Phentermine hydrochloride use (**Amanullah 2017**)
- Cocaine
- Low levels of vitamin E

- Involvement of the Rho/Rho-kinase pathway
- Protein kinase C
- Ca^{++} handling
- G-proteins
- Ion channels
- Magnesium deficiency
- Gene polymorphisms of endothelial NO synthase (NOS), paraoxonase

Mechanisms of coronary artery spasm

Main causes	Mechanism	Comments
Imbalance in autonomic nervous activity	Frequent events at night when vagal tone is predominant Directly induced by catecholamines or by stimuli (exercise, cold pressor test, cocaine, amphetamines).	Night attacks frequently occur during rapid eye movement sleep, when a reduction in vagal activity is associated with an increase in adrenergic activity. Spontaneous events are frequently preceded by a reduction of vagal activity, and followed by an increase in coronary levels of catecholamines.
Inflammation	Elevated peripheral white blood cell and monocyte counts, hs-CRP, interleukin-6, and adhesion molecules.	Inflammation is prevalent in CAS and atherosclerosis, it, therefore, may not constitute by itself a major direct cause.
Endothelial dysfunction	Acetylcholine, ergonovine, serotonin, or histamine, all of which are endothelium-dependent vasodilators, cause vasodilation by inducing nitric oxide release from the normal endothelium. While in the presence of endothelial dysfunction, they can induce CAS.	Endothelial dysfunction is not always present in CAS.
Smooth muscle cell hypercontractility	Rho-kinase activity is enhanced in coronary artery smooth muscle cells by inflammation in a porcine model. Spontaneous CAS has been developed in K_{ATP} mutant or SUR2 K_{ATP} knockout mice. Mice deficient in α_{1H} T-type calcium channel have reduced relaxation in response to acetylcholine.	Their relevance to CAS in humans remains to be elucidated.
Oxidative stress	NO could be degraded by oxygen free radicals. Oxygen-reactive species have a detrimental effect on the vessel wall, leading to inflammation, endothelial damage and vascular smooth muscle cell constriction. In CAS, there are low plasma levels of vitamin E and high plasma levels of thioredoxin	Deficient basal release of nitric oxide (NO) due to endothelial dysfunction, There is no endothelial NO deficiency and dysfunction in patients with CAS.

Main causes	Mechanism	Comments
Genetic factors	Mutation or polymorphism of the endothelial NO synthase gene, polymorphism of paraoxonase I gene, polymorphisms for adrenergic and serotoninergic receptors, angiotensin-converting enzyme, and inflammatory cytokines. NADH/NADPH oxidase p22 phox gene is a susceptibility locus in men, while stromelysin-1 and interleukin-6 genes are susceptibility loci in women.	Studies of genetic mutations or polymorphisms in the pathogenesis of CAS have been inconsistent. NO gene polymorphisms are found in only one-third of the patients. Family history is not a risk factor for CAS.

Endothelial Dysfunction

Although it has been suggested that endothelial dysfunction is involved in CAS, it seems unlikely to be a direct cause, although it can facilitate the effects of vasoconstrictor stimuli in the spastic segment. The endothelium has a crucial role in the physiological regulation of coronary vascular tone, mainly through the release of several vasodilators, the most important of which is nitric oxide (NO). Therefore, a significant endothelial damage might impair vasodilation, thus favoring CAS in response to vasoconstrictor stimuli (**Vanhoutte 1989**).

It is important to observe that various vasoactive stimuli (eg, acetylcholine, serotonin, histamine) cause vasodilation by inducing NO release by the endothelium, but, at the same time, they may cause vasoconstriction through direct stimulation of VSMCs. Thus, in the presence of endothelial dysfunction, their release in the vessel wall can lead to vasoconstriction or CAS (**Furchgott 1980**). Experimental support of the possibility that endothelial dysfunction can play a major role in CAS can derive from an earlier porcine model developed by Shimokawa et al (**Shimokawa 1985**), in which the authors managed to make a coronary segment susceptible to spasm in response to serotonin and histamine by the association of endothelium removal and high-cholesterol feeding, which also promoted the formation of atherosclerotic plaques in the vasospastic segment. In patients with variant angina, on the other hand, an involvement of endothelial dysfunction in the pathogenesis of CAS is suggested by the following observations: (1) endothelial dysfunction can be shown in nonspastic coronary arteries, and in peripheral arteries, as well (**Okumura 1996; Moriyama 2001**); (2) a higher prevalence of mutations of NO synthase gene associated with a reduced production of NO by endothelial cells has been reported (**Kaneda 2006**); (3) some forms of treatment (eg, vitamin E, statins), known to improve endothelial function, have been reported to also decrease symptoms (**Motoyama 1998; Yasue 2008b**). Other observations, however, challenge the hypothesis of a primary role of endothelial dysfunction in the pathogenesis of CAS. First, endothelial injury is very common in patients with cardiovascular risk factors or atherosclerosis (**Rodriguez-Porcel 2003**), whereas CAS is rare. Second, in animal models, endothelial denudation of the vessel wall usually results in increased vasoconstriction, rather than in CAS, in response to constrictor stimuli (**Furchgott 1980**). Third, although, in the experimental model by Shimokawa et al (**Shimokawa 1985**), endothelium removal, together with atherosclerotic changes, can appear to be the major abnormality responsible for the inducibility of CAS, the development of VSMC hyperreactivity was not excluded, and was in fact found to contribute to spasm susceptibility in a subsequent study (**Yamamoto 1987**). Fourth, the use of substance P, a pure endothelial-dependent vasodilator, has shown that endothelial dysfunction at the site of CAS is not always present in patients with variant angina (**Egashira 1992**). Finally, in patients with variant angina, some studies failed to demonstrate endothelial dysfunction in nonspastic coronary arteries as well as in peripheral arteries (**Ito 1999**), and other studies also failed to show the higher prevalence of NO synthase polymorphisms associated with endothelial dysfunction (**Casas 2006**). It is noteworthy that endothelial damage has also been suggested to be involved in catheter-induced CAS during coronary angiography. A direct stimulation of VSMCs, however, might also play a major role in this case.

In summary, an impairment of endothelium-mediated vasodilation seems unlikely to be responsible by itself for CAS, although it might favor its induction by vasoconstrictors at the site of predisposed segments.

Primary nonspecific hyperreactivity of Vascular Smooth Muscle Cells -(VSMCs)

There is consistent evidence to suggest that, in patients with variant angina, a primary nonspecific hyperreactivity of VSMCs of coronary artery wall is the key abnormality responsible for CAS. The pathogenetic role of local VSMC hyperreactivity is suggested by the observation that the vasoconstrictor stimuli that induce CAS in localized coronary segments of patients with variant angina are unable to induce CAS in other coronary segments of the same patients (**Kaski 1991**), and in patients with other forms of angina (in particular, stable angina), as well (**Bertrand 1982; Kaski 1989**). Furthermore, in patients with variant angina, CAS can be elicited by several stimuli that act through different receptors and different cellular mechanisms (**Yasue 1986; Crea 1986; Heupler 1978; McFadden 1991; Ginsburg 1981**), suggesting an intracellular, postreceptorial localization of the alteration responsible for the hyperreactivity. VSMC contraction, however, is regulated by a complex, not yet fully elucidated, system of different intracellular pathways that involve various G proteins, enzymes, and regulatory substances. A simplified scheme of the main pathways regulating myosin light chain (MLC) phosphorylation, which eventually results in the activation of actin-myosin filaments (**Hirano 2007**). Theoretically, abnormalities in any of these pathways might be responsible for coronary VSMC hyperreactivity. Evidence that induction of functional abnormalities could result in VSMC hyperreactivity and CAS has been obtained in experimental models for some of these pathways. The possibility to induce VSMC hyperreactivity in a coronary segment was first demonstrated by Shimokawa et al in a porcine model in which the adventitia of a coronary segment was exposed to an inflammatory stimulus (interleukin-1β). After 2 weeks, a coronary stenosis developed in the segment, which also exhibited a spastic response to the administration of serotonin, histamine, and platelet-activating factor (**Shimokawa 1996**). Similar effects in this model were obtained by the use of other inflammatory cytokines, like interleukin-1α, tumor necrosis factor-α (**Fukumoto 1997**), and platelet-derived growth factor (**Kozai 1997**). Interestingly, the development of a spastic response by VSMCs was associated with histological evidence of phenotypic changes toward VSMC dedifferentiation (**Fukumoto 1997**). Subsequent data suggested that, in this animal model, a major mechanisms of VSMC hyperreactivity was represented by an increase in Rho-kinase activity (**Kandabashi 2000**), an enzyme that favors VSMC constriction by increasing sensitization to Ca^{2+} of MLCs both through a direct effect and, indirectly, through inhibition of myosin phosphatase (**Hirano 2007**). Rho-kinase was indeed found overexpressed in this model, and a Rho-kinase inhibitor, hydroxyfasudil, was able to prevent CAS (**Shimokawa 1999**). Importantly, the Rho-kinase inhibitor fasudil has been shown to prevent acetylcholine-induced CAS in patients with variant angina, suggesting that this enzyme may actually have a role in the clinical setting (**Masumoto 2002**), and might therefore constitute an important therapeutic target (**Shimokawa 2008**). In this same model, however, susceptibility to CAS seemed also be mediated by

activation of protein kinase C (PKC), which also increases Ca^{2+} sensitivity of MLCs by inhibiting myosin phosphatase activation. PKC activators were indeed able to favor, whereas PKC inhibitors prevented, CAS induction by serotonin and histamine (**Kadokami 1996**). More recently, another experimental model of CAS characterized by VSMC hyperreactivity has been developed in knockout mice for SUR-2, a component of the ATP-dependent K^+channel (**Chutkow 2002**). In this model, spontaneous spasm occurred in completely normal coronary arteries and caused premature sudden death. However, sudden death resulted from severe bradyarrhythmias, rather than from tachyarrhythmias, as, instead, most frequently happens in patients with variant angina (**Sanna 2009; Romagnoli 2007; Maseri 1982**). This model, however, highlights 2 major findings: (1) mutations in proteins of ion channels have the potential to cause VSMC hyperreactivity and contribute to the pathogenesis of CAS, and (2) VSMC hyperreactivity can be caused by functional abnormalities in the absence of atherosclerotic lesions.

In summary, some experimental models of CAS have had the merit to demonstrate that VSMC hyperreactivity can develop and cause CAS, also showing that this can occur through different pathways. The relevance of these models in the clinical setting, however, remains to be established.

Other Potential Substrates for CAS Clinical Risk Factors: smoking, genetic factors such as the gene encoding for NO synthase,. serotoninergic receptors,67,68 or antioxidant enzymes, angiotensin-converting enzyme, and inflammatory cytokines.69 –71 ethnic groups, Other mechanisms have been proposed to explain the susceptibility to CAS of epicardial coronary arteries in patients with variant angina. It was suggested that a passive mechanical collapse may play a significant role in the pathogenesis of CAS. The hypothesis was based on the notion that, in presence of an eccentric stenosis, an increase of vascular tone and the poststenotic reduction of perfusion pressure could interact in favoring CAS (**Mc Alpin1980**). CAS, however, often occurs in normal coronary arteries. Based on the presence of a local fibromuscular hyperplasia of the vessel reported in some postmortem studies (**Roberts 1982**), it was also suggested that CAS can occur because of an abnormal production of growth factors (by VSMCs, endothelial cells, platelets, etc) but, again, in many patients with variant angina coronary angiography does not show any coronary narrowing and remains unchanged for years (**Kaski 1992**). Adventitial abnormalities might also play some role in the pathogenesis of CAS. The adventitia is the site of neural terminations and can also be the site of inflammatory infiltrates (**Gutterman 1999**). Accordingly, excessive adventitial release of vasoconstrictor substances might cause CAS. Adventitial accumulation of mast cells, in particular, has been found in a patient with variant angina who died suddenly (**Forman 1985**), but also in the culprit vessel of patients who died of acute myocardial infarction (**Laine 1999**), suggesting that CAS was triggered by vasoconstrictor agents released by mast cells (mainly histamine, but also prostaglandin D2 and leukotriene C4), which were responsible for the events. Adventitial abnormalities, however, have not been described in the few other autopsy studies of patients with variant angina (**Roberts 1982; Trevi 1976**), suggesting that their exact role in the pathogenesis of CAS needs further assessment. Nevertheless, as suggested by the Shimokawa model (**Shimokawa 1996**), inflammation of vascular adventitia might be the substrate for VSMC hyperreactivity. Finally, some abnormalities able to favor an excessive intracellular calcium inflow and/or release in

coronary VSMCs have also been suggested to be involved in the pathogenesis of CAS. In particular, magnesium deficiency has been reported in some studies (**Goto 1990**), and we have found an increased activity of the membrane Na-H exchanger (**Lanza 2003**). These systemic abnormalities, however, when present, may simply favor the local occurrence of CAS in some patients with VSMC hyper-reactivity.

Causes of Coronary VSMC Hyperreactivity

Although local coronary VSMC hyperreactivity seems to constitute the substrate for CAS, the causes of the vascular abnormality in the clinical setting remain largely undefined.

Clinical Risk Factors

Common cardiovascular risk factors do not seem to show a significant association with CAS, with the exception of smoking. Indeed, active smokers constitute ≈75% of patients with variant angina (**Sugiishi 1993**). Why smoking favors CAS, however, remains unknown. Cigarettes contain several toxic substances for the vascular system, including nicotine and carbon monoxide, besides proinflammatory substances that might cause spasmogenic alterations in the VSMCs in predisposed subjects (**Morrow 1995**).

An excessive alcohol consumption has also been associated with variant angina (**Fernandez 1973**), although the epidemiological evidence is not robust. Furthermore, it is known that the consumption or abuse of several other substances (eg, cocaine, amphetamines, marijuana, 5-fluorouracil, capecitabine, sumatriptan, etc) can provoke or favor CAS (**El Menyar 2010; Bathina 2010; Sestito 2006; Wasson 2004**).

Inflammation

The possible role of inflammation in the pathogenesis of CAS was suggested by the detection, in postmortem studies, of inflammatory cells, in particular mast cells, in coronary vasospastic segments, as previously discussed (**Forman 1985; Wasson 2004**). Furthermore, as also shown above, adventitial coronary stimulation with inflammatory cytokines induced spasmogenic changes of VSMCs in animal models (**Shimokawa 1996**). Moreover, higher levels of C-reactive protein have been reported during the active phases of variant angina, in comparison with the inactive phases (**Katayama 2005**).

However, inflammation is highly prevalent in, and most often associated with, atherosclerosis, whereas variant angina is a rare condition. Thus, although inflammation may favor or predispose to CAS and may have a role in some patients, it is unlikely to constitute by itself a major direct cause of CAS in the whole population of patients with variant angina.

Oxidative stress

An increased production of oxygen-reactive species may occur in several conditions (**Park 2009; Keaney 2003; Rodrigo 2011**), and has a detrimental effect on the vessel wall, causing both endothelial dysfunction and inflammation, but also increasing the constrictor response of VSMCs (**Rodrigo 2011**). Smoking suppresses acetylcholine-induced endothelium-dependent relaxation, which is improved by antioxidants, such as vitamins C and E, suggesting NO could be degraded by oxygen free radicals during the hot phases of the disease (**Miwa 1996**) and of an increased cardiac consumption of vitamin E, associated with an increased transcardiac release of lipoperoxides (**Miwa 1999**). Oxygen-reactive species have a detrimental effect on the vessel wall, leading to inflammation, endothelial damage and the constrictor response of vascular smooth muscle cells. In CAS, a pathogenetic role for oxidative stress has been suggested by the presence of low plasma levels of vitamin E and high plasma levels of thioredoxin. However, while oxidative stress may predispose patients to CAS, there are debates over its effects on endothelial dysfunction as it has been reported that there is no endothelial NO deficiency or dysfunction in some patients with CAS. In patients with variant angina, a possible pathogenetic role has been. Again, it should be noticed that oxidative stress is highly prevalent in subjects with CAD, whereas variant angina is a rare condition. Therefore, although oxidative stress may predispose to CAS or facilitate its induction, it is unlikely that it constitutes a major direct cause of the VSMC hyperreactivity. Oxidative stress is highly prevalent in subjects with CAD or cardiovascular risk factors, whereas Prinzmetal is a rare condition.

Autonomic Nervous System

Among the potential triggers of CAS, the autonomic nervous system has received a great deal of attention. The relationship between autonomic nervous system and CAS, however, is rather complex, because both an increase in sympathetic tone and an increase in parasympathetic tone appear able to induce CAS.

Sympathetic Activity

Noradrenaline, the neurotransmitter of efferent sympathetic fibers, can trigger vasoconstriction in VSMCs through stimulation of α-adrenergic receptors. Clinical studies have confirmed that CAS can be induced by catecholamines (**Yasue 1986**) or by stimuli (eg, exercise, cold pressor test) (**Specchia 1979; Raizner 1980**) that increase sympathetic outflow. In addition, the induction of CAS by some substances (eg, cocaine, amphetamines) has been suggested to be related to sympathetic activation and/or VSMC sensitization to catecholamines (**El Menyar 2006**). Furthermore, it is known that β-blockers may exacerbate angina attacks in patients with variant angina, probably because of the blockade of vasodilator coronary β_2 receptors, which leaves vasoconstrictor α-adrenergic receptors unopposed (**Robertson 1982**). However, it has been found that an increase in coronary levels of catecholamines may follow, rather than precede, spontaneous ischemic episodes of CAS (**Robertson 1983**). Moreover, α-blockade has often been shown to be ineffective in controlling symptoms in variant angina patients (**Winniford 1983; Chierchia 1984**).

Vagal Activity

In physiological conditions, acetylcholine, the neurotransmitter of parasympathetic nerve fibers, causes vasodilation through the endothelial release of NO, whereas at high doses it may induce vasoconstriction through direct stimulation of VSMC muscarinic receptors. Thus, in case of VSMC hyperreactivity, even small concentrations of acetylcholine might induce CAS. In the clinical setting, some findings suggest a role for vagal activity as a trigger of spasm. In patients with variant angina, attacks often occur during the night, when vagal tone is higher (**Waters 1984; Lanza 1999**), and the intracoronary administration of acetylcholine is known to induce CAS (**Kaski 1989**).

However, the relation between acetylcholine-induced CAS and the role of vagal activation in triggering spontaneous spasm in patients remains uncertain. Indeed, the frequent occurrence of ischemic episodes during the night does not necessarily imply that CAS is induced by vagal activation. The assessment of cardiac autonomic changes associated with spontaneous episodes of ST-segment elevation, indeed, has shown that ischemic episodes are often preceded by a reduction, rather than by an increment, of vagal activity (**Lanza 1996**). In agreement with these data, the occurrence of vasospastic angina attacks at night is more frequent during the rapid eye movement phases of sleep, when vagal withdrawal occurs in association with an increase in adrenergic activity (**King 1973**).

Genetic Polymorphisms

veral genetic mutations have been described as potentially involved in the predisposition of patients with variant angina to CAS. They mainly concern the gene encoding for NO synthase (**Romagnoli 2007**), but polymorphisms have also been described for other proteins able to modulate vascular tone, like adrenergic and serotoninergic receptors (**Park 2006; Kaumann 2006**), or antioxidant enzymes, angiotensin-converting enzyme, and inflammatory cytokines (**Inoue 1998; Nakano 2002; Oike 1995**). However, not all the studies have been consistent (**Miwa 2005**). Moreover, family history is not a risk factor for variant angina, and disease activity often shows significant fluctuations over the short term (eg, circadian variations) and long term (with active and inactive phases), or may even subside completely, thus suggesting that genetic factors are unlikely to be a major element in the pathogenesis of CAS.

Ethnic Influences

The role of genetic factors in the pathogenesis of CAS has also been suggested by the observation of a different prevalence of vasospastic angina in Japanese and white people. In cohorts of white patients with angina pectoris, indeed, the prevalence of variant angina is 1% to 2% only (**Lanza 2007**), whereas it is much higher in Japanese cohorts (**Shimokawa 1988**). Furthermore, some differences between these two ethnic groups in CAS features emerge from published studies. Japanese patients, indeed, more frequently show diffuse and multivessel CAS, whereas they show a lower prevalence of significant coronary artery disease (**Beltrame 1999**). Together with the obvious genetic differences, however, consistent differences between the 2 ethnic groups in diet, lifestyle, and cardiovascular risk profile might also account for the different CAS features, as suggested by the

fact that Japanese individuals who live in Western countries may assume a pattern of cardiovascular disease more similar to that of white people (**Marmot 1975**). Furthermore, although a different vasomotor reactivity of coronary arteries has been shown in a head-to-head comparison of patients of the 2 ethnic groups in the acute phase of myocardial infarction (**Pristipino 2000**), no clinical studies have directly compared white and Japanese patients with variant angina. Thus, it cannot be excluded that differences emerging from independently published studies might have been, at least in part, biased by differences in patient selection, definition of CAS, and use of provocative tests. For example, in white patients, the prevalence of multivessel CAD was much higher in the earliest studies, when CAS was believed to mainly occur at the site of stenosis (Severi 1980), whereas in recent studies it is present in <10% of patients (**Lanza 2007**). Furthermore, in patients with chest pain and nonobstructive coronary artery disease, provocative tests of CAS are much more frequently performed in Japan than in Western countries. Accordingly, the diagnosis of vasospastic angina was mainly based on clinical evidence of typical angina symptoms and ST-segment elevation in Western studies (**Lanza 2007**), whereas it is often based on the results of intracoronary provocative tests in Japanese studies (**Takagi 2011**). This might result in the under diagnosis of less typical cases in Western countries, but it cannot be excluded that, in the absence of angina attacks typical of variant angina, it might also result in some false-positive diagnoses in some Japanese studies, thus apparently increasing the difference in prevalence.

Thus, the understanding of ethnic differences, and how they may help in elucidating mechanisms and causes of CAS, will need well-designed prospective comparative studies, including patients assessed with identical methods.

Triggering Stimuli of CAS

The stimuli that trigger CAS are also still incompletely understood, and may not be readily identifiable in individual patients. However, several vasoconstrictor stimuli can likely trigger the spasm in the same patient when acting at the site of the hyperreactive coronary segment. Accordingly, vasodilator agents that act through antagonism of specific membrane receptors typically do not prevent CAS. They, in fact, contrast only one of the several potential trigger stimuli, leaving the other pathways of vasoconstriction unopposed and, therefore, able to induce CAS. It is possible, however, that in some patients the alteration more often concerns one or a few vasoconstrictive pathways and, therefore, that specific antagonists may result in a significant improvement of symptoms.

Other Triggering Stimuli of CAS

Some studies suggested that an abnormal platelet activation, perhaps favored by endothelial damage/dysfunction, may be a possible trigger of CAS. Activated platelets, indeed, release large amounts of vasoconstrictor substances, including thromboxane A_2 (TxA_2) and serotonin. In patients with variant angina, in fact, serotonin can induce spasm (**Heupler 1978**), and the serum levels of thromboxane can be found increased (**Tada 1981**). Coronary sinus concentrations of TxA_2, however, were found to increase late during ischemic attacks, suggesting that, in most cases, platelet activation may follow, rather than precede, the spasm (**Robertson 1981**). Furthermore, the administration of PGI_2 (**Chierchia 1982a**) and

aspirin (that blocks TxA_2 synthesis) (**Chierchia 1982b**) and of antiserotonergic drugs (**De Caterina 1984**) was ineffective in reducing anginal symptoms in patients with variant angina. However, platelet activation caused by blood stagnation at the site of spasm might perpetuate spasm and facilitate thrombus formation, as suggested by the increased levels of fibrinopeptide A found following ischemic episodes (Irie 1989).

An increased release of the powerful vasoconstrictor endothelin-1 (ET-1) by endothelial cells has also been suggested to be another possible trigger of CAS. Serum ET-1 concentrations, indeed, have been found increased in patients with variant angina (**Toyo-oka 1991**). However, ET-1 is known to be a potent constrictor of distal rather than of proximal coronary arteries (**Larkin 1989**).

Kounis syndrome is defined as the coincidental occurrence of an ACS with hypersensitivity reactions following an allergic event. The three reported variants of Kounis syndrome are:

1. Vasospastic allergic angina
2. Allergic myocardial infarction and
3. Stent thrombosis with occluding thrombus.

The syndrome is caused by various inflammatory mediators. The pathophysiological characteristics of Kounis syndrome involve CAS and/or atheromatous plaque erosion or rupture during an allergic reaction. Several causes have been described to induce Kounis syndrome, and their number is increasing rapidly. The haemodynamic effect of the syndrome complicated by cardiogenic shock seems to combine allergic shock with extensive peripheral vasodilation and myocardial suppression with the characteristics of cardiogenic shock. Treatment of Kounis syndrome is challenging because it needs management of both cardiac and allergic manifestation simultaneously.(**Mitsis 2017**)

Histamine has also been suggested to contribute to CAS (**McFadden 1991**). As discussed above, mast cell infiltrates were found in spastic coronary arteries in some studies (**Gutterman 1999; Laine 1999**). Furthermore, allergic reactions can trigger angina attacks (**Ga´zquez 2010**), and increased concentrations of histamine in the coronary circulation have been found in some patients (**Sakata 1996**). The role of histamine as a trigger of spasm in the general population of variant angina, however, remains poorly defined.

Finally, hyperventilation is a well-known stimulus for CAS (**Magarian 1991**). Hyperventilation acts by increasing arterial pH, which leads to an increased intracellular calcium influx, and can be a possible unrecognized trigger of spasm in at least some patients with variant angina.

Epidemiology

The reported prevalence of vasospastic angina varies considerably between clinical studies, depending in large part on the geographic location of the population studied, as well as on the criteria used to test and define the condition (**Adlam 2005**). In the United States, the frequency is among the lowest in the world, with about 4% of patients who undergo coronary angiography showing evidence of focal spasm (defined as a 75% reduction in artery diameter on the administration of ergonovine) (**Harding 1992**).

The frequencies of multiple spasms (≥2 spastic coronary arteries) by provocative testing in Japanese (24.3%) (**Sueda 2004**) and Taiwanese populations (19.3%) (**Hung 2010**) are markedly higher than those in western populations (7.5%) (**Bertrand 1982**). Japanese patients with a recent MI report a higher incidence of inducible CAS than Caucasian studies, an observation recently supported by a controlled study (**Beltrame 1999**).

In France, about 12% of patients had positive ergonovine-based studies (**Bertrand 1982**), whereas in Japan, where the greatest number of publications on CAS originate, positive study rates are in the range of 30% (**Sueda 2004**).

The incidence of CAS may be increasing in Japan, at least on the basis of provocation of spasm by the administration of acetylcholine (**Sueda 2010**).

Age: The age at which symptoms first appear is highly variable, but on average, patients are in their 50s at symptom onset (**Bory 1996**).

Sex: Variant angina is believed to be more common in female patients (**Mayer 1998; Selzer 1976**), although some prognostic studies of patients with variant angina suggest a male preponderance. A 2012 study of Korean patients showed that men were more likely to develop CAS in response to an intracoronary acetylcholine challenge (**Rha 2012**). Among women, variant angina may be relatively more common in white patients (22%) than in Japanese patients (11%).

Race: Japanese patients are much more likely to develop CAS than Caucasian. When evaluated by the same team, Japanese had a 3-fold higher incidence of CAS than their Caucasian counterparts even though the 2 groups of patients had similar average basal coronary tone (**Pristipino 2000**). Aldehyde dehydrogenase 2 (ALDH2*2) and tobacco smoking (TS) are significant risk factors for CAS. ALDH2*2 exacerbated TS risk for CAS more than the multiplicative effects of each (**Mizuno 2016**).

History and Physical Examination

Patients with CAS typically describe anginal symptoms, including retrosternal pain or pressure with radiation to the neck, jaw, left shoulder, or arm. This may be particularly true if there is significant coexistent atherosclerosis (**Figueras 2006**). Notably, symptoms associated with vasospastic angina often occur at rest and may exhibit a circadian pattern, with most episodes occurring in the early hours of the morning (**Yasue 2008**). In severe cases, associated arrhythmias may be present, ranging from heart block to ventricular tachycardia (**Previtali 1983**). Distinguishing unstable angina pectoris related to coronary atherosclerosis from variant angina may be difficult and require special investigations for diagnosis, including coronary angiography. In some patients, the distinction may be an arbitrary one because it is likely that vasospasm is both a cause and a consequence of plaque rupture and thrombosis in patients with unstable angina pectoris. CAS is abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia. CAS induces not only depressed myocardial contractility, but also incomplete myocardial relaxation, which leads to elevated ventricular filling pressure. Eventually is observed acute heart failure(AHF) caused by CAS. Acetylcholine provocation test with simultaneous right heart catheterization Is useful for the diagnosis of elevated ventricular filling pressure as well as CAS. We should add CAS to a differential diagnosis for repeated AHF.(**Adachi 2017**) In addition, many patients with variant angina have obstructive CAD. Indeed, in as many as 60% of cases, CAS occurs at a site with preexisting coronary atherosclerosis (**Bertrand 1982**), which suggests that underlying arterial dysfunction may be a predisposing factor for spasm. Although spasm is more likely to occur in the presence of atherosclerotic lesions, the absence of traditional risk factors for atherosclerotic CAD may make vasospastic angina more likely; the exception is cigarette smoking, which is a common risk factor for both clinical syndromes (**Harding 1992**). CAS is found more often in patients with symptoms that occur at rest (55.5%) than in those with exertional angina (27.7%) (**Sueda 2004**). A minority of patients with variant angina may have a more systemic abnormality of vasomotor tone; this may include symptoms of migraine headache and Raynaud phenomenon (**Rosamond 2004**).

No features on physical examination are specific for vasospastic angina. Signs may be absent between symptomatic episodes. During periods of angina, physical findings relating to ischemia and ventricular dysfunction may be present, including rales, jugular venous distention, peripheral edema, extra heart sounds, ectopy or other arrhythmia (eg, tachycardia or bradycardia), and murmurs (such as occur with ischemic mitral regurgitation).

Electrocardiographic changes

ECG may appear normal at the beginning of CAS or when the CAS is mild **(Yasue 2008a.).** Total or CAS of a major coronary artery results in STE in the leads corresponding to the distribution of that coronary artery. However, CAS may cause ST-segment depression, indicating less severe, subendocardial myocardial ischemia than does STE.

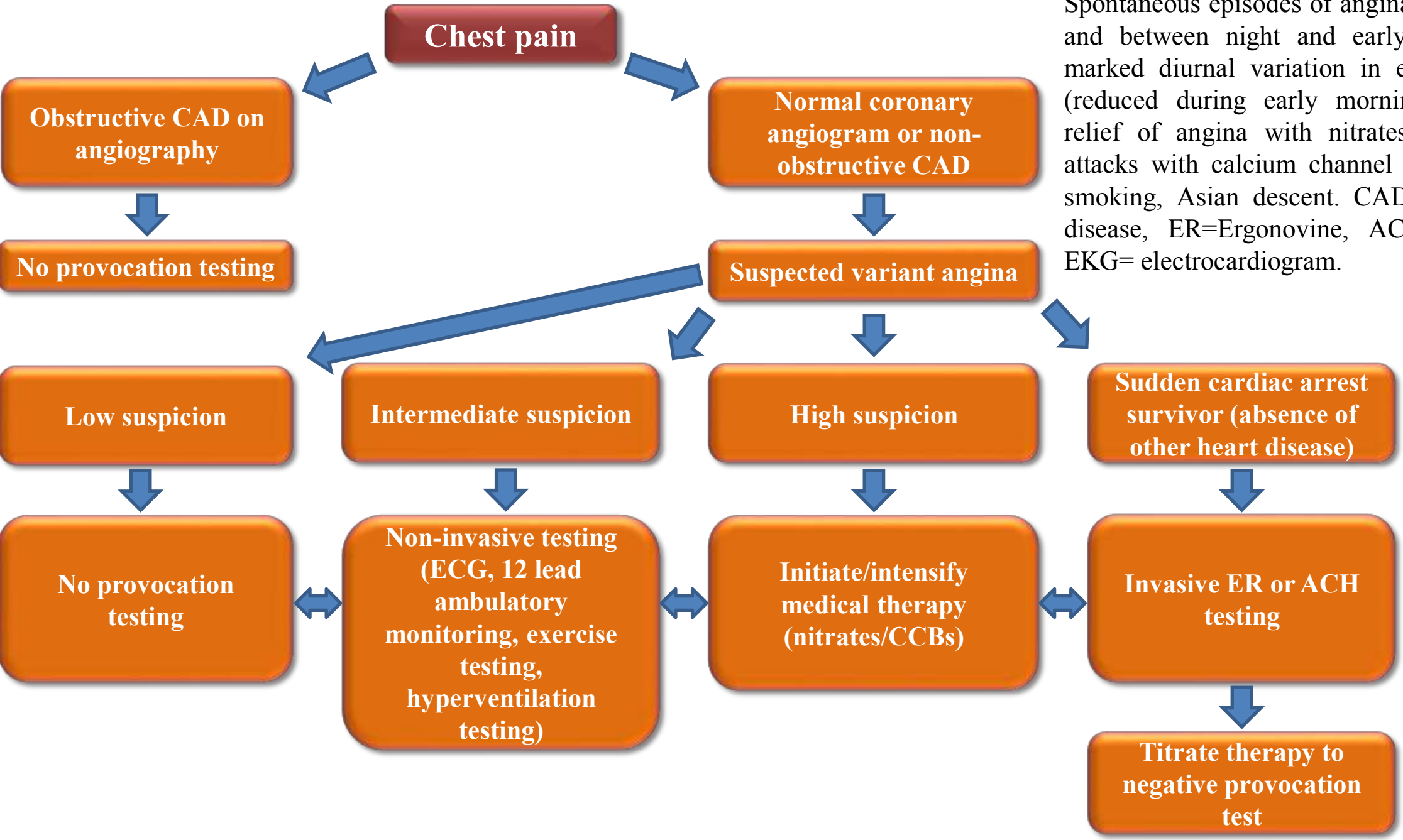
CAS is more frequently associated with ST-segment depression rather than STE **(Cheng 2008; Nakagawa 2009).** ST-segment depression occurs when CAS of a major artery is less severe, when a major artery receiving collaterals is completely occluded, or when a small artery is completely occluded **(Yasue 1981).** This situation occurs in many cases of unstable angina/non-STE myocardial infarction. Approximately 45% of patients with angina at rest and ST-segment depression alone had CAS **(Bertrand 1982).** In addition to ST-segment changes, a delay in the peak and an increase in the height and width of R wave, a decrease in magnitude of S wave, peak T wave and negative U wave may also appear **(Yasue 2008).** While the location of CAS is fixed over time in some patients, CAS may fluctuate from one vessel to another in others **(Ozaki 1995).**

Alternating STE and depression could occur in the same patient or even in the same lead within minutes or hours**(Maseri 1978).**

There is variability of ECG changes during repeated provocative testing and recurrent spontaneous attacks **(Waters 1981; Whittle 1982).** Thus, the direction and extent of STE or depression may change over time. Occasionally, pseudonormalization of a previously depressed ST-segment may appear **(Yasue 2008a)** CAS is associated with arrhythmias, including sinus bradycardia, sinus arrest with or without junctional escape beats, complete atrioventricular block, paroxysmal AF , PVC, VT, VF and asystole (**Hung 2007; Yasue 2008a; Whittle1982**). CAS-associated life-threatening arrhythmias often occur in patients with ACS (**Hung 2007**). Furthermore, CAS-related sudden death most frequently results from bradyarrhythmias, rather than from tachyarrhythmias (**Maseri 1982**).

While VF can often be terminated by cardioversion (**Bertrand 1982**), VF rarely terminates spontaneously (**Olgin 2005.**) as CAS-related spontaneous reversion of VF has been reported to do (**Hung 2007**). Spontaneous termination of VF has been documented in a 62-year-old woman following an acute lateral myocardial infarction (**Choquette 1956**), a 67-year-old woman with a syncopal episode after awakening from sleep (**Patt**.), and a 21-year-old woman during exertion at night (**Dubner 1983**), although CAS was not documented in those reports. In a study of VF episodes in patients with implantable cardioverter defibrillators (**Farmer 2003**), 43% were asymptomatic and 40% were nonsustained episodes. If VF is <10 seconds in duration then the incidence of syncope or pre-syncope is 25%, compared with 62% if the arrhythmia is ≥10 seconds. Therefore, CAS should be considered in the differential diagnosis of syncope.

Variant angina algorithm



Suspicion is based on clinical factors: Spontaneous episodes of angina occurring at rest and between night and early morning hours, marked diurnal variation in exercise tolerance (reduced during early morning hours), quick relief of angina with nitrates, suppression of attacks with calcium channel blockers (CCBs), smoking, Asian descent. CAD=coronary artery disease, ER=Ergonovine, ACH=Acetylcholine, EKG= electrocardiogram.

Prognosis

The natural history of patients undergoing medical therapy for CAS may involve significant morbidity, but mortality is low in most cases, even on long-term follow-up (**Bory 1996**). Patients often have 3- to 6-month clusters of recurrent attacks, separated by relatively asymptomatic periods, with a gradual reduction of symptoms in the long term (**Yasue 2008**). In a study of 59 patients followed for an average of 5.9 years, 93% experienced rest angina and 19% sustained frank Mis (**Bott-Silverman 1983**). However, there were no cardiac deaths.

Long-term survival is believed to be good, especially in patients who tolerate calcium antagonists and avoid smoking (**Bory 1996**). Predictors of poorer prognosis include the presence of concurrent coronary atherosclerosis (**Mishra 2006**), ongoing smoking, intolerance of calcium antagonists, and spasm of multiple coronary arteries (**Yasue 1988**).

In patients with no or even single-vessel atherosclerosis, the prognosis is benign, with survival rates as high as 99% at 1 year and 94% at 5 years. On the other hand, survival in patients with multivessel atherosclerotic disease fell to 87% at 1 year and 77% at 5 years. Survival rates were also lower in patients with multivessel spasm (**Onaka 1999**).

A 3-year follow-up to the CAS as a Frequent Cause for Acute Coronary Syndrome (CASPAR) study concluded that patients with ACS who do not have a culprit lesion have a better prognosis than patients with obstructive ACS (**Ong 2011**). Persistent angina is challenging, and repeated coronary angioplasty may be required.

The Japanese Coronary Spasm Association (JCSA) derived the "JCSA risk score" to guide prognostication for patients with coronary vasospasm. Elements of the score include the following: History of out-of-hospital cardiac arrest (4 points); Smoking, angina at rest alone, organic coronary stenosis, multivessel spasm (2 points each); Beta blocker use, ST elevation during angina (1 point each)

Stratification of patients by score led to differentiation in their risk of major adverse cardiac events (MACE). Patients with a low score of 0-2 had a MACE of 2.5%. Those with an intermediate score of 3-5 had a MACE of 7%, and those whose scores were 6 or higher had a MACE of 13% (**Takagi 2013**).

Complications

Myocardial infarction (MI) is a potential complication of variant angina, especially in the myocardial territory corresponding to the location of the electrocardiographic (ECG) changes during previous anginal attacks. The incidence of MI depends on diagnostic criteria, but has been reported to be as high as 30% in some series.

The incidence and prognosis of MI in patients with variant angina appear to be associated with the extent and severity of any underlying atherosclerotic coronary stenosis. Adverse outcomes are more likely and survival poorer in patients with multivessel atherosclerotic CAD (**Mishra 2006**).

Practice guidelines for coronary spasm provocation testing

Guidelines	Classification	Level of evidence	Recommendations
2006 European Society of Cardiology; stable angina (**Fox 2006**)	Class IIa	B	• IC Provocation testing known anatomy, non-obstructive CAD
2008 Japanese Circulation Society; vasospastic angina (**JCS Joint Working Group 2010**)	Class I	-	• IC Provocation testing during angiography in patients with suspected variant angina without a diagnosis by non-invasive measures (ECG, Holter, exercise, hyperventilation) • recommended protocol
2011 ACCF/SHS; unstable angina/non ST-elevation MI (**Anderson 2011**)	Class IIb	C	• Provocation testing indicated: known coronary anatomy • failed empiric treatment • life-threatening disease and verification of spasm is necessary
2011 ACCF/AHA/SCAI; percutaneous coronary intervention (**Levine 2011**)	-	-	None
2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS; stable ischemic heart disease (**Fihn 2012**)	-	-	None
2012 ACCF/AHA; unstable angina/non-ST elevation MI (**Jneid 2012**)	-	-	None

After >60 years since the description of variant angina, our knowledge of the mechanisms and triggers of CAS in the clinical setting is still limited. Experimental and clinical studies point out that CAS requires the presence of hyperreactivity of coronary VSMCs to constrictor stimuli. VSMC hyper-reactivity is nonspecific, and seems therefore related to 1or more of the intracellular pathways that regulate vascular tone. The causes of VSMC hyperreactivity also remain poorly understood, but they are likely to be different among patients. Although it has been suggested that endothelial dysfunction is involved in CAS, it seems unlikely to be a direct cause, although it can facilitate the effects of vasoconstrictor stimuli in the spastic segment. Several potential triggers of CAS have been identified that may act in the same patient to cause angina attacks in different conditions. Accordingly, they usually represent an elusive therapeutic target. Knowledge of the postreceptorial mechanisms responsible for VSMC hyperreactivity and CAS, on the other hand, might constitute the basis to develop valuable therapeutic options in patients who present poor clinical response to nonspecific vasodilator therapy.

Management

Any factor that may precipitate CAS, especially smoking, must be avoided.

A. Pharmacological approach:

1. **Calcium antagonists:** these drugs are the main pharmacological armamentarium. Of them, long-acting calcium antagonists are suggested to be given at night when attacks of CAS are frequent. A high-dose long-acting calcium antagonist (e.g. nifedipine 80 mg/day, amlodipine 20 mg/day, diltiazem 360 mg/day, or verapamil 480 mg/day) has been suggested as the initial treatment and should be individually titrated to a dose that achieves adequate symptomatic response and avoid adverse effects, such as reductions in blood pressure and heart rate. The combination of 2 calcium antagonists (dihydropyridine and non-dihydropyridine) may be required for more severe symptoms. Furthermore, ischemic ST-segment depression can be reversed by treatment with calcium antagonists.
2. **Long-acting nitrates** prevent the CAS recurrent events; however, nitrate tolerance may limit their use as a first-line approach. Nicorandil, a nitrate
3. **K-channel activator**, also suppresses CAS attacks
4. **Magnesium**
5. **Antioxidants**
6. **Rho-kinase inhibitors** fasudil, and fluvastatin may have beneficial effects on CAS. β-blockers should be avoided.

Drug-refractory CAS, defined as CAS not responding to treatment with 2 calcium antagonists plus a long-acting nitrate, is noted in ≈20% of patients with CAS. For those drug-refractory patients, coronary stenting may represent an alternative treatment.

B. Coronary stenting is effective in controlling symptoms at 6-month follow-up in 6 of 9 patients with drug-refractory CAS (up to 960 mg diltiazem or 100 mg nifedipine and nitrates). Although coronary stenting is thought to be effective in suppressing CAS, the use of calcium antagonists after stenting in previous reports indicates that CAS may develop at locations different from the previous stenting site. Collectively, these observations suggest that coronary stenting in combination with adequate medical treatment should be considered only in CAS patients who have significant coronary stenosis, with myocardial ischemia. It is unclear whether coronary stenting is useful to prevent anginal events in drug-refractory CAS patients without coronary stenosis.

C. Implantable cardio defibrillators (ICDs) play in the management of patients with CAS-associated VT/VF remains unclear. The use of an ICD + aggressive medical treatment has been reported to be effective in CAS patients who are survivors of cardiac arrest, or VF.

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