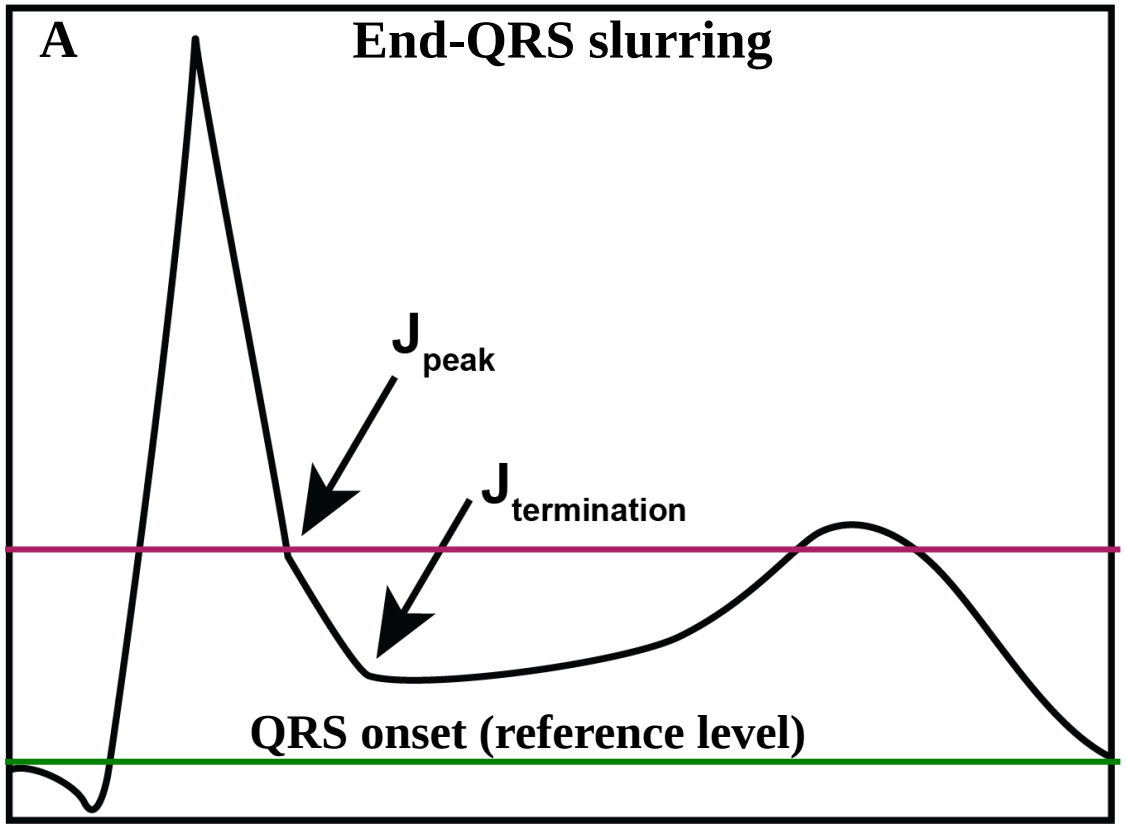
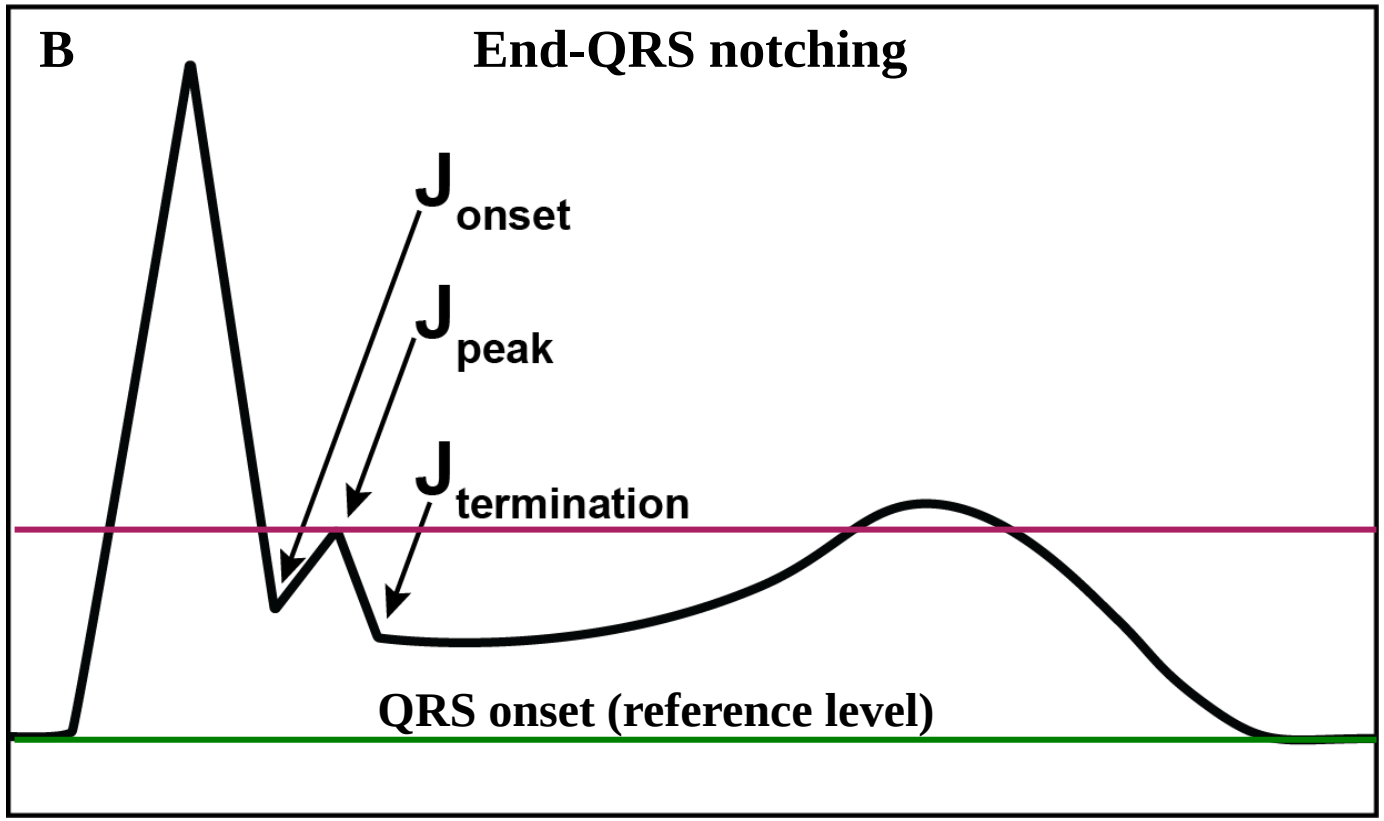
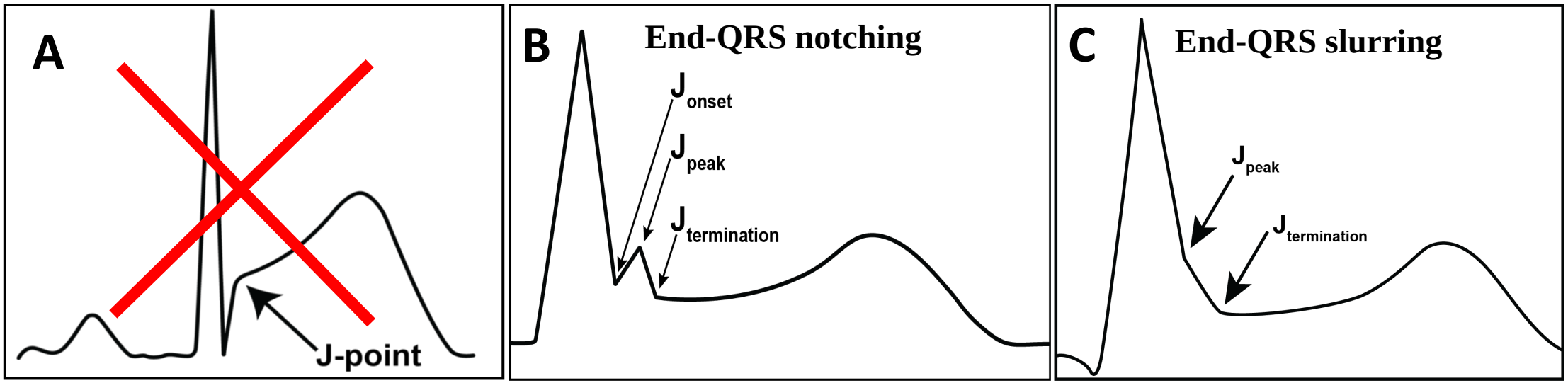
There are two shape J-wave patterns: **End QRS slurring and End QRS notching**





The numerous nomenclatures for J wave (Gussak I, et al. 1995)

Camel "hump sign (**Abbott JA, 1976.; Chou TC, 1991.),** Osborn wave, late delta (δ) wave, hathook junction, hypothermic wave or hypothermic hump (**Rothfeld EI: 1970**.), J point wave (**Fenichel NN, 1962**), K wave (**Mirvis DM,1993**), H Wave (**Hugo N, et al, 1988**.), and current of injury (**Osborn JJ.. 1953. Trevino A, et al, 1971**.).



The simple elevation of the J point and ST segment in the absence of a J wave (**A**) should not be considered an ERP

J-wave syndromes (JWS) encompass congenital (ie, BrS and ERS) and acquired (ie, Osborn wave and STEMI) disorders that represent a continuous spectrum of ventricular arrhythmogenic potential.(**Antzelevitch C, Yan G-X. J wave syndromes. Heart Rhythm 2010;7:549–58**)

J-wave etiologies

A) Hypothermic mediated (**Tomaszewski W. 1938.; Kossmann CE, 1940, Grosse-Brockhoff F, et al 1943. Bigelow WG, et al 1950.; Juvenelle A,1952. Osborn JJ.. 1953.**, **Emslie-Smith D, et al. 1959**., **West TC, et al. 1959**.)

B) Normothermic conditions: (Patel A, et al 1994).

a) Normal variant (Shipley R et al, 1936., **Myers, C . Et al, 1947, Goldman, M J, 1953** . **Antonio Pelliccia et al 2015)** Predominant in young, healthy individuals and young competitive athletes ranging from 14% to 44%)

- **Juvenile ST pattern (Walsh B 2019).**
- **Elite athletes (Noseworthy PA, 2011)(Pelliccia A, 2015)**

b) Congenital or Inherited primary arrhythmia syndromes

- **ERS or inferolateral J-wave syndromes (Kalla H, et al 2000, Haissaguerre M, 2008., Rosso R 2008, Tikkanen JT et al 2009, Sinner MF 2010; Haruta D,et al 2011, Tikkanen JT et al 2011**). Exclusion criteria included BrS(non-type 1 anterior early repolarization (NT1-AER)), positive provocative testing with class I antiarrhythmic drugs, metabolic disturbances, or structural heart disease.
- **BrS (Brugada P,1992**)
- J-wave syndromes**.** This term incorporates 2 arrhythmogenic conditions, BrS and ERS, characterized by terminal QRS and ST segment abnormalities and by increased risk of cardiac events. **(Antzelevitch C et al. 2010.; Nam GB, 2010., Sung Hwan Kim, et al 2012, Georgopoulos S,et al 2018; Kamakura T, et al. 2020; Voskoboinik A et al.2020**; **Landaw J,et al 2020)**

c) Acquired forms

- Pathological variants

❑ Hipothermia: Hypothermic J- wave or Osborn wave ECG features Aizawa Y, et al.2018.

❑ Ischemic-mediated “J waves” or induced by ischemia in the setting of structural heart disease

➢ Acute myocardial infarction with STEMI, (Rudic, B., et al. 2012).

➢ Vasospastic angina, Variant angina. Pinzmetal angina, (Maruyama M, et al. 2002.)

➢ Stable coronary artery disease . (Patel RB, et al.)

➢ Stanford Type A Acute aortic dissection (Kosuge M. et al 2013)

➢ Takotsubo cardiomyopathy

❑ Hyperthermia (Lacunza J, et al 2009)

❑ Acute myopericarditis: Acute diffuse inflammation of the pericardial sac and superficial epicardium (Chan TC, et al. 1999)

❑ Myocarditis ex Chagasic myocarditis(Antzelevitch, C et al.2017)

❑ Arrhythmogenic Cardiomyopathy AC

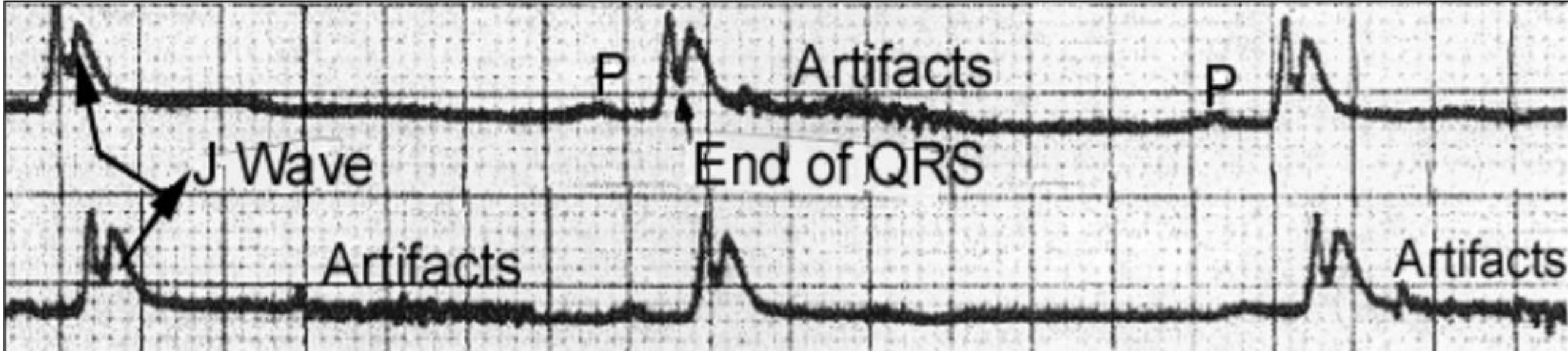
❑ Myocardial tumors(Akgun T, et al. 2020) (Rochelson E, et al. 2019.)

- **Neurogenic: head injuries:**
  - **Brain injury(Hersch C.et al. 1961.)**
  - **Subarachnoid hemorrhage/intracerebral bleeding (De Sweit J. et al.1972.)**
  - **Cardiopulmonary arrest from over sedation (Jain U, et al 1990.).**
  - **Postictal event**
- **Severe hypercalcaemia (Kraus F. Et al.1920, Sridharan MR, et al. 1984.; Yan GX, 1, et Al. l996., Asbeutah AAA 2019)**
- **Illicit drug overdose (Asbeutah AAA 2019) Cannabis and Bonsai abuse (Murat Yalçın et al. 2015)**
- **Patients with implantable cardioverter-defibrillators (Patel RB, et al, 2010).**
- **Hypercapnia (Murat Yalçın et al. 2015)**
- **Cocaine abuse (Al-Sadawi M, 2019)**

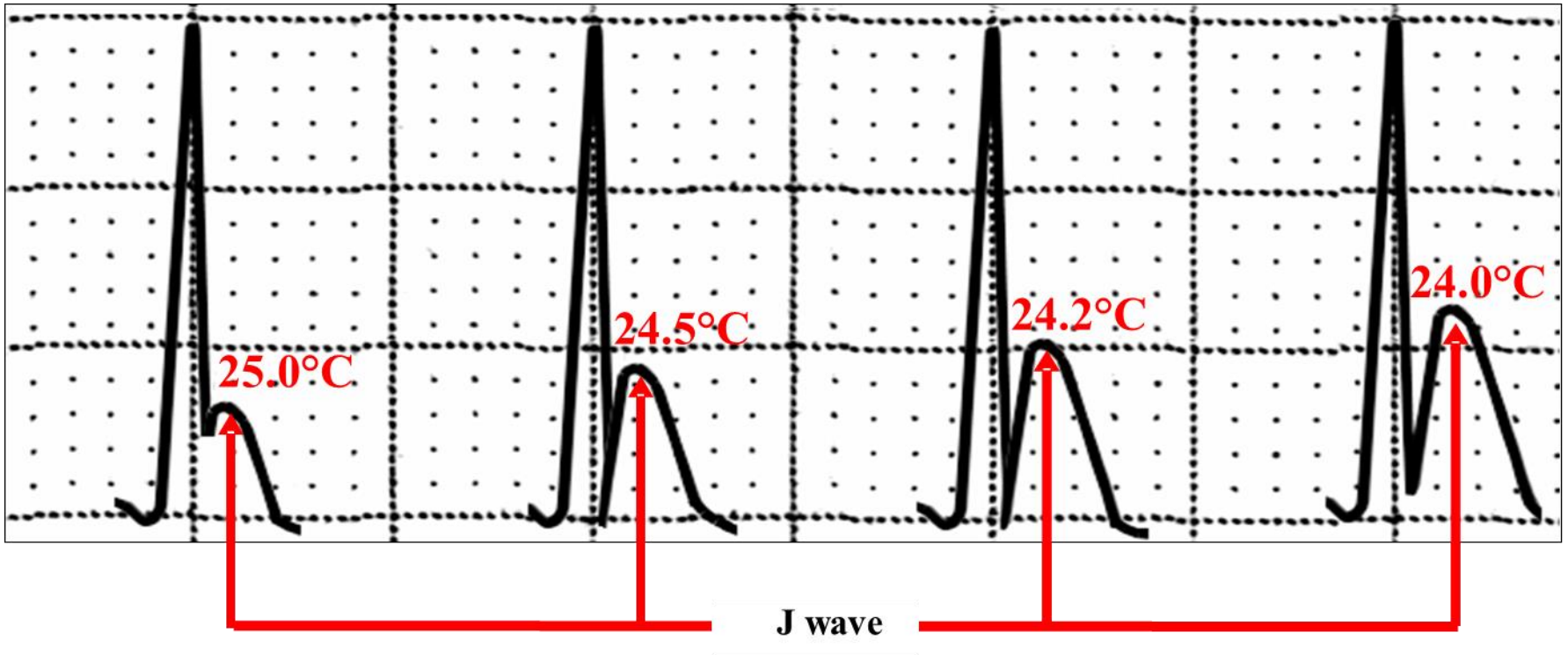
A. Hypothermic mediated (hypothermic J- wave or Osborn wave ECG features)

Hypothermia is defined as the condition where central temperature (rectal, esophageal or tympanic) is below 35ºC. Hypothermia may be accidental, metabolic, or therapeutic. Accidental hypothermia is more frequent in countries with cold weather, during winter season. The hypothermal state is characterized by drop in basal metabolism, decrease in O2 consumption and greater production of CO2. During hypothermia, a gradual decrease of heart rate is observed and systolic volume, with progressive drop of blood pressure later, which becomes significant when central temperature values close to 23ºC are reached. The main ECG characteristics in hypothermia are:

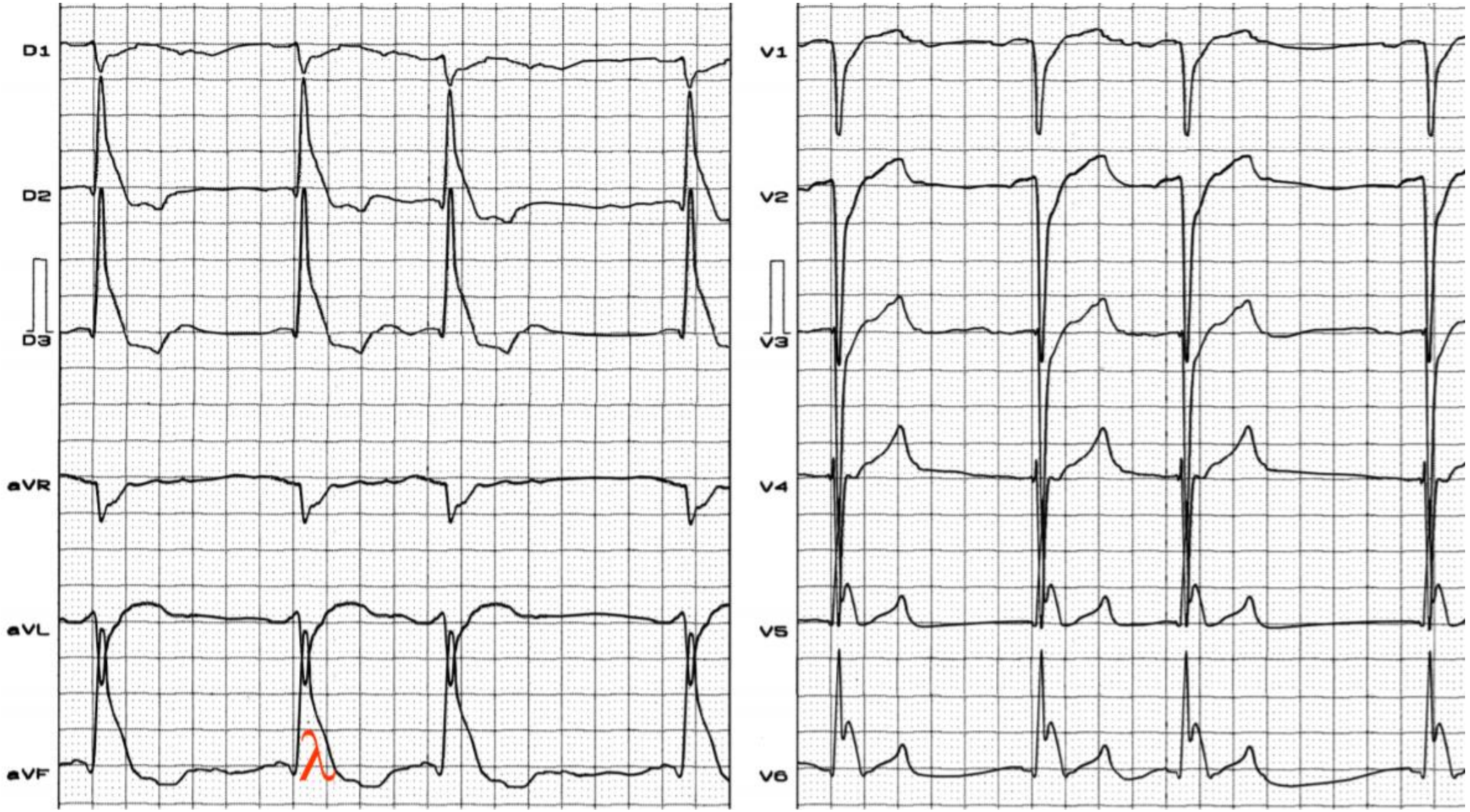
- Sinus bradycardia, but in the initial phase tachycardia by release of adrenaline.
- Atrial fibrillation (50% of cases), temperature < 32ºC.
- Artifacts: fluctuation in the baseline caused by the muscular trembling. Only in the initial phase (of struggle), when body temperature is between 36 and 32ºC.
- PR interval prolongation.
- QRS complex: decrease in voltage and increase in duration.
- QT and QTc intervals prolongation.
- Both supraventricular and ventricular arrhythmias.
- Very characteristic extra wave, called J wave between the end of QRS complex and ST segment onset, not pathognomonic (may be observed in normothermic conditions, positive and prominent in V5 and V6 .
- Inverse correlation between J wave voltage (mm) and central temperature.



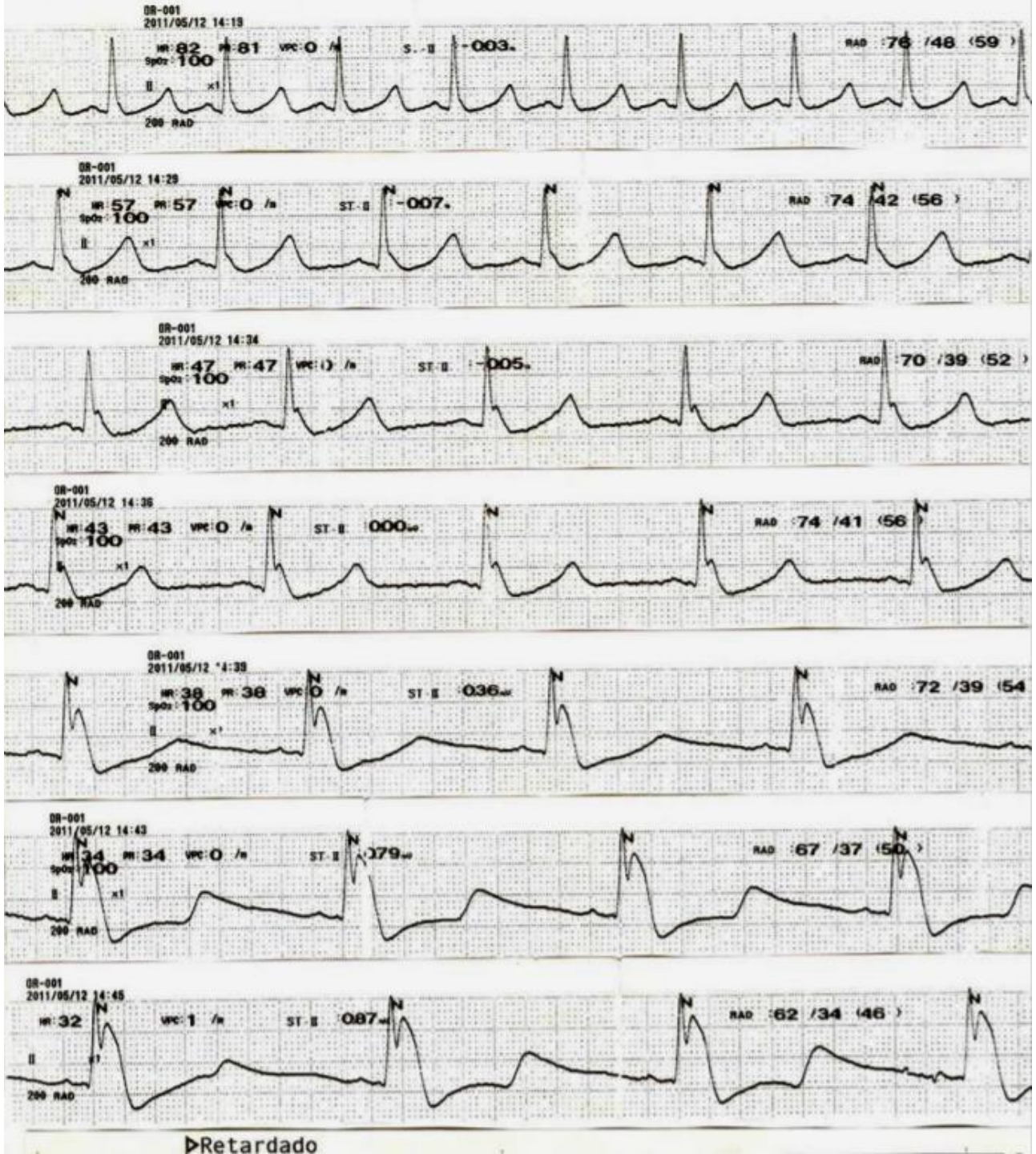
Inverse and significant correlation between J wave voltage (mm) and central temperature in hypothermia



Name: PASA; Gender: Male; Age: 47 y/o; Ethnic group: Afro-descendant; Weight: 61 Kg; Height: 1.68 m; Date: 03/07/2008; Central body temperature: 29ºC.



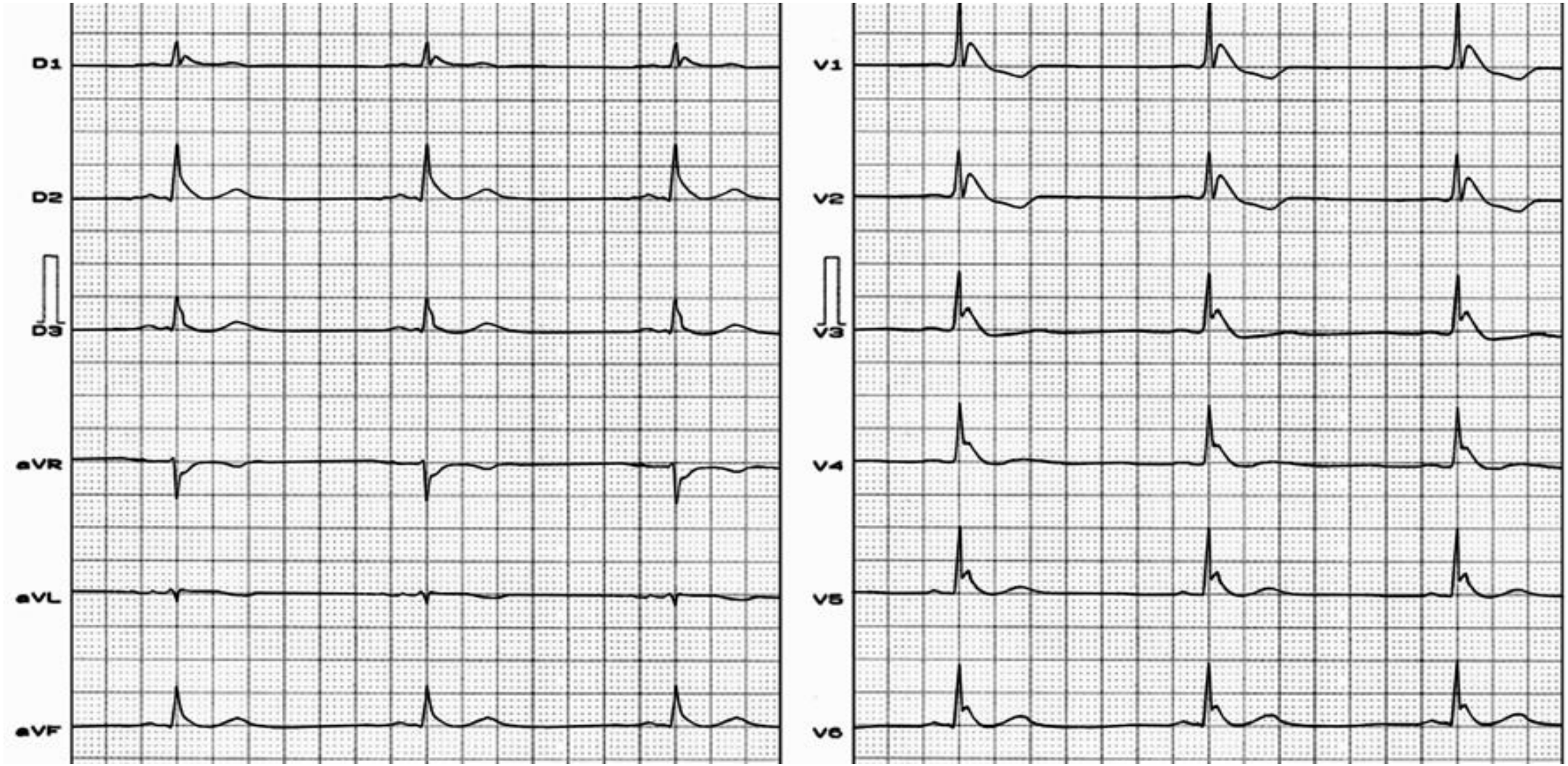
Severe hypothermia. Atrial fibrillation with slow ventricular response. Left posterior fascicular block pattern. Gussak wave or lambda wave



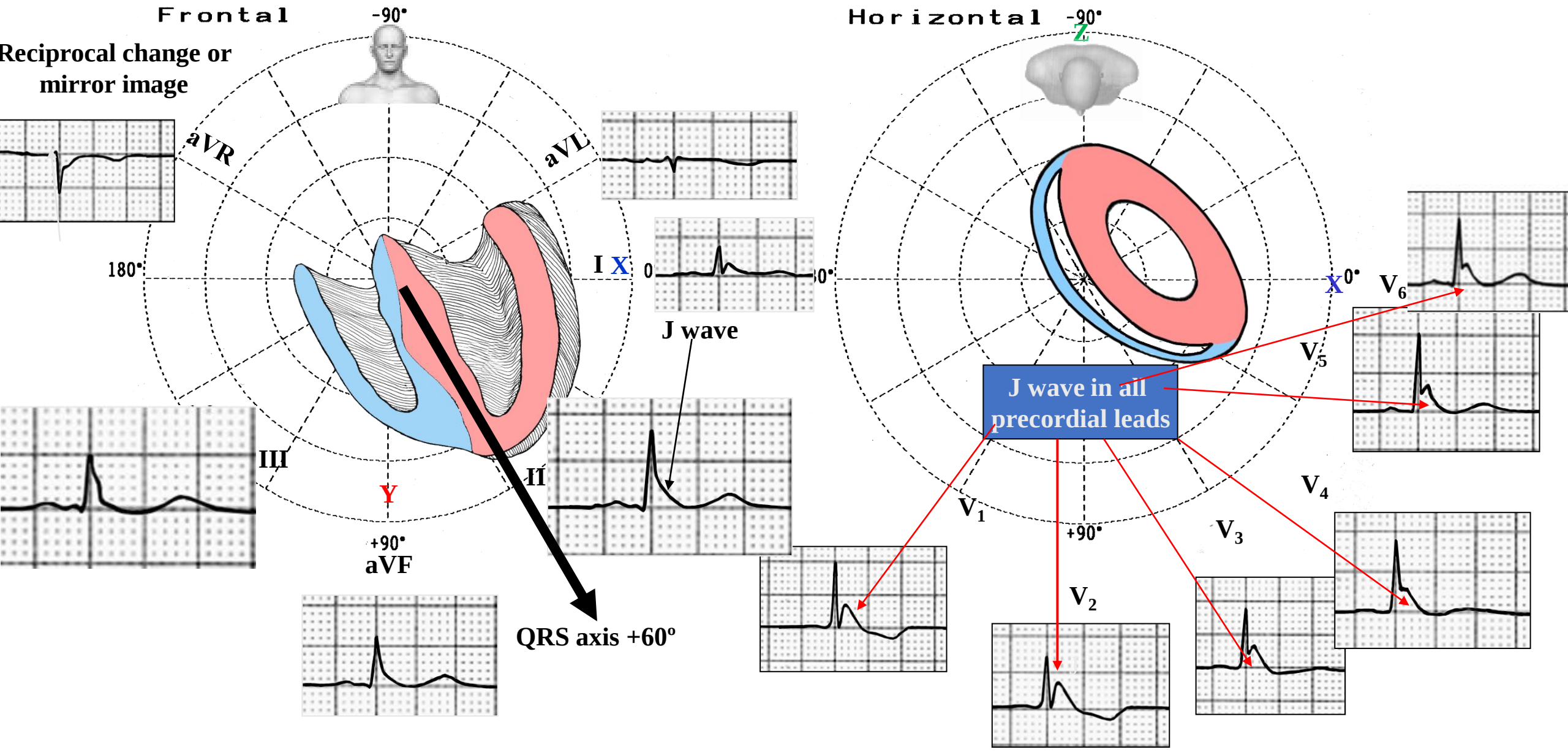
The tracing was obtained during cooling of the blood before a surgical procedure of the heart. Although the ECG obtained was somewhat expected, what was striking is that the progressive development and augmentation of the J wave was recorded. Most of the hypothermia cases are published in the moment when the patient is rescued and after recovery. On the other hand, in this case we can see the time course of changes up to the simulation of a monophasic action potential. Additionally, significant bradycardia is observed and the QT interval was too prolonged, something that usually is not given much attention in the published cases.

Courtesy from Prof. Dr. Raimundo Puerta from Cuba

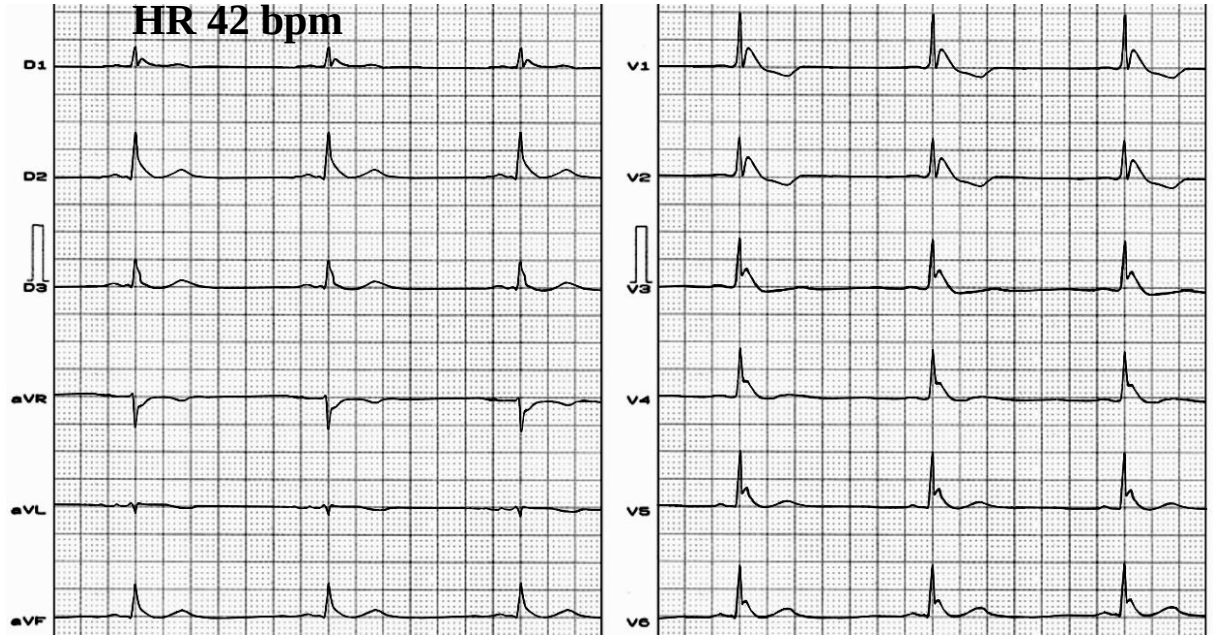
Malignant Early Repolarization global J waves diffuse J waves with early repolarization pattern



Subtype 3 shows an ER pattern registered globally in the inferior, lateral and right precordial leads. This variant is associated with the highest level of risk for the development of VF storms (**Nam 2008**). In subtype 3, the Brugada waves may be seen together with giant J waves in other ECG leads. Although the Brugada waves are not called ER, their underlying mechanism is identical to that of the ER patterns



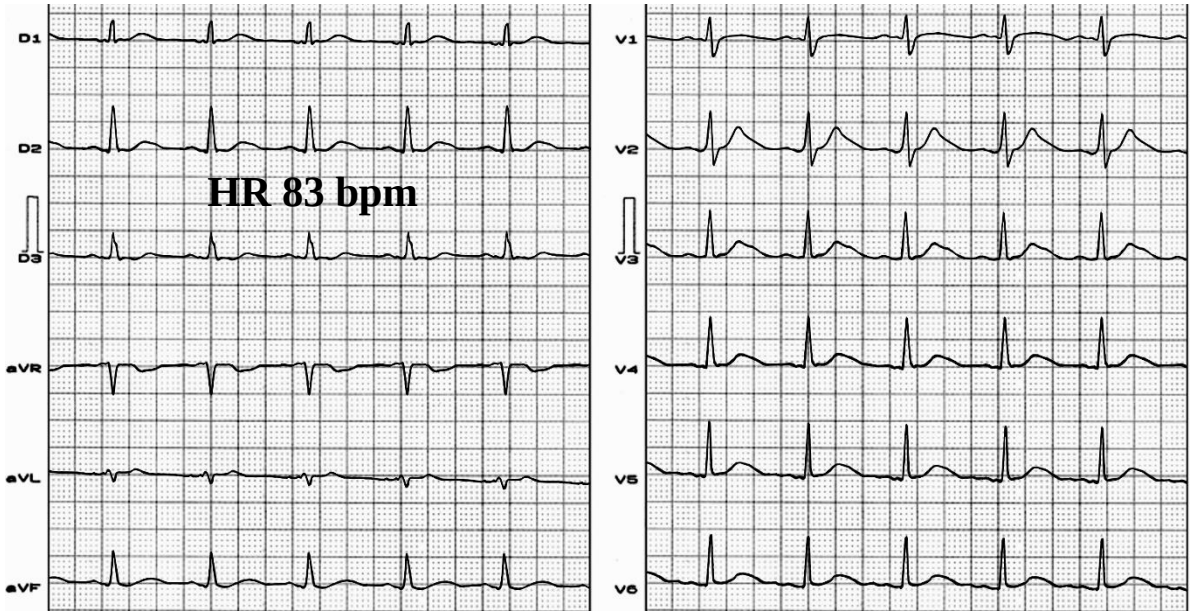
Classical case of Type 3 Early Repolarization Syndrome (ERS) (Yan 1996; Antzelevitch 2005)



A: Basal tracing. We observe J-wave across all precordial and inferior leads.

B: ECG after two days after oral quinidine 1500 mg/day

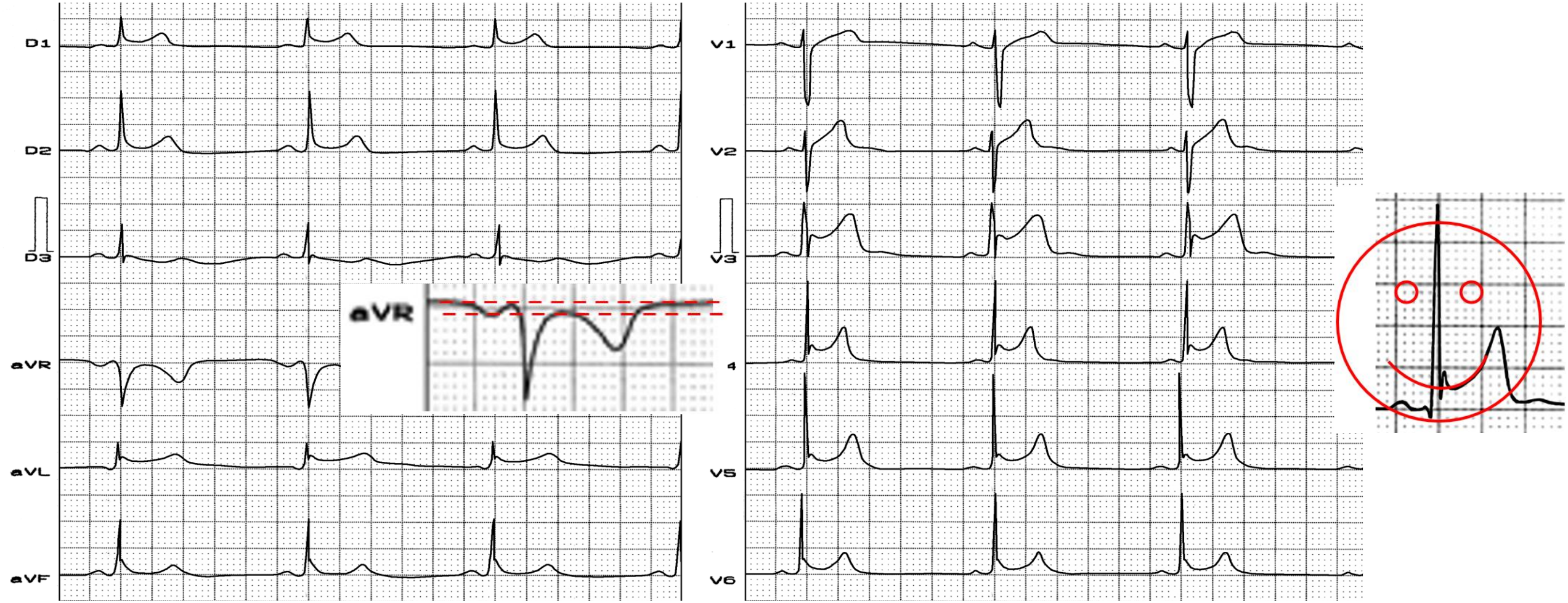
Comments: The drug reduces the magnitude of the Ito channel – mediator of phase 1 and consequently normalize the elevation of the ST segment. Additionally, it could improve repolarization due to its vagolytic effect (M2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone.



In the consensus statement published in 2017 (**Antzelevitch C, Yan G-X, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. Heart Rhythm 2016;13:e295–324**.),(.**Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AAM.J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Europace. 2017 Apr 1;19(4):665-694. doi: 10.1093/europace/euw235.)** the presence of J waves in global leads (ie, right precordial + inferolateral leads) was reported to be a high-risk factor for the development of VF in patients with JWS. However, limited clinical data supporting this risk stratification are currently available because the majority of the studies investigating J waves excluded the right precordial leads from the analysis. Kamakura et al., in a multicenter long-term study showed that the presence of global J waves was associated with a higher incidence of VF recurrence in patients with JWS. **Kamakura T, et al. Heart. 2020 Feb;106(4):299-306. doi: 10.1136/heartjnl-2019-315007. Epub 2019 Aug 7.PMID: 31391205**

Normal variant (Shipley R et al, 1936., Myers, C . Et al, 1947, Goldman, M J, 1953 . Antonio Pelliccia et al 2015) Predominant in young, healthy individuals and young competitive athletes ranging from 14% to 44%) **Elite Athletes (Noseworthy PA, 2011)(Pelliccia A, 2015) Juvenile ST pattern (Walsh B 2019)**

Name: DAS**; Age:** 24y**; Sex:** Male; **Race:** Black; **Weight:** 82 kg; **Height:** 1.91 m**; Biotype:** Athletic; **Profession:** professional basketball player

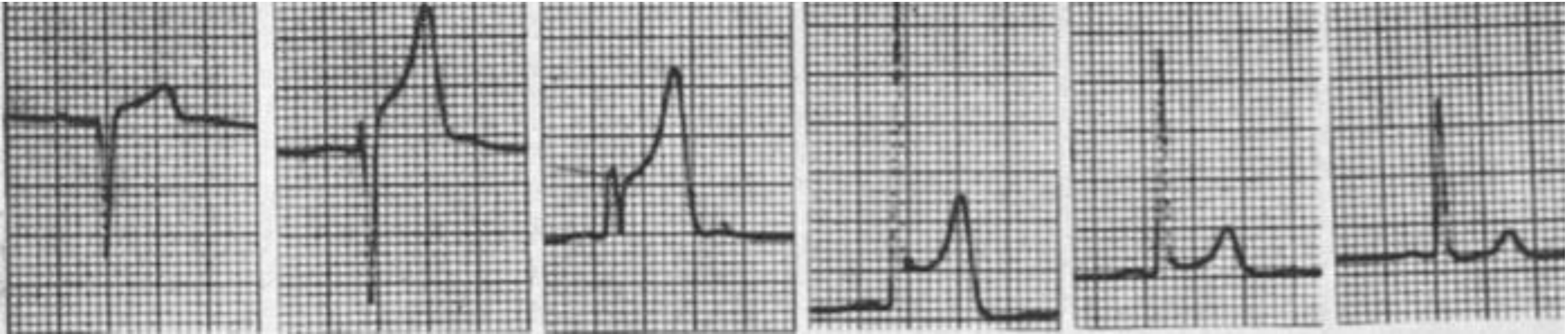


ECG diagnosis: sinus bradycardia, (HR 50 bpm). J point and ST segment with elevation > 4 mm in precordial leads from V_3-v_5 of superior concavity. Notch or slurring of terminal portion of the QRS complex (J point). ST segment elevation > 4 mm in precordial leads V_3, V_4 and V_5. A tall, near symmetric T wave, is generally considered to be benign. (**Wasserburger RH, et al. 1961**).

Conclusion: sinus bradycardia, early repolarization pattern. Typical ECG of early repolarization pattered in an athlete with bradycardia.

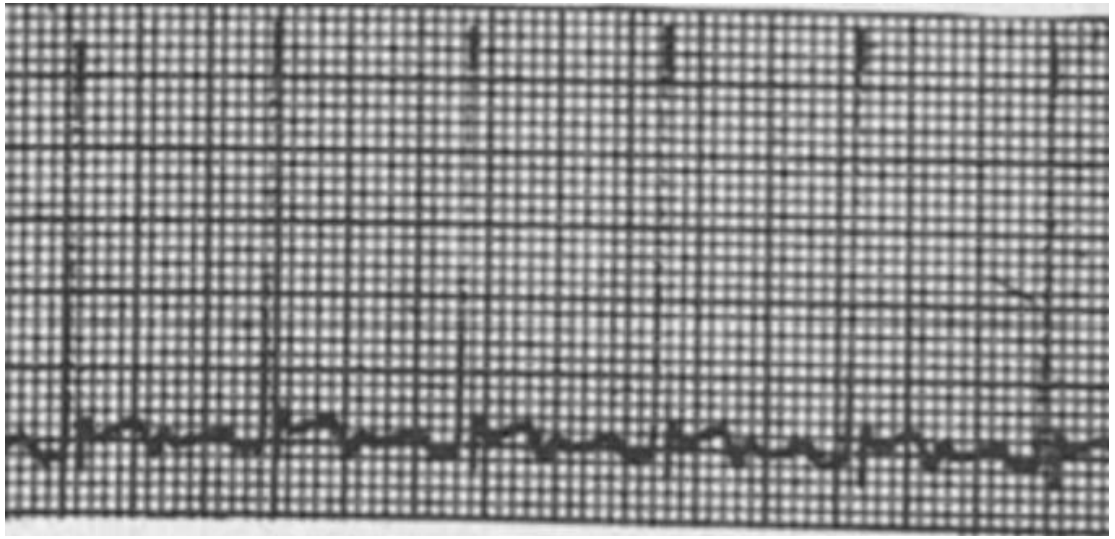
“Benign Early Repolarization” characterization

1. Benign early repolarization (BER) is an ECG pattern most commonly seen in young, healthy patients <50 years of age. BER is less common in the over 50s, in whom ST elevation is more likely to represent myocardial ischemia.
2. BER produces widespread ST elevation that may mimic pericarditis or acute MI.
3. Up to 10-15% of ED patients presenting with chest pain will have BER on their ECG, making it a common diagnostic challenge for clinicians.
4. The physiological basis of BER is poorly understood. However, it is generally thought to be a normal variant that is not indicative of underlying cardiac disease.
5. BER is rare in the over 70s.
6. Avoid diagnosing BER in patients over the age of 50, especially those with risk factors for ischemic heart disease.
7. This pattern is usually seen in the mid- and left precordial leads V3, V4 and V5, or widespread concave ST elevation, most prominent in the mid- to left precordial leads (V2-V5) (**Goldman MJ 1953**)

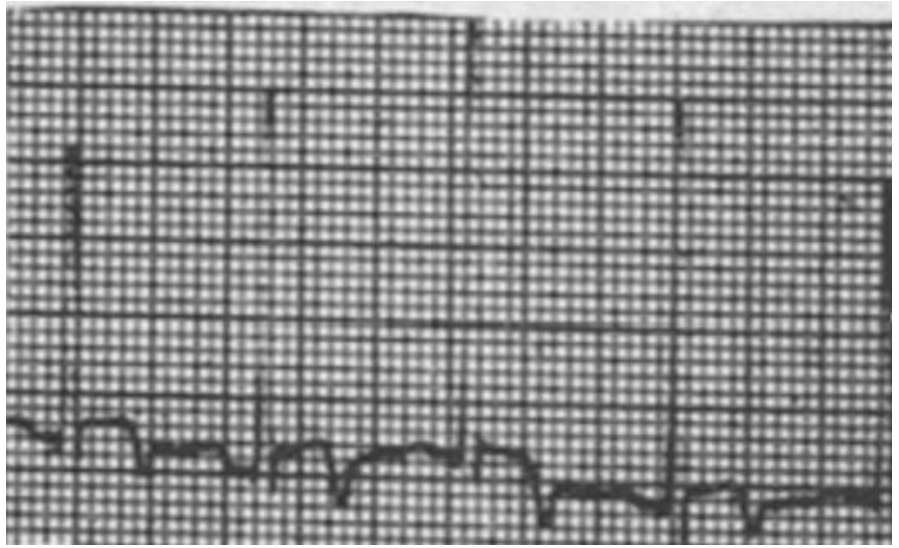


8. Notching or slurring at the J-point.
9. Prominent, slightly asymmetrical or pseudo-symmetric T-waves that are concordant with the QRS complexes (pointing in the same direction).
10. The degree of ST elevation is modest in comparison to the T-wave amplitude (less than 25% of the T wave height in V6)
11. ST elevation is usually < 2mm in the precordial leads and < 0.5mm in the limb leads, although precordial STE may be up to 5mm in some instances.
12. No reciprocal ST depression to suggest STEMI (except in aVR).
13. ST changes are relatively stable over time (no progression on serial ECG tracings).
14. Hyperventilation : frequent marked T wave inversion in the precordial leads exhibiting the elevated RS-T segment . A similar degree of precordial T wave inversion was observed following both brief hyperventilation and exercise

Post-hyperventilation



Post-exercise

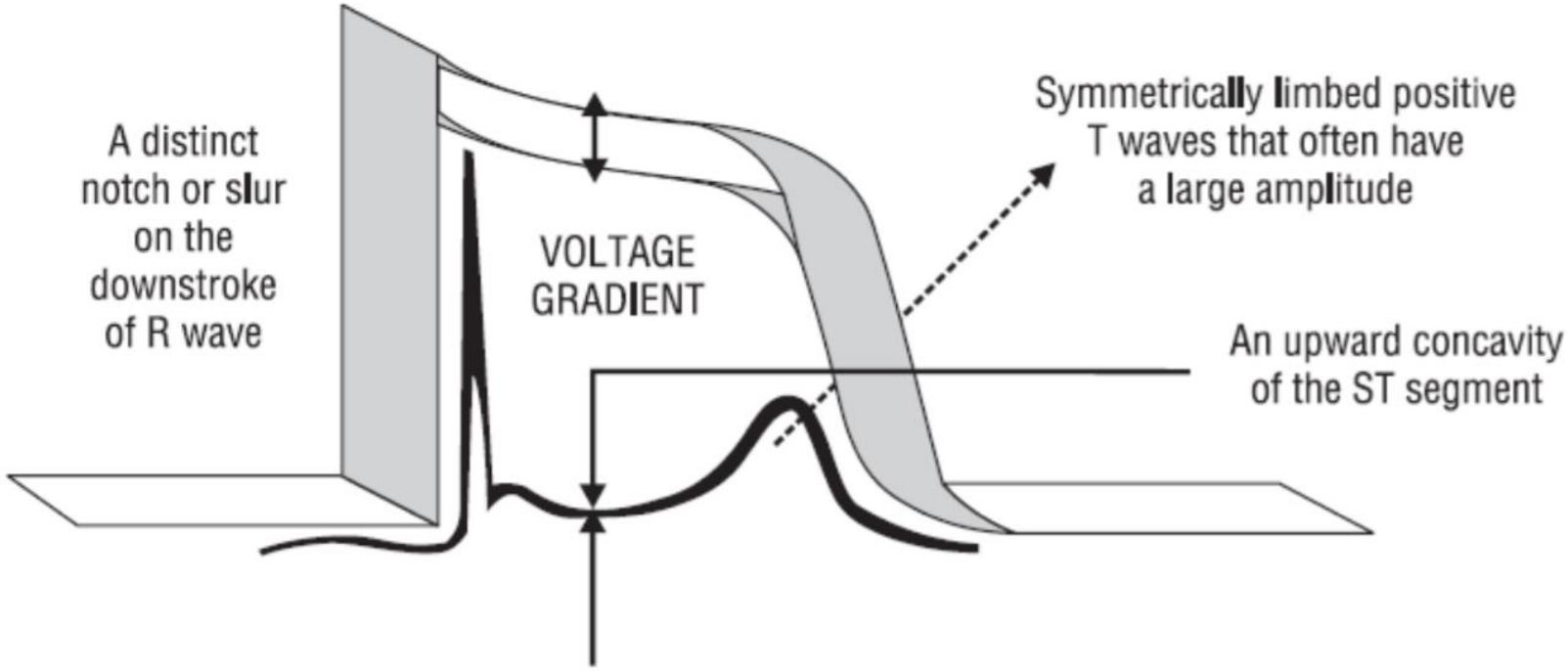


15. Characteristically associated with moderate degrees of counterclockwise rotation

Differences between Benign vs Malignant variant of J wave syndromes (Sethi KK, et al 2014)

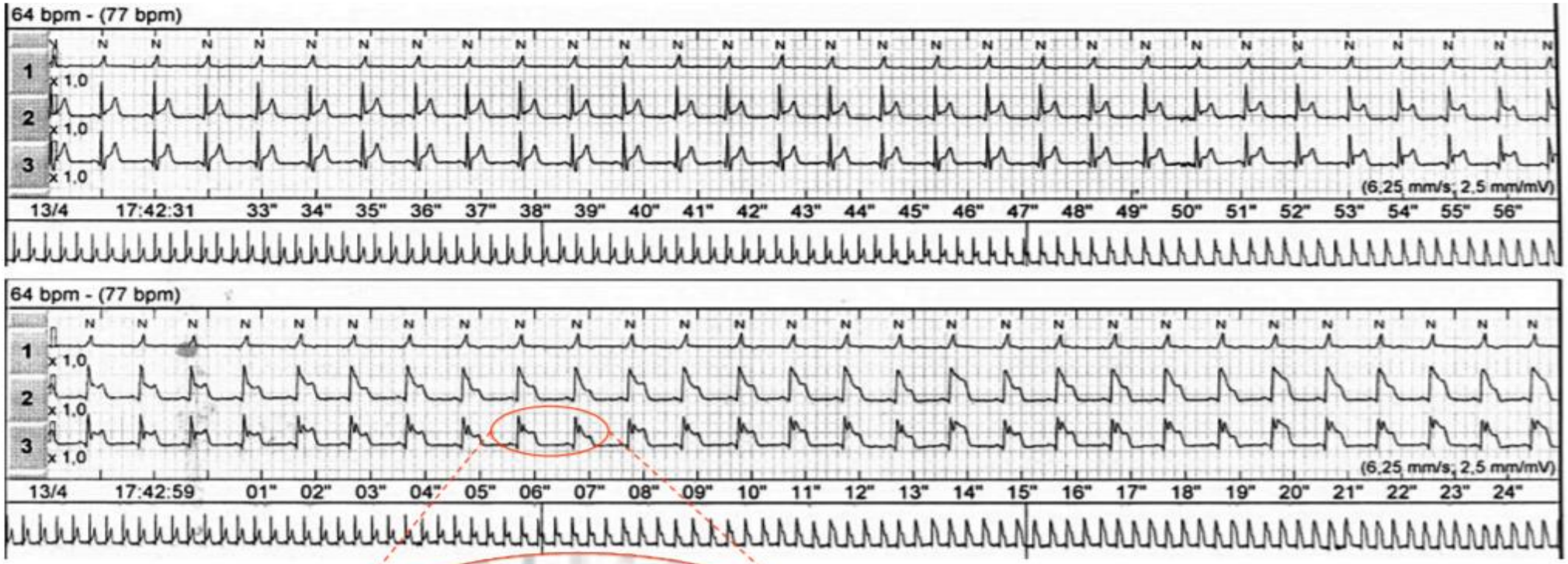
Characters	Physiological J Wave	Pathological J wave
J point Elevation	<0.1 mV	>0.2 mV
Height of J wave	1-2 mm	>2mm
Descent of J wave	Upsloping	Horizontal or downsloping
Magnitude of J point elevation before events or bradycardia	Dramatic augmentation	Unchanged
ECG leads	Only V4-6 or II, III, aVF	Both, V4-6 plus II, III, aVF

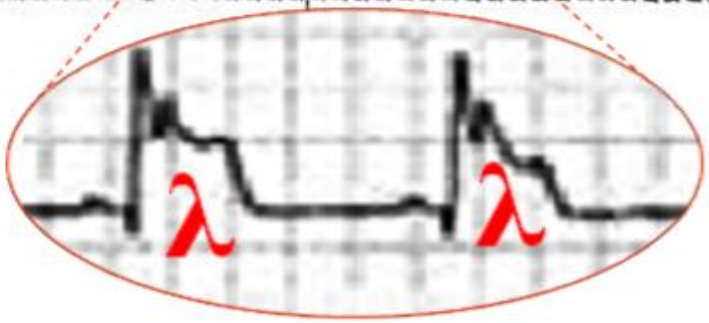
Benign early repolarization mechanism



Ischemia- mediated VT/VF: Vasospastic angina, Prinzmetal J waves/ Ischemic J-Waves

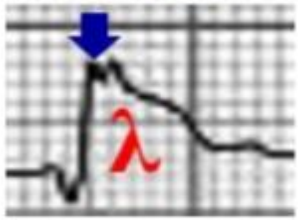
Holter monitoring during myocardial ischemia in patients with Prinzmetal vasospastic angina. J-wave augmentations caused by myocardial ischemia during coronary spasms has lambda wave morphology. The presence and augmentation of J waves, especially prominent J waves with the characteristic ST-elevation patterns, were associated with VF (Sato 2012). We show a continuous Holter monitoring below belonging to a man who had coronary revascularization a time ago, during an episode of angina and concomitant ST segment elevation and ischemic giant J-wave "lambda-like type" associated with Premature Ventricular Contractions with Bigeminy sequence and very short coupling. The PVCs disappear immediately after cessation of vasospastic ischemia with administration of sublingual nitrate.

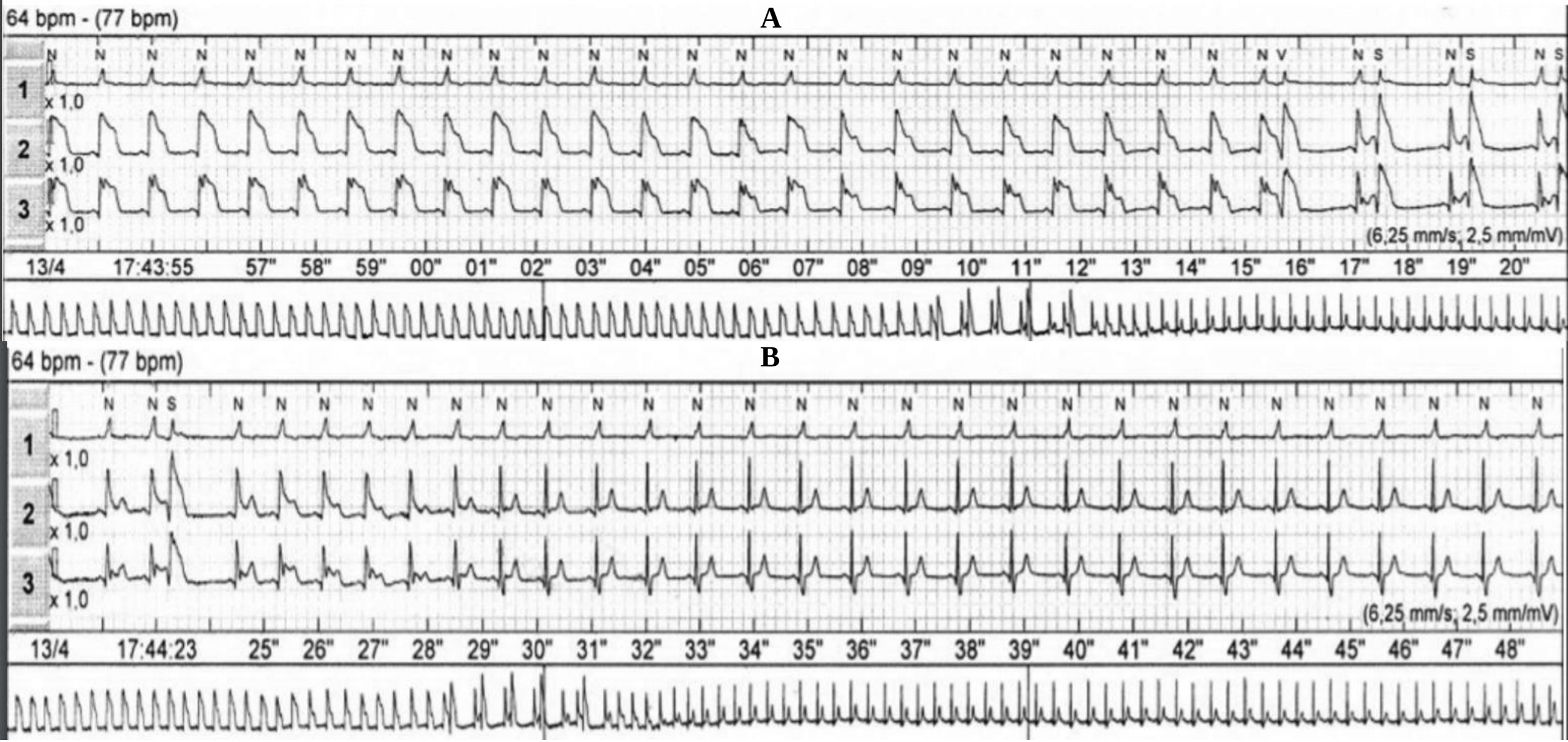




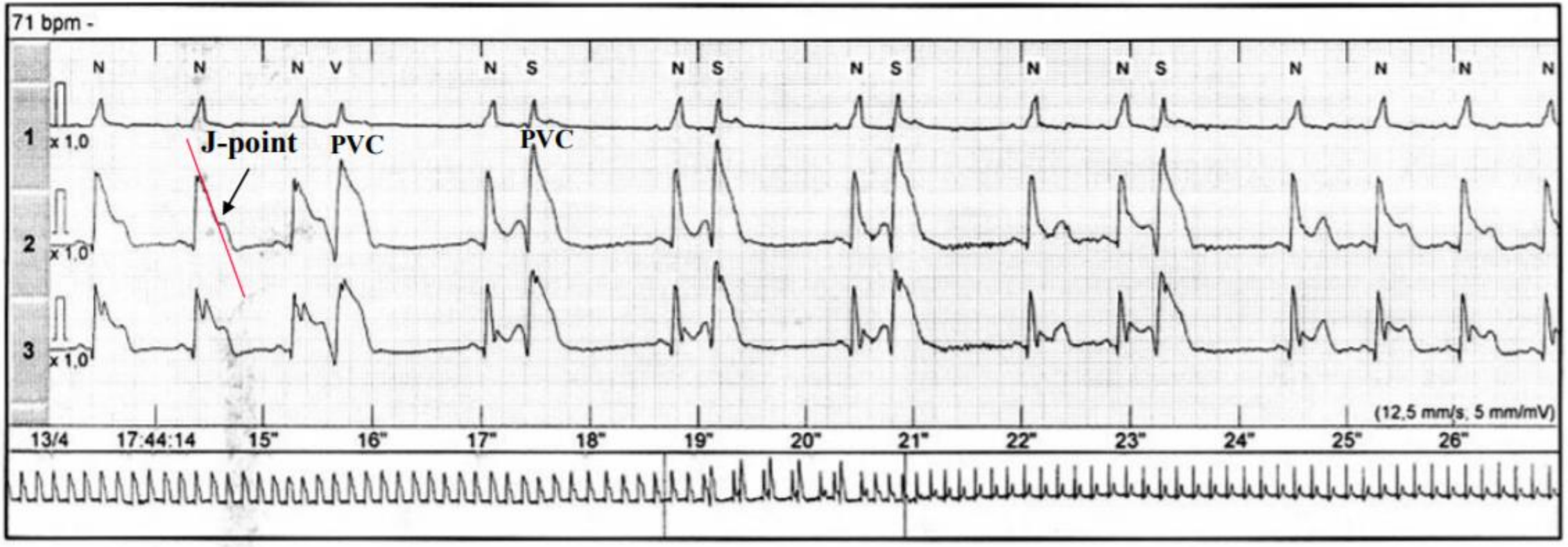
Observation: the pattern is very similar with ECG-2 from the present case because we have f-QRS + lambda wave.

ECG-2





A) Holter monitoring shows STSE with lambda wave pattern during Prinzmetal angina. The last 4 group of beats are formed by sinus beat followed by premature ventricular contraction. B)The first beat is sinus rhythm with minimal STSE. The second one has drastically augmentation of STSE followed by short coupled PVC. From third to eighth beat there are minimal STSE. The remaining trace has normal ST segment level.



Premature ventricular contractions (PVCs) occurring after each sinus beat (bigeminy) with lambda wave shape.

Ikeda et al studied 286 patients (136 males) with clinically suspected vasospatic angina (VSA) who underwent intracoronary provocation An association between ERP and VF has been reported in patients with vasospastic angina (VSA). VSA) who underwent intracoronary provocation tests with acetylcholine or ergonovine. Patients were divided into a VSA group [n = 94, positive provocation test as induction of coronary arterial spasm (>90% stenosis)] and a non-VSA group (n = 192). Detailed EPR data were compared between groups. The VSA group showed a higher frequency of smokers than the non-VSA group. On baseline 12-lead ECG, ERP in both or either of inferolateral leads) was found in 39 patients (inferior leads, n = 27; inferolateral leads, n = 12). ERP was found more frequently in the VSA group (28.7%) than in the non-VSA group. Multivariate analysis revealed ERP as an independent predictor of VSA . ERP features including inferior lead, higher amplitude, notched type and horizontal/descending ST segments were associated with increased risk of VSA. In patients with resting chest pain, ERP was a predictor of VSA that could be particularly related to the inferior lead, higher amplitude, notched type and horizontal/descending ST segment.(1)

1. **Hiroyuki Ikeda, et al Early repolarization in the inferolateral leads predicts the presence of vasospastic angina: a novel predictor in patients with resting angina. Coron Artery Dis. 2020 Nov 13. doi: 10.1097/MCA.0000000000000983.**

J-wave in Hyperthermia/ Heat stroke

Heatstroke is a condition caused by body overheating, usually as a result of prolonged exposure to physical exertion in high temperatures. This most serious form of heat injury, heatstroke, can occur if body temperature rises to ≥104 F (40 C). The condition is most common in the summer months. Heatstroke requires emergency treatment. Untreated heatstroke can quickly damage your brain, heart, kidneys and muscles. The damage worsens the longer treatment is delayed, increasing your risk of serious complications or death.

Heatstroke signs and symptoms include. A core body temperature of ≥104 F (40 C), obtained with a rectal thermometer, is the main sign of heatstroke, altered mental state or behavior. Confusion, agitation, slurred speech, irritability, delirium, seizures and coma can all result from heatstroke, alteration in sweating. In heatstroke brought on by hot weather, the skin will feel hot and dry to the touch. However, in heatstroke brought on by strenuous exercise, your skin may feel dry or slightly moist, nausea and vomiting, flushed skin that may turn red as your body temperature increases. Rapid breathing. Your breathing may become rapid and shallow.Racing heart rate. Your pulse may significantly increase because heat stress places a tremendous burden on your heart to help cool your body.

Causes

Heatstroke can occur as a result of: Exposure to a hot environment. In a type of heatstroke, called nonexertional (classic) heatstroke, being in a hot environment leads to a rise in core body temperature. This type of heatstroke typically occurs after exposure to hot, humid weather, especially for prolonged periods. It occurs most often in older adults and in people with chronic illness. Strenuous activity. Exertional heatstroke is caused by an increase in core body temperature brought on by intense physical activity in hot weather. Anyone exercising or working in hot weather can get exertional heatstroke, but it's most likely to occur if you're not used to high temperatures.

In either type of heatstroke, your condition can be brought on by: Wearing excess clothing that prevents sweat from evaporating easily and cooling the body

Drinking alcohol, which can affect your body's ability to regulate your temperature

Becoming dehydrated by not drinking enough water to replenish fluids lost through sweating

Risk factors

Several factors increase the risk:

Age. The ability to cope with extreme heat depends on the strength of your central nervous system. In the very young, the central nervous system is not fully developed, and in adults over 65, the central nervous system begins to deteriorate, which makes your body less able to cope with changes in body temperature. Both age groups usually have difficulty remaining hydrated, which also increases risk.

Exertion in hot weather. Military training and participating in sports, such as football or long-distance running events, in hot weather are among the situations that can lead to heatstroke.

Sudden exposure to hot weather. It may be more susceptible to heat-related illness if you're exposed to a sudden increase in temperature, such as during an early-summer heat wave or travel to a hotter climate.

Limit activity for at least several days to allow to acclimate to the change. However, you may still have an increased risk of heatstroke until you've experienced several weeks of higher temperatures.

A lack of air conditioning. Fans may make you feel better, but during sustained hot weather, air conditioning is the most effective way to cool down and lower humidity. Certain medications. Some medications affectthe body's ability to stay hydrated and respond to heat. It is important be especially careful in hot weather if take medications that narrow your blood vessels (vasoconstrictors), regulate your blood pressure by blocking adrenaline (beta blockers), rid your body of sodium and water (diuretics), or reduce psychiatric symptoms (antidepressants or antipsychotics). Stimulants for attention-deficit/hyperactivity disorder (ADHD) and illegal stimulants such as amphetamines and cocaine also make you more vulnerable to heatstroke. Certain chronic illnesses, such as heart or lung disease, might increase the risk of heatstroke. So can being obese, being sedentary and having a history of previous heatstroke.

Complications Heatstroke can result in a number of complications, depending on how long the body temperature is high. Severe complications include: Vital organ damage. Without a quick response to lower body temperature, heatstroke can cause your brain or other vital organs to swell, possibly resulting in permanent damage. Death. Without prompt and adequate treatment, heatstroke can be fatal.

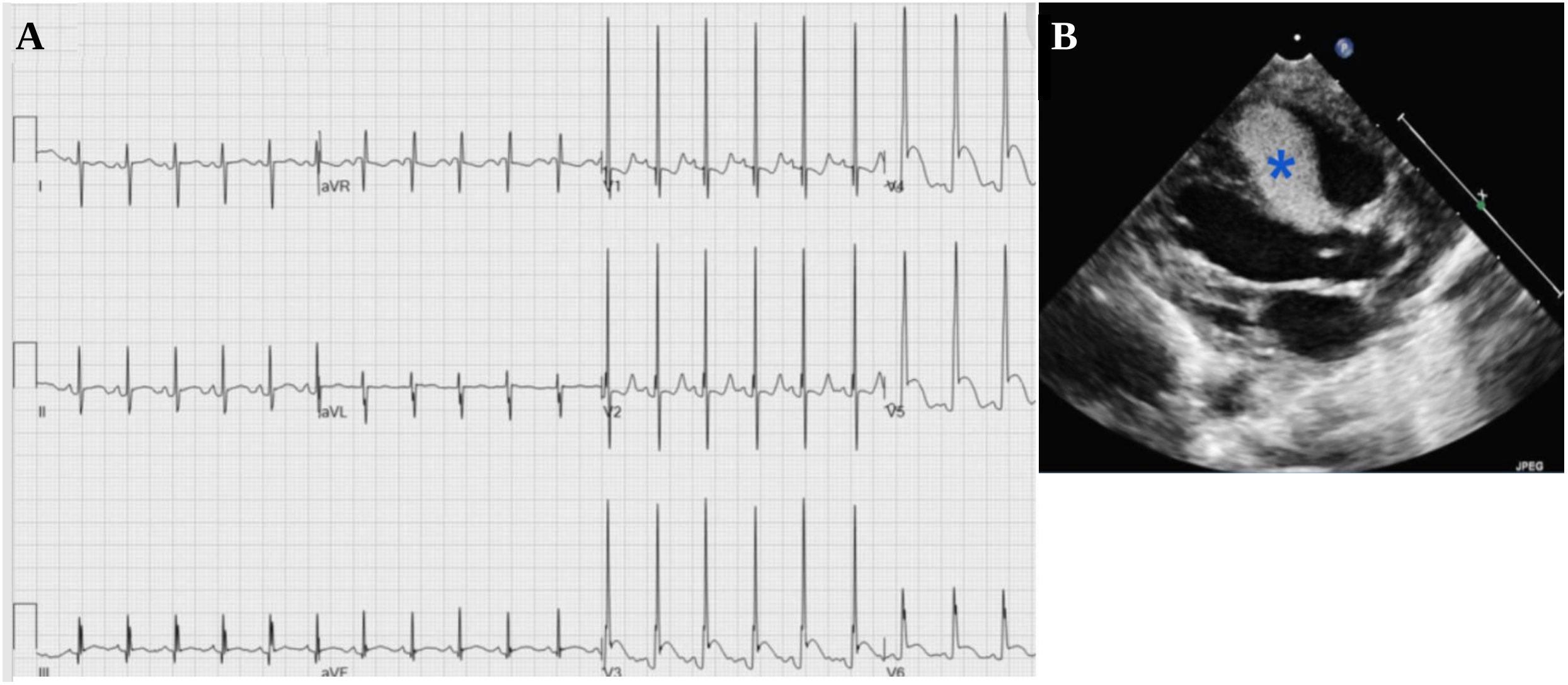
Prevention Heatstroke is predictable and preventable. Take these steps to prevent heatstroke during hot weather: Wear loose-fitting, lightweight clothing. Wearing excess clothing or clothing that fits tightly won't allow your body to cool properly. Protect against sunburn. Sunburn affects your body's ability to cool itself, so protect the outdoors with a wide-brimmed hat and sunglasses and use a broad-spectrum sunscreen with an SPF of at least 15. Apply sunscreen generously, and reapply every two hours — or more often if is swimming or sweating. Drink plenty of fluids. Staying hydrated will help the your body sweat and maintain a normal body temperature. Take extra precautions with certain medications. Be on the lookout for heat-related problems if you take medications that can affect your body's ability to stay hydrated and dissipate heat. Never leave anyone in a parked car. This is a common cause of heat-related deaths in children. When parked in the sun, the temperature inside the car can rise 20 degrees F (more than 6.7 C) in 10 minutes. It's not safe to leave a person in a parked car in warm or hot weather, even if the windows are

cracked or the car is in shade. When the car is parked, keep it locked to prevent a child from getting inside. Take it easy during the hottest parts of the day. If the patient can't avoid strenuous activity in hot weather, drink fluids and rest frequently in a cool spot. Try to schedule exercise or physical labor for cooler parts of the day, such as early morning or evening.

The ECG findings in hyperthermia include:

1. Sinus tachycardia[**Akhtar MJ, et al (1993). "Electrocardiographic abnormalities in patients with heat stroke". Chest. 104 (2): 411–4. PMID 8339628**.] in ≈ 80% of cases.
2. Ischemic changes in 30% of cases(L**. Mimish⁎ Electrocardiographic findings in heat stroke and exhaustion: A study on Makkah pilgrimsJ Saudi Heart Assoc. 2012 Jan; 24(1): 35–39. doi: 10.1016/j.jsha.2011.08**.00)
3. Diffuse non specific ST segment changes[**Chen WT, Lin CH, Hsieh MH, Huang CY, Yeh JS (2012). "Stress-induced cardiomyopathy caused by heat stroke". Ann Emerg Med. 60 (1): 63–6. doi:10.1016/j.annemergmed.2011.11.005. PMID 22153997**.]
4. Non specific ischemic changes **Akhtar MJ, al-Nozha M, al-Harthi S, Nouh MS (1993). "Electrocardiographic abnormalities in patients with heat stroke". Chest. 104 (2): 411–4. PMID 8339628**][**Chen WT, Lin CH, Hsieh MH, Huang CY, Yeh JS (2012). "Stress-induced cardiomyopathy caused by heat stroke". Ann Emerg Med. 60 (1): 63–6. doi:10.1016/j.annemergmed.2011.11.005. PMID 22153997**.]
5. Prolonged QT interval[**Akhtar MJ, al-Nozha M, al-Harthi S, Nouh MS (1993). "Electrocardiographic abnormalities in patients with heat stroke". Chest. 104 (2): 411–4. PMID 8339628**]
6. Brugada syndrome with J wave in the right precordial leads [**Lacunza J, San Román I, Moreno S, García-Molina E, Gimeno J, Valdés M (2009). "Heat stroke, an unusual trigger of Brugada electrocardiogram". *Am J Emerg Med.* 27 (5): 634.e1–3. doi:10.1016/j.ajem.2008.09.036.**]

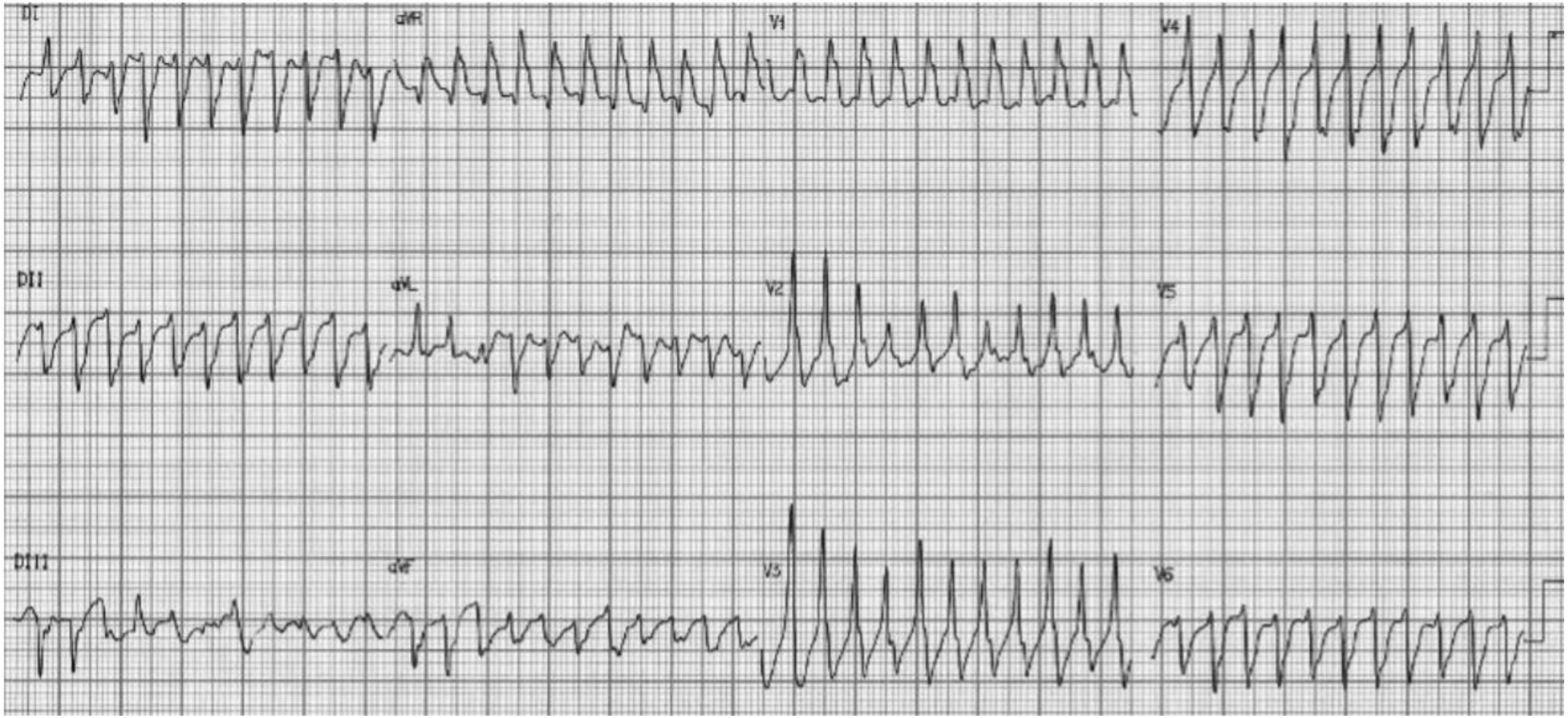
Myocardial tumor J-wave



Electrocardiogram on first day of life. A) A 12-lead ECG shows right ventricular hypertrophy, PR-segment depression, J-point elevation, and STE in the precordial leads, consistent with a pericarditis pattern. Pronounced STE (approximately 8 mm in V4), notched J-wave in a newborn with tuberous sclerosis and ventricular rhabdomyomas. B) Postnatal echocardiogram**:** Large intracardiac mass in the right ventricular side of interventricular septum, extending from level of pulmonic valve down to the apex. **(Rochelson E, et al. 2019.)**

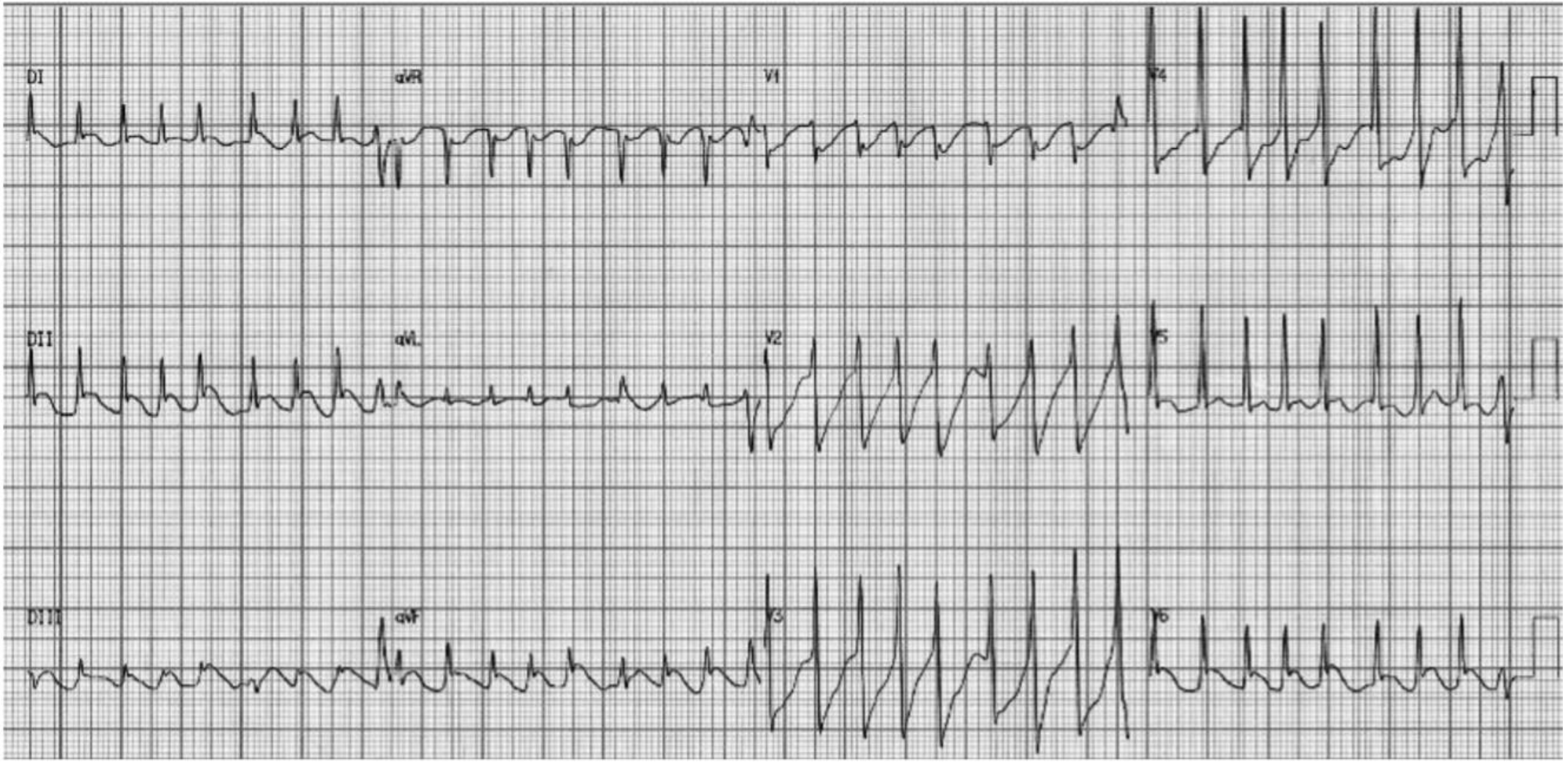
Subarachnoid hemorrhage/intracerebral bleeding with masive J wave

A 56-year-old female who presented to the emergency department with a decreased level of consciousness following intensification of a two-week long worsening headache. The patient's past medical history was significant for hypertension for which she was on no medication. On physical exam, she was unconscious (Glasgow Coma Scale (GCS) 6).. Bellow ECG at admission (08:32 A.M.)

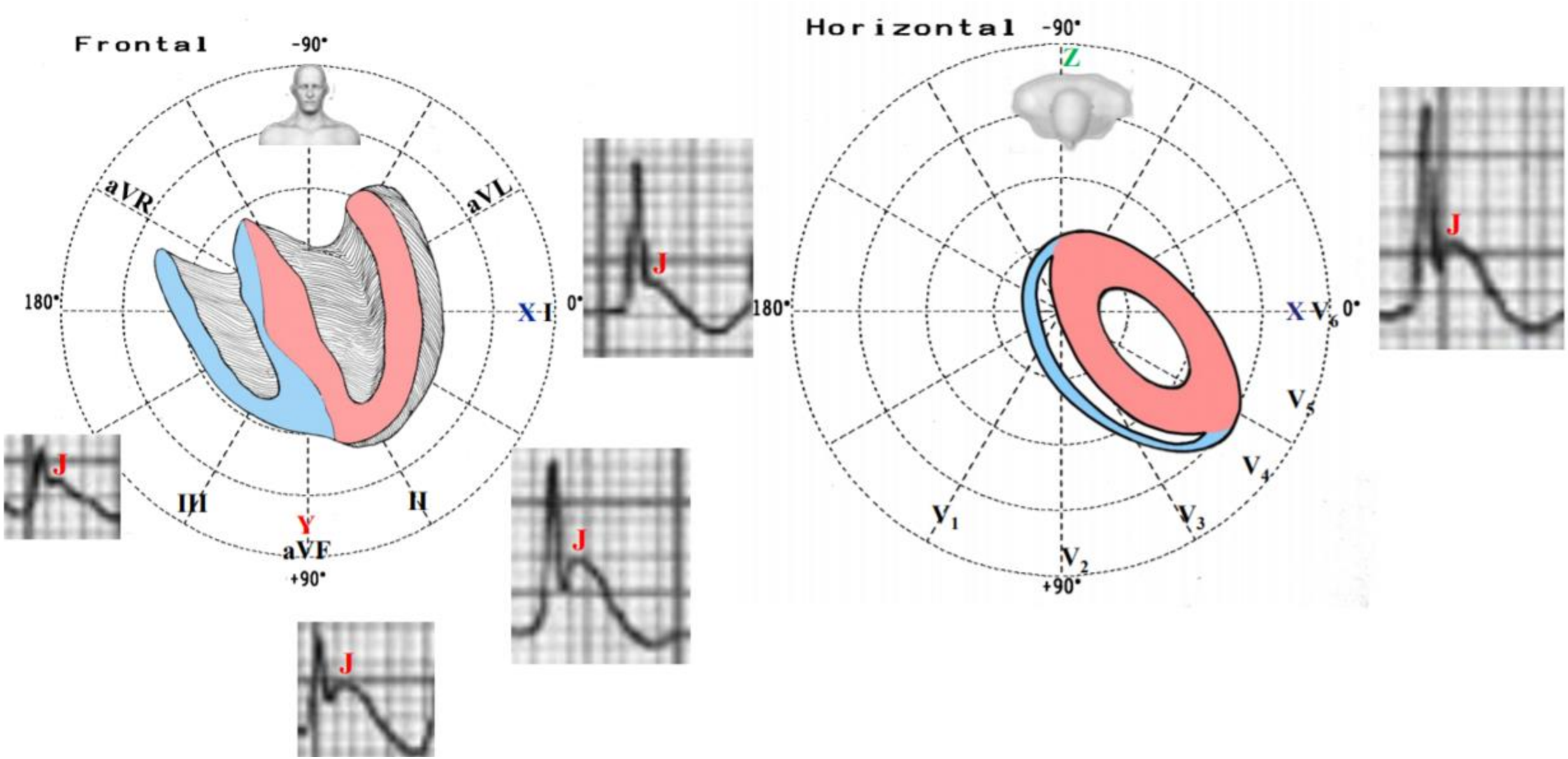


ECG diagnosis: Wide-QRS complex VT (160 ms) HR 294 bpm with visible fusion and capture beats. Monophasic R-waves in leads V1– V2 indicated left ventricular focus origin

ECG performed at 08:40 A.M. – after cardioversion

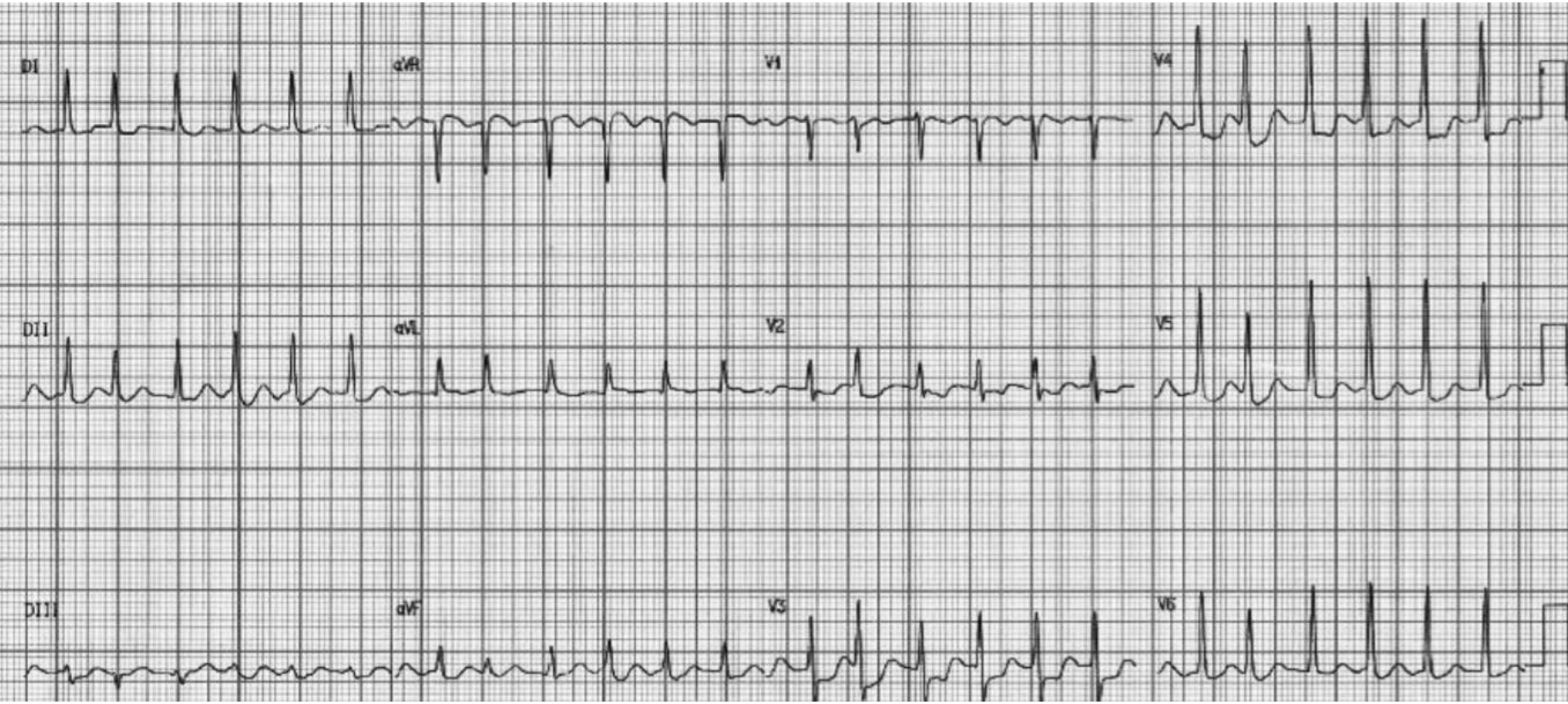


ECG diagnosis: The patient was electrically cardioverted and a second ECG performed after 8 minutes demonstrated rapid AF at 188 bpm and massive J-waves (maximal amplitude: 0.47 mV in lead II) with ST-segment elevation in the inferolateral leads and ST-segment depression in the anterior leads (V1–V4).



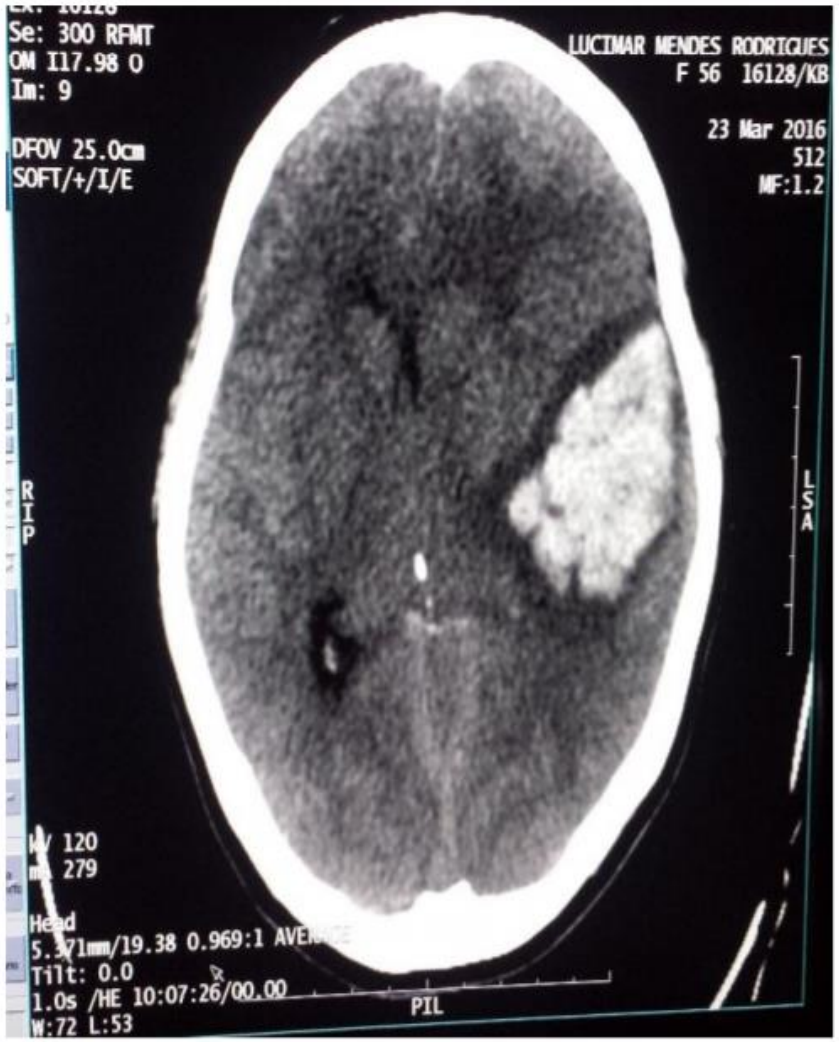
Conspicuous J-waves in anterolateral leads

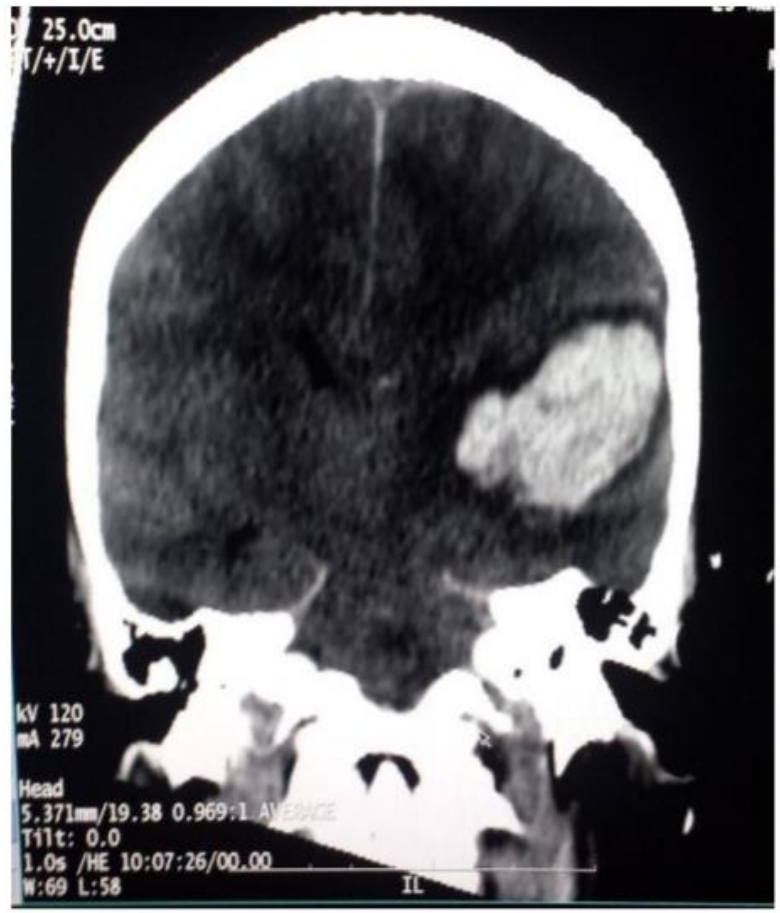
ECG performed at 09:57 A.M.

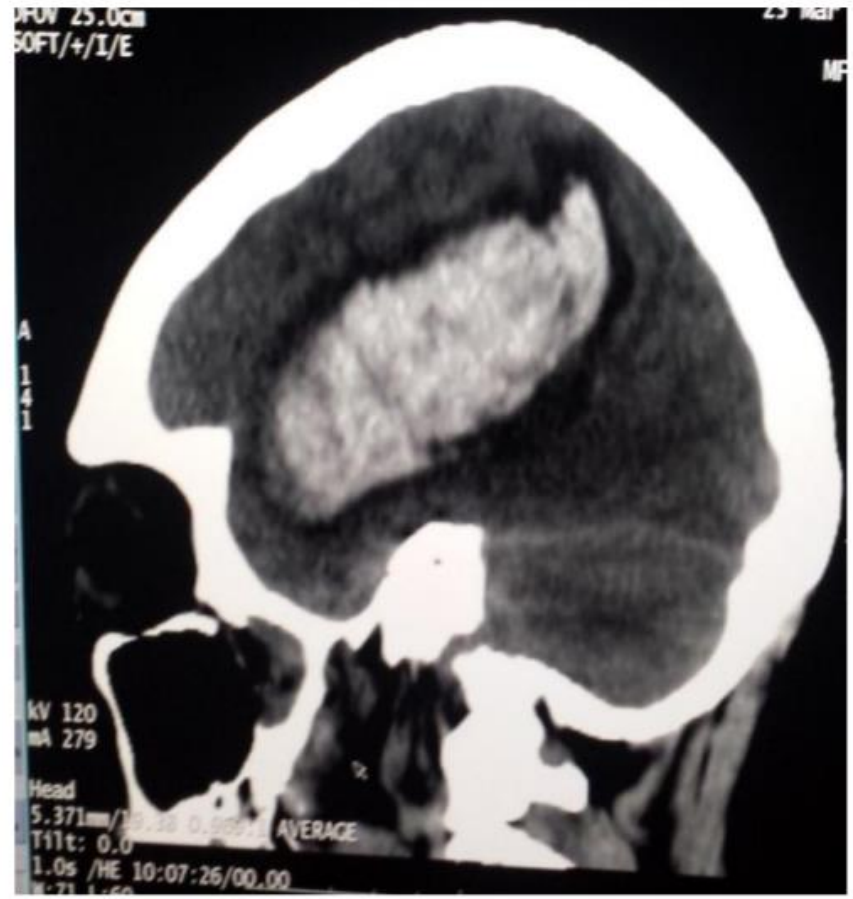


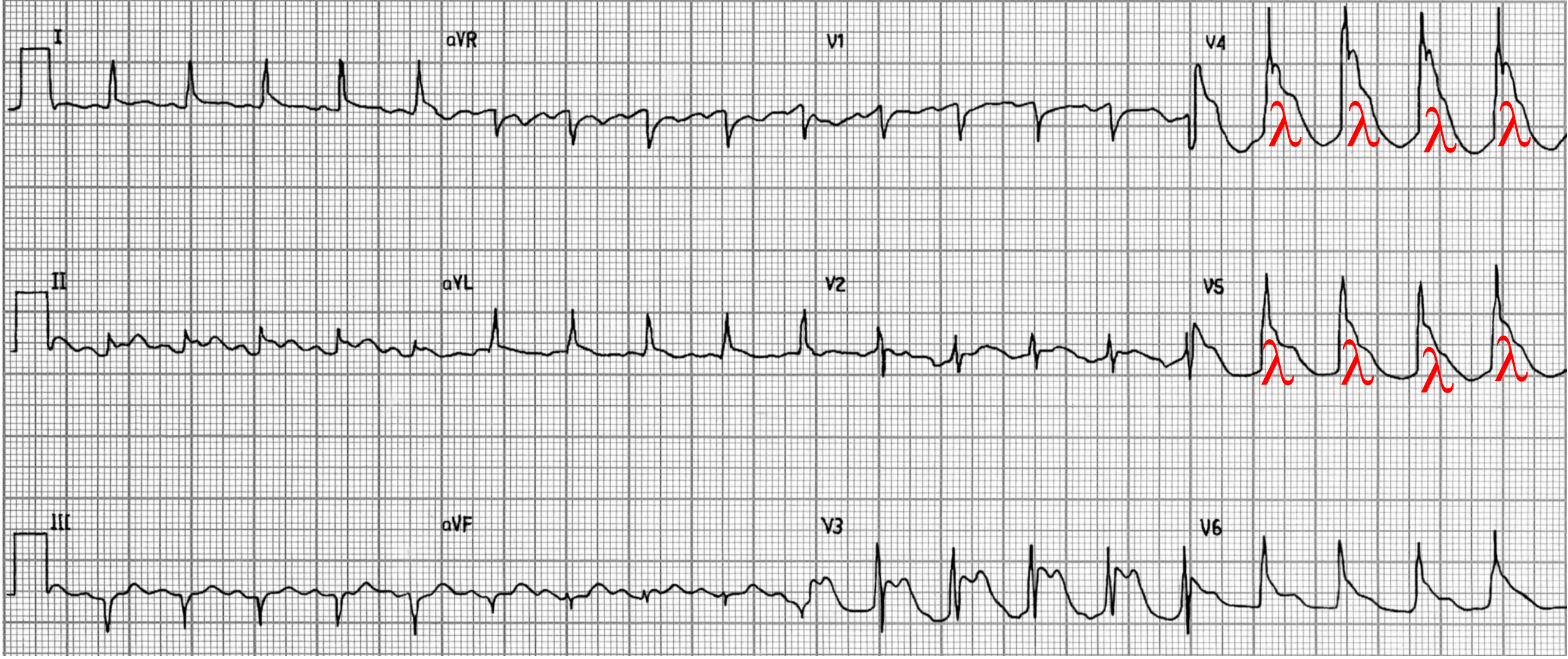
ECG diagnosis: Third ECG performed after 1 hour 17 minutes after the second one depicted AF at 145 bpm, ST-segment abnormalities and spontaneous disappearance of the J-waves.

Computed tomography of the brain shows a massive intraparenchymal hematoma.





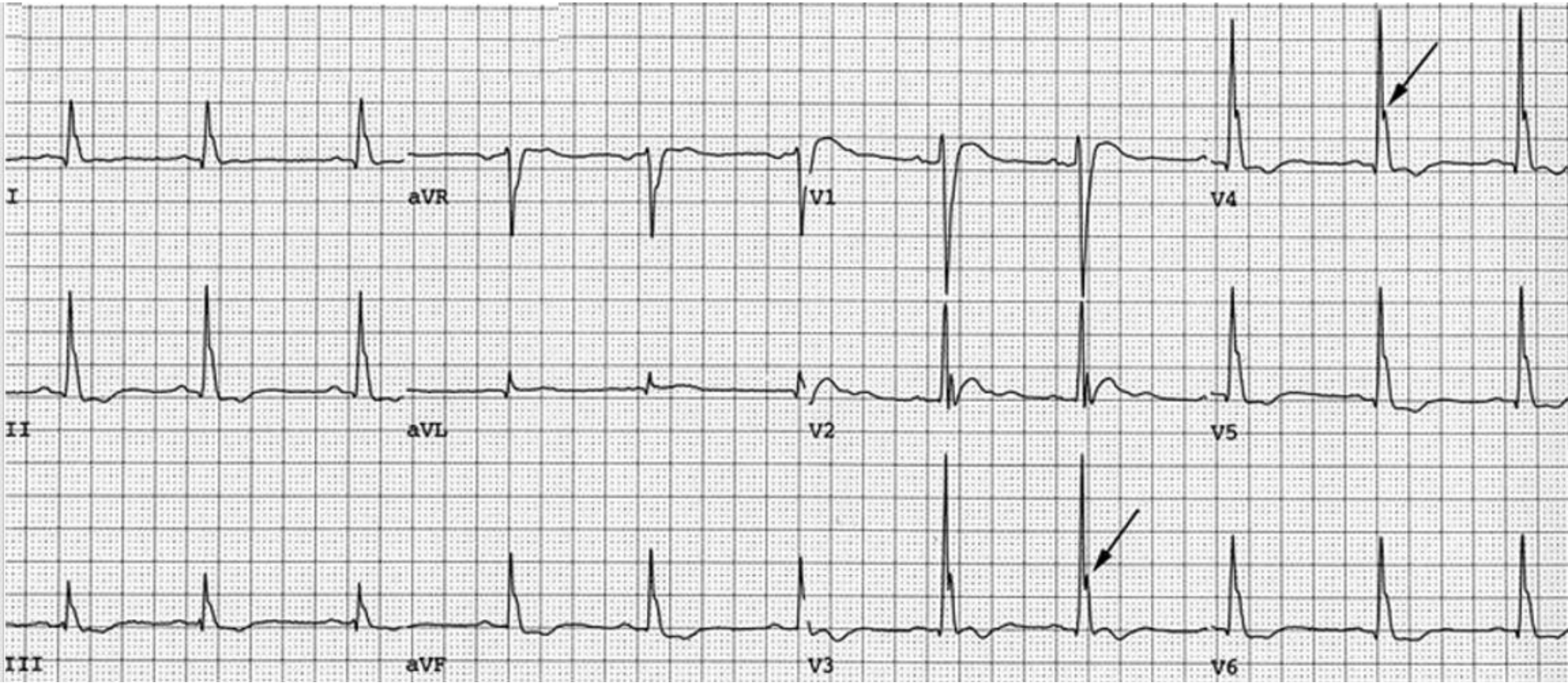




Clinical diagnosis: ECG performed subsequent postictal confusion/hemiplegia with left-sided upper and lower extremity hemiparesis: cerebral and cardiac hypoperfusion (ischemia) following a postictal event with an increase in sympathetic tone.

ECG diagnosis: Lambda waves in the setting of cerebral injury such as trauma or hemorrhage; however, ECG evidence of a dynamically displaced J-point has not been previously described in the setting of postictal hemiplegia

Normothermic J- wave induced by severe hypercalcemia (serum calcium level 16.3 mg/dL (normal, 8.6 to 10.6 mg/dL) **)**



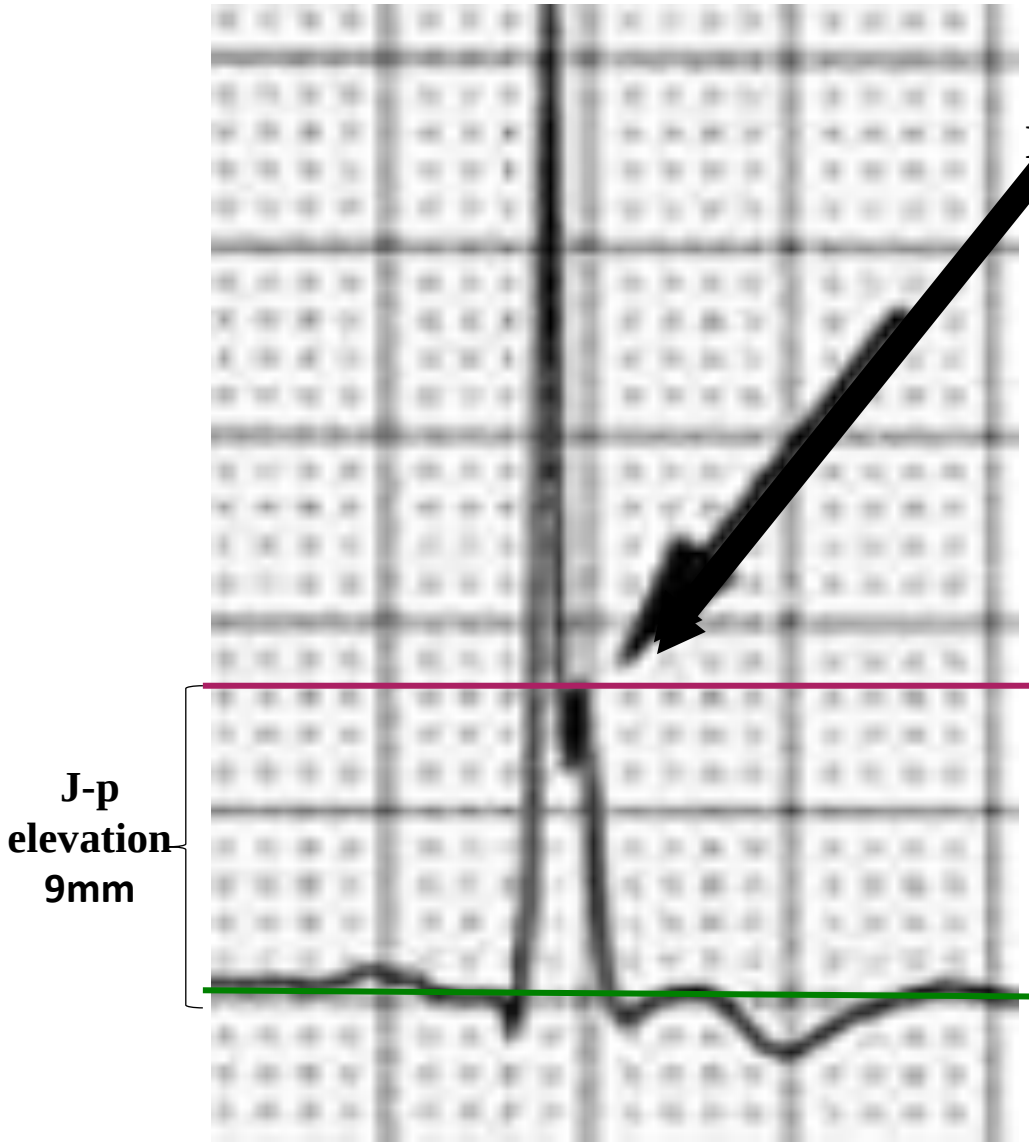
Clinical diagnosis: parathyroid adenoma confirmed by biopsy in a young man of 33 years of age,

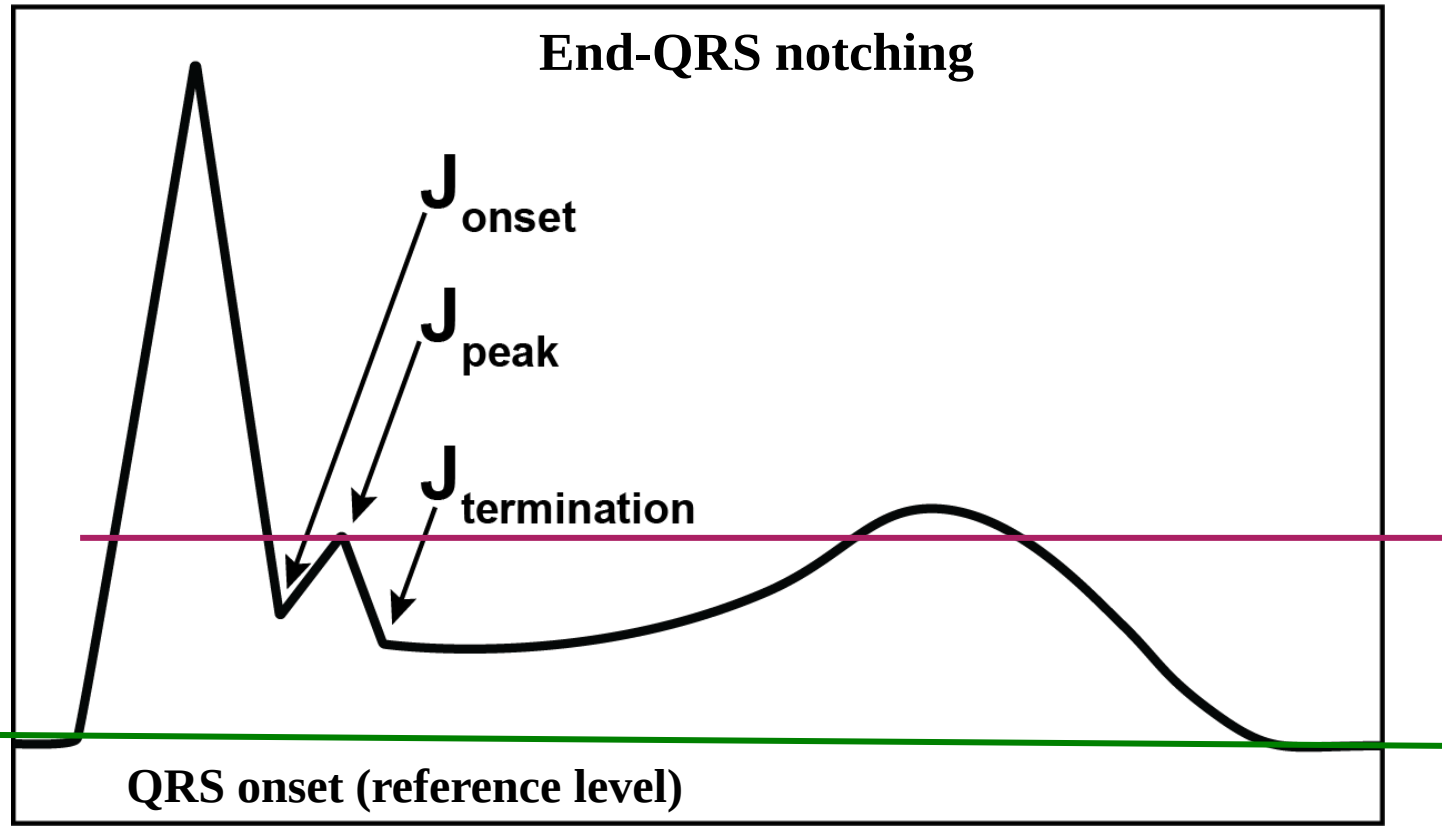
ECG: Diffuse J-wave slurring and notched in inferior, lateral and anteroseptal leads: Early Repolarization Pattern and very short QT interval .

Javier Otero, Daniel J. Lenihan, the "Normothermic" Osborn Wave Induced by Severe Hypercalcemia. Tex Heart Inst J. 2000; 27(3): 316–317.

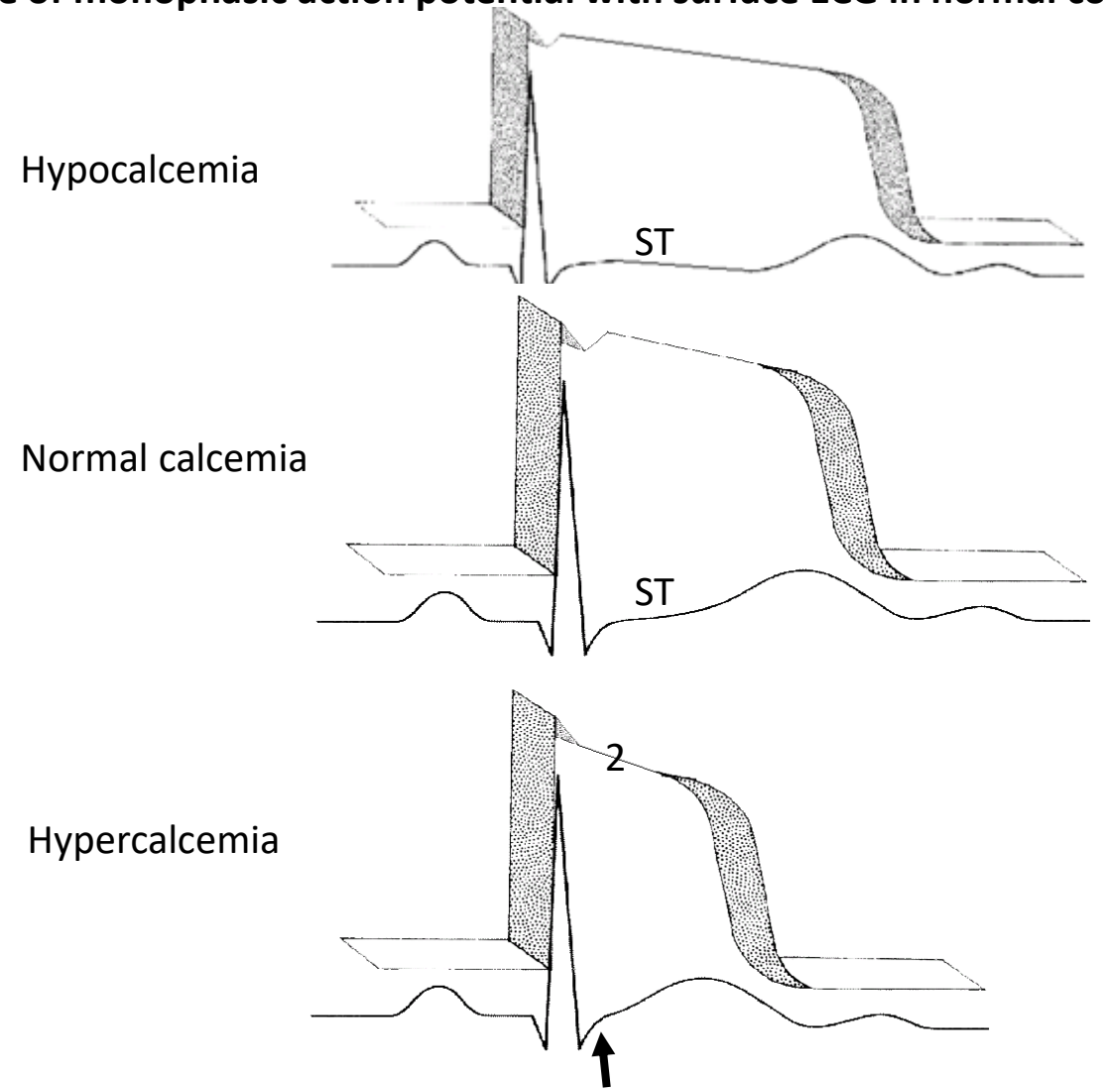
Why Early Repolarization Pattern (ERP)?

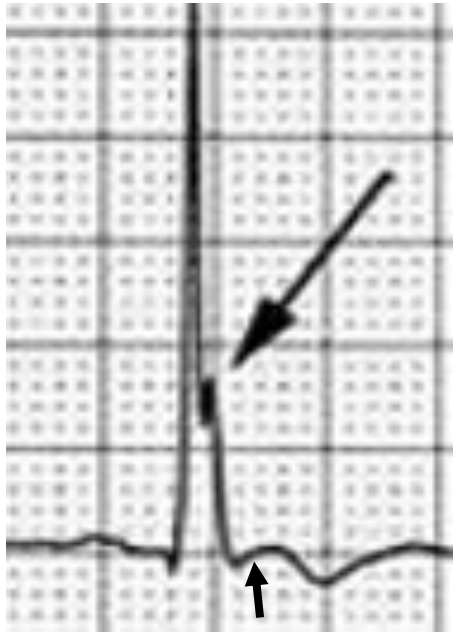
Because ERP can be diagnosed in the presence of J-point elevation≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG





Comparative outline of monophasic action potential with surface ECG in normal conditions and in hypercalcemia





Almost absent ST segment

QTc interval shortening, Q-oTc interval shortening: interval from Q wave onset to T wave onset corrected according to HR.

Q-aT interval decrease: interval between QRS onset to T wave apex. Values below 270 ms are diagnostic.

Pseudo J-wave or J wave-like intraventricular conduction delay

J wave is an ECG manifestation an I_{to}-mediated repolarization component, and its property is determined by the features of I_{to} which can help to distinguish J wave from depolarization abnormalities resembling J wave (pseudo J wave). (Badri M, Patel A, Yan GX. Cellular and ionic basis of J-wave syndromes. Trends Cardiovasc Med. 2015;25:12–21; Antzelevitch C, Yan GX. J-wave syndromes: Brugada and early repolarization syndromes. Heart Rhythm. 2015;12:1852–1866.) In this landmark study, they pointed out that the so-called "right bundle branch block" in cases of VF by Brugada brothers in 1992 was in fact a prominent J wave.[7] Since then, J wave has not been simply viewed as a hallmark of hypothermia, but also linked to VF.

The major difference between Ito-medicated J wave and pseudo J wave (intra-ventricular conduction delay) is their distinguished responses to changes in heart rate. Delayed conduction becomes aggravated during prematurity of fast heart rate, which leads to an accentuation of the QRS notch; whereas repolarization abnormality weakens, leading to a decreased or disappeared Ito-mediated J wave during tachycardia or premature beats. And traditional ER or Ito-mediated J wave is usually accentuated during slower heart rate or long pauses. Very recently, Aizawa et al showed that "J wave" in a general population was not related to idiopathic VF and augmented in amplitude at shorter RR intervals (Aizawa Y, Sato M, Kitazawa H, et al. Tachycardia-dependent augmentation of "notched J waves" in a general patient population without ventricular fibrillation or cardiac arrest: not a repolarization but a depolarization abnormality? Heart Rhythm. 2015;12:376–383) which, we believe, it is a pseudo J wave.

Nademanee et al. conducted a multicenter study with ERS or JWS in 52 young adults patients (4 women; median age, 35 years) to evaluate mapping and ablation of VF substrates or VF triggers. Using epicardial electroanatomical mapping of both ventricles during sinus rhythm and VF for localization of triggers, substrates, and drivers. Ablations were performed on VF substrates, defined as areas that had late depolarization abnormalities characterized by low-voltage fractionated late potentials, and VF triggers. Ablations were performed on VF substrates, defined as areas that had late depolarization abnormalities characterized by low-voltage fractionated late potentials, and VF triggers.

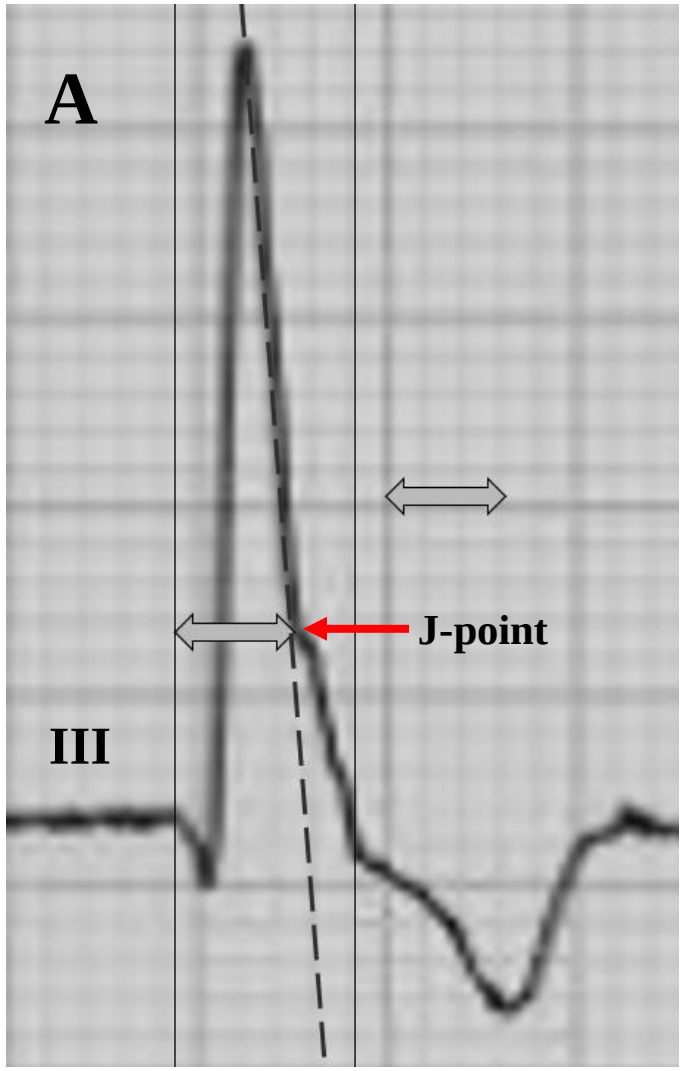
Detailed mapping revealed two phenotypes of ERS/J-WS: **Group 1** with late depolarization abnormalities predominantly at the RV epicardium (n=40) Group 1A ERS + BrS = JWS with late depolarization abnormality as the underlying mechanism of high-amplitude J-wave elevation that predominantly resides in the RVOF. The anterior RVOT/RV epicardium and the RV inferior epicardium are the major substrate sites for group 1

Group 2: with VF triggers associated with Purkinje sites. Ablation is effective in treating symptomatic patients with ERS/J-wave syndrome with frequent VF episodes.(**Koonlawee Nademanee, Michel Haissaguerre, Mélèze Hocini, Akihiko Nogami 4, Ghassen Cheniti 3, Josselin Duchateau 3, Elijah R Behr 5, Magdi Saba 5, Ryan Bokan 6, Qing Lou 6, Montawatt Amnueypol 2, Ruben Coronel 7, Apichai Khongphatthanayothin 1, Gumpanart Veerakul 8 Mapping and Ablation of Ventricular Fibrillation Associated With Early Repolarization Syndrome.Circulation. 2019 Oct 29;140(18):1477-1490. doi: 10.1161/CIRCULATIONAHA.118.039022. Epub 2019 Sep 23.**

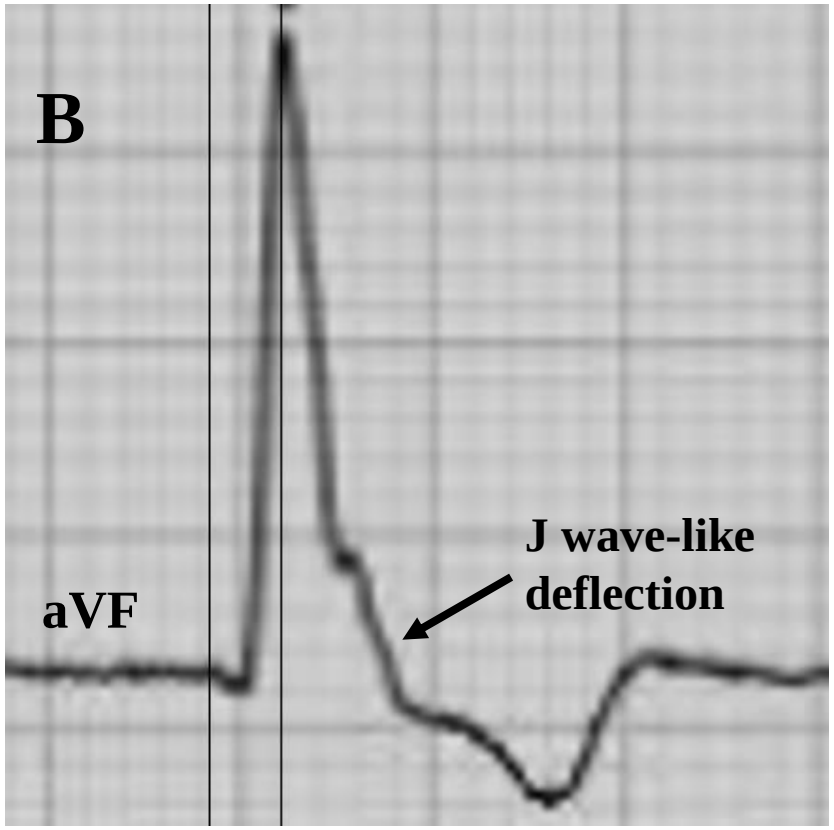
The difference between Ito-mediated J wave and Pseudo J wave (i.e. intra-ventricular conduction delay, IVCD)

	Ito-mediated J wave	Pseudo J wave
Male predominance	Yes	No
Age	Young adults	Older adults
Mechanisms	Early repolarization component	Depolarization abnormality
Response to heart rate	Bradycardia- and pause-dependent augmentation that may be accompanied by paradoxical T wave inversion	Tachycardia and premature beat-dependent augmentation of the notch
QRS slur morphology	often occur at the final 50% of R-wave downslope	often occur beyond the final 50% of R-wave downslope
Upwardly concave ST Elevation	Common	Rare
Quinidine's Effect	Reduce the amplitude	no effect
Structural heart diseases	Rare	Common
Association of Q wave	Rare	Relatively common
Association of right bundle branch block	Rare	Relatively common
Arrhythmic Initiation	Always from a short-coupled PVC on T wave	Occurrence of PVCs often after T wave
Types of Arrhythmias	Polymorphic VT or ventricular fibrillation	Monomorphic
All-cause mortality	Not increased	Increased

J-wave-like deflection at the terminal portion of the QRS in a patient with intraventricular conduction delay

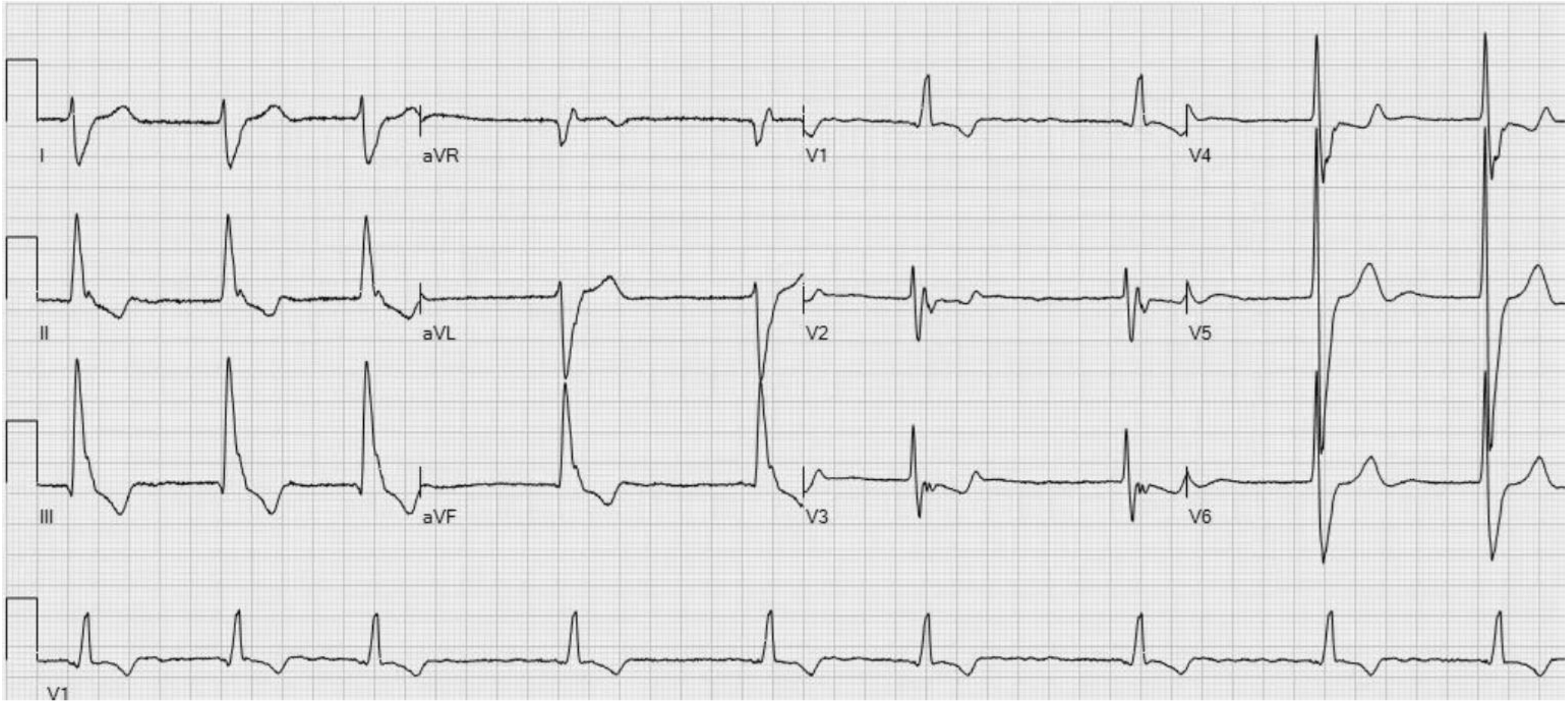


End-QRS slurring

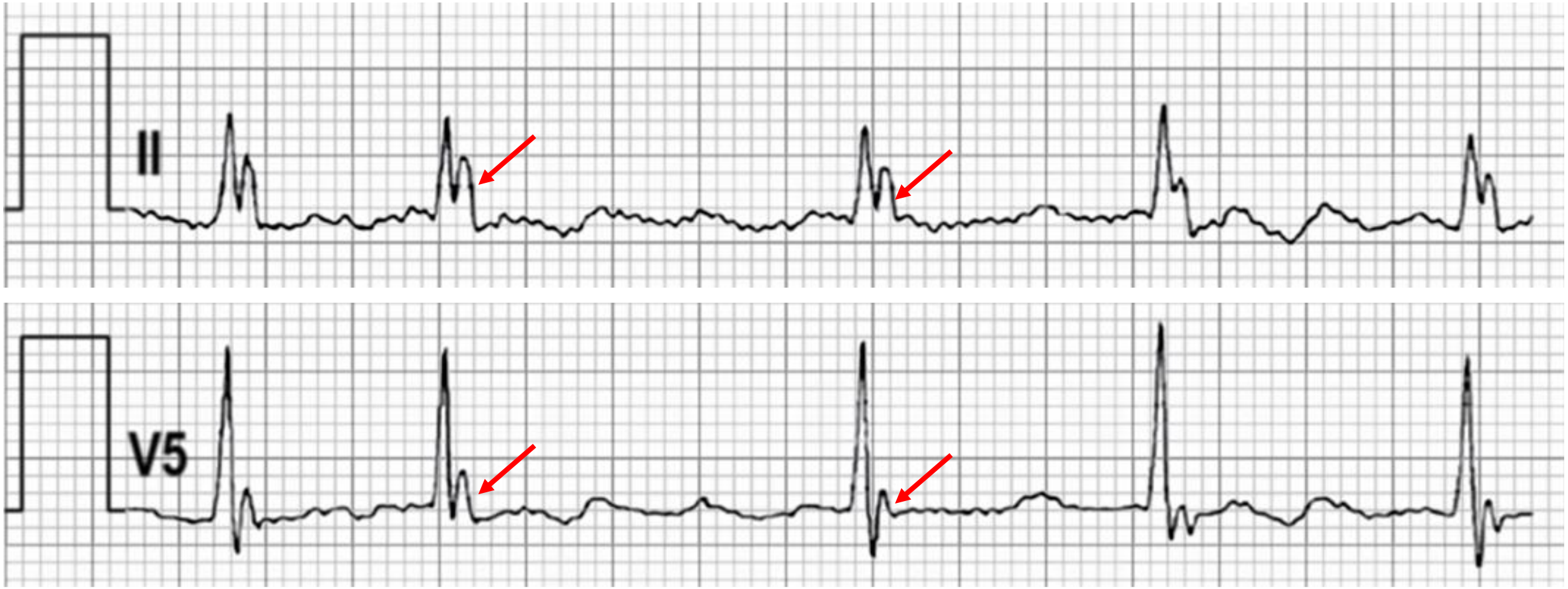


End-QRS notching

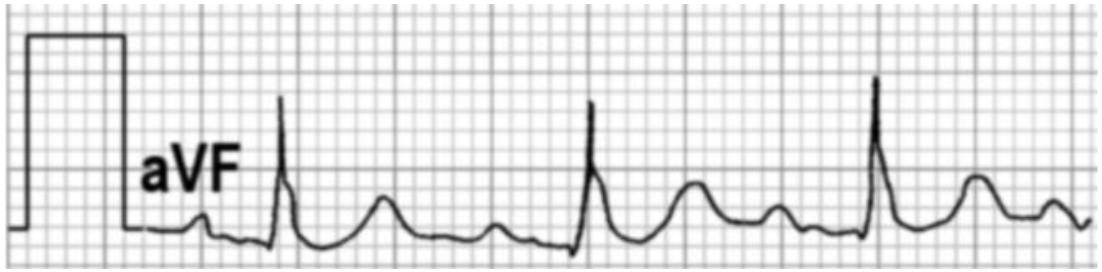
Example of increased pseudo J wave amplitude after shorter RR intervals

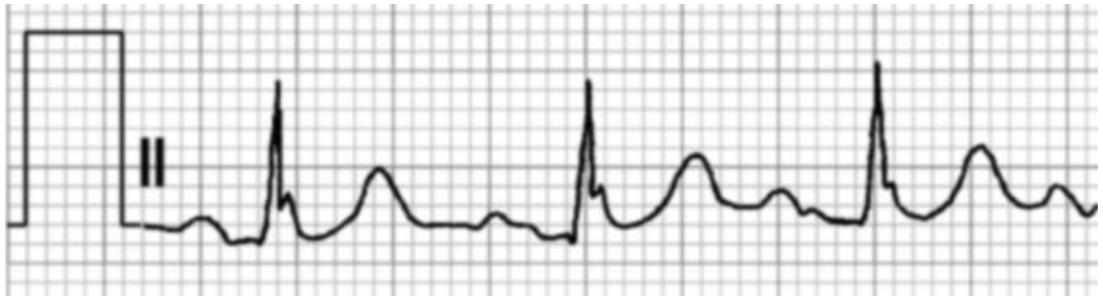


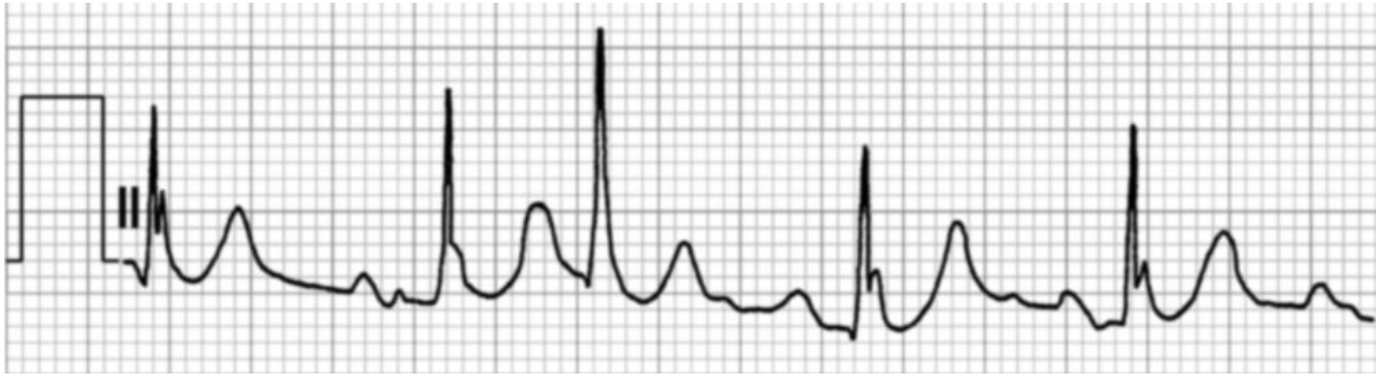
Diagnosis: Atrial fibrillation, left posterior fascicular block associated with right bundle branch block, pseudo J-wave in the inferior leads: end-QRS notching in II, and end-QRS slurring in III.

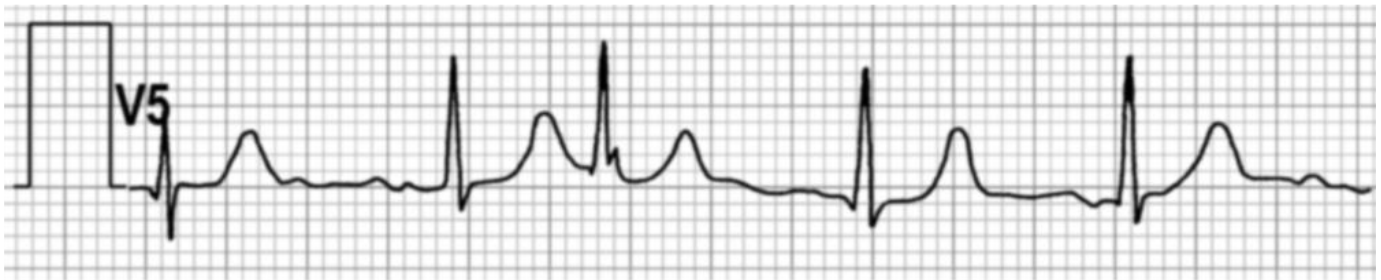


A J-wave-like deflection at the terminal portion of the QRS in a patient with intraventricular conduction delay



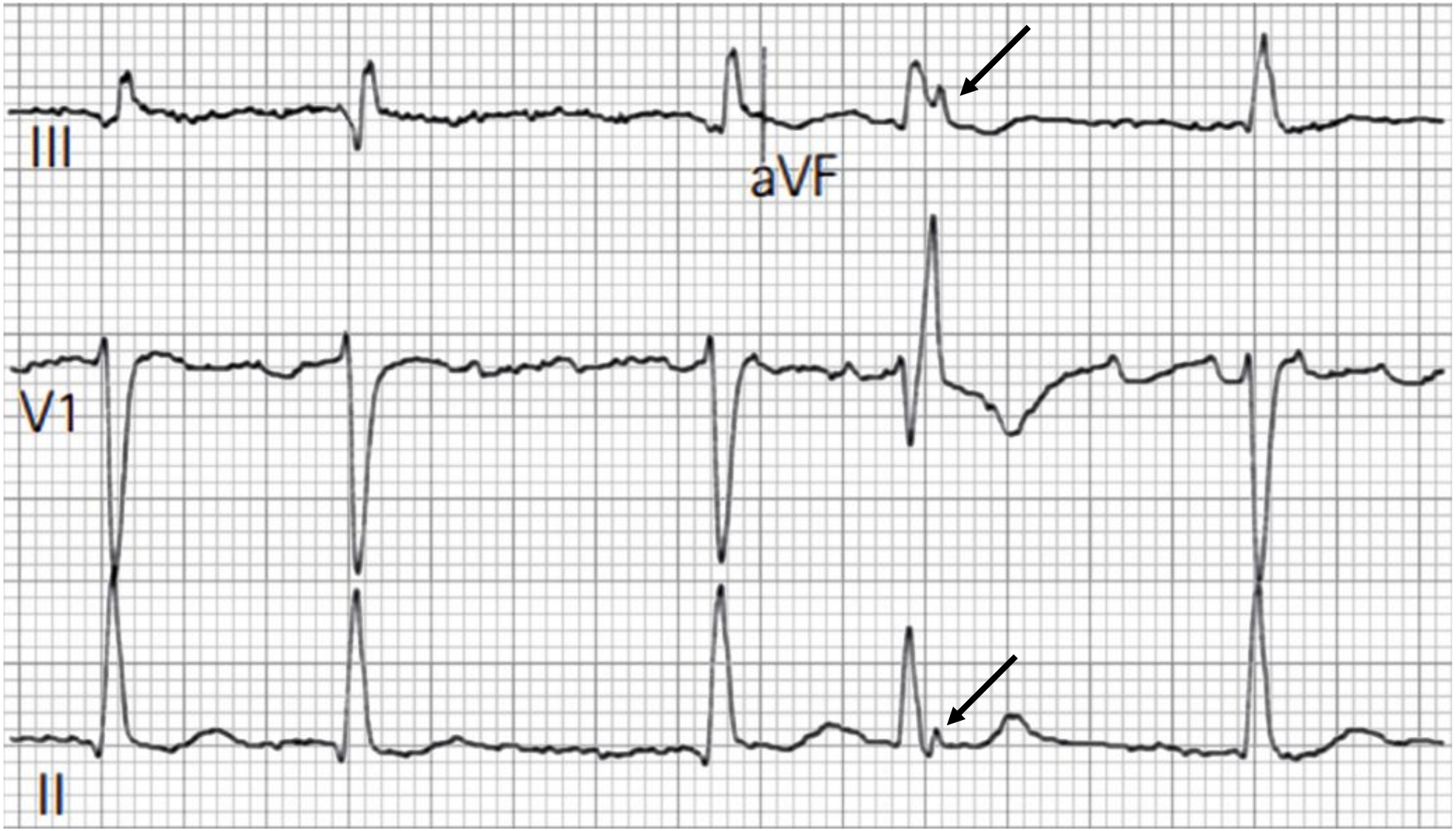






Two examples of increased pseudo J wave amplitude after shorter RR intervals

RBBB – Pseudo J wave in inferior leads



An example of right bundle branch block can cause pseudo J waves in inferior leads. IVCD: intraventricular conduction delay, RBBB: right bundle branch block.

Similarities between BrS and ERS

Both entities display several clinical similarities, suggesting similar pathophysiology. (**Priori 20013; Antzelevitch 2016**)

1. **Gender:** males predominance in both syndromes. The possible mechanism(s) is testosterone modulation of ion currents underlying the epicardial AP notch
2. **Average age of first event:** the highest incidence of VF or SCD occurs in the third or fourth decade of life. In both syndromes
3. **Heart rate:** the appearance of accentuated J waves and ST segment elevation are generally associated with bradycardia or pauses, and VF events have been proposed to occur mostly during sleep or at a low level of physical activities.
4. **Predominant moment of event occurrence:** VF/PVT often occurs during sleep or at a low level of physical activity. Additionally, VT/VF are triggered by premature ventricular contractions with short coupled intervals triggered by phase 2 reentry
5. **Dynamicity of ECG repolarization:** It is high in both entities. This is caused autonomic modulation of ion channel currents underlying early phases of the epicardial AP
6. **Response to quinidine:** ERS and BrS also share similarities with respect to the response to pharmacological therapy, e.g. quinidine. Inhibition of Ito and possible vagolytic effect and bepridil by inhibition of Ito and possible vagolytic effect. In ERS therapeutic efficacy of quinidine is accepted, there is no consensus on dose. In this report, we used graded doses and found that .1 g/d may be required.
7. **Response to isoproterenol denopamine and milrinone:** Ameliorative response caused by increased ICa and faster heart rate
8. **Genetic mutation shared BrS and ER Syndrome shared several gene mutations**

Similarities between early repolarization pattern and Brugada syndrome

- Both are much more frequent in the male gender.
- Both are predominantly observed in young adults.
- Both do not present apparent structural heart disease.
- Both frequently present conduction disorder patterns in the right His system.
- Both may present discrete QRS interval widening. In the ERP of athletes' hearts, a mild increase in QRS duration is observed (100 ms to 110 ms); in 15% of the cases caused by physiological hypertrophy of the RVOT, which is translated in the ECG into the appearance of final r' wave that does not exceed 5 mm and that is lower than the preceding S in the same lead: rSr'(196). In BrS, as we have already mentioned, there may be a selective increase of QRS duration in the right precordial leads (Pitzalis 2003).
- Both may display saddleback pattern quite frequently.
- Both may reverse ventricular repolarization pattern during stress test.
- Both improve ventricular repolarization with endovenous isoproterenol, probably because the drug reduces repolarization dispersion which triggers VF events (Hiss 1962).
- Both have a shortening of phase 2 action potential due to electrophysiological substrate, in the ventricular epicardium thickness by intensification of the notch in phase 1, mediated by the *I*to channel (Yan 1996).
- Both may have modification in the *I*to and $I_{Ca}{}^{++}{}_{-L}$ channels by electrophysiological substrate, which explains the J point and ST segment elevation causing intensification of the notch in phase 1 and decrease in phase 2 duration in the ventricular epicardium thickness (Antzelevitch 2000).
- Both may affect in different degrees, ventricular repolarization in the right precordial leads (Bianco 2001) as well as in the lateral wall (V4-V6) and inferior leads I, II, and III (atypical forms of BrS).

Similarities between Brugada and early repolarization syndrome and possible underlying mechanisms

	Brugada Syndrome	Early Repolarization Syndrome	Possible Mechanism(s)
Male predominance	Yes (>75%)	Yes (>80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	30-50	30-50	
Associated with mutations or rare variants in KCNJ8, CACNA1C, CACNB2, CACNA2D, SCN5A, ABCC9, SCN10A	Yes	Yes	Gain of function in outward currents (IK-ATP) or loss of function in inward currents (ICa or INa)
Relatively short QT intervals in subjects with Ca channel mutations	Yes	Yes	Loss of function of ICa
Dynamicity of ECG repolarization	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VF often occurs during sleep or at a low level of physical activity	Yes Yes	Yes Yes	Higher level of vagal tone and higher levels of Ito at the slower heart rates
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
Ameliorative response to quinidine and bepridil	Yes	Yes	Inhibition of Ito and possible vagolytic effect
Ameliorative response to isoproterenol denopamine and milrinone	Yes	Yes	Increased ICa and faster heart rate

	Brugada Syndrome	Early Repolarization Syndrome	Possible Mechanism(s)
Ameliorative response to cilostazol	Yes	Yes	Increased ICa, reduced Ito and faster heart rat
Ameliorative response to pacing	Yes	Yes	Reduced availability of Ito due to slow recovery from inactivation
Vagally mediated accentuation of ECG pattern	Yes	Yes	Direct effect to inhibit ICa and indirect effect to increase Ito (due to slowing of heart rate)
Effect of sodium channel blockers on unipolar epicardial electrogram	Augmented J waves	Augmented J waves	Outward shift of balance of current in the early phases of the epicardial AP
Fever	Augmented J waves	Augmented J waves	Accelerated inactivation of INa and accelerated recovery of Ito from inactivation
Hypothermia	Augmented J waves mimicking BrS	Augmented J waves	Slowed activation of ICa, leaving Ito unopposed. Increased phase 2 reentry but reduced pVT due to prolongation of APD(Morita et al 2007)

Genetic defects associated with Early Repolarization Syndrome and genetic mutation shared with BrS

	Locus	Gene/protein	Gene shared with BrS	Ion channel	% of probands
ERS1	12p11.23	KCNJ8, Kir6.1	BrS8	↑ $I_{K\text{-}ATP}$	Rare
ERS2	12p13.3	CACNA1C, $Ca_v1.2$	BrS3	↓ I_{Ca}	4.1%
ERS3	10p12.33	CACNB2b, $Ca_v\beta2b$	BrS4	↓ I_{Ca}	8.3%
ERS4	7q21.11	CACNA2D1, $Ca_v\alpha2\delta1$	BrS9	↓ I_{Ca}	4.1%
ERS5	12p12.1	ABCC9, SUR2A	Brs13	↑ $I_{K\text{-}ATP}$	Rare
ERS6	3p21	SCN5A, $Na_v1.5$	BrS1	↓I_{Na}	Rare
ERS7	3p22.2	SCN10A, $Na_v1.8$	BrS17	↓ I_{Na}	Rare
ERS8	1p13.2	KCND3, $K_v4.3$	BrS10	↑I_{TO}	Rare
ERS9 or IVF	7q36.2	DPP6/Dipeptidyl aminopeptidase-like protein 6	Familial idiopathic VF (1)	↑I_{TO}	Rare
ERS10 (2) (2020)	3p24	GPD1L/ glycerol-3-phosphate dehydrogenase 1-like	BrS2 (3) 2007 + SIDS (4) 2007	↓ I_{Na}	Rare

Alders, M., et al, 2009.; Jun Fan,et al 2020.; London B,et al.2007.; Van Norstrand DW, et al.2007)

Genes associated with Brugada syndrome and Early Repolarization Syndrome				
Gene/ OMIM	**BrS**	**ERS**	**Protein /Locus**	**Functional effect/author**
SCN5A/ # 601144	Yes BrS1	Yes	Cardiac sodium channel alpha subunit (Nav1.5) / Locus on chromosome 3p21	Loss of function, reduced Na1 current (**Chen Q et al 1998**). 20-30% of all cases.
GPD1-L/ # 911778	Yes BrS2	No	Glycerol-6-phosphatedehydrogenase / Locus on chromosome 3p22.3	Loss of function, reduced Na1 current (**London B et al 2007**)
CACNA1c/ # 114205	Yes BrS3	Yes	L-type calcium channel α subunit (Cav1.2) / Locus on chromosome 12p13.3	Loss of function, reduced Ca21 current (**Antzelevitch C et al 2007**)
CACNB2/ 114205	Yes BrS4	Yes	L-type calcium channel β subunit (Cav1.2) / Locus on chromosome 10p12.33-p12.31	Loss of function, reduced Ca21 current(**Antzelevitch C et al 2007**)
SCN1B/ # 612838	Yes BrS5	No	Cardiac sodium channel beta1 subunit /19q13.1	Loss of function, reduced Na1 current (**Watanabe H et al 2008**)
KCNE3/ # 613119	Yes BrS6	No	Transient outward current beta subunit-transient outward current /11q13-14	Gain of function, increased K1 Ito current (**Delpon E et al 2008**)
SCN3B/ # 6081214	Yes BrS7	No	Cardiac sodium channel beta-3 subunit / 11q23.3	Loss of function, reduced Na1 current (**Hu D et al** 2009)
HCN4 # 613123	Yes BrS8	Yes	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4/ Locus on chromosome 15q24.1	↑$\mathbf{I_{K=ATP}}$ 2% (**Ueda K, et al 2009**.) (**Crotti, L, et al.2012**) (**Barajas-Martinez H, et al. 2012**)
KCND3 # 616399	Yes BrS9	Yes	Potassium voltage-gated channel subfamily D member 3 or K_v4.3/Locus on chromosome 1p13.	Transient outward current or ↑Ito gain-of-function (**Giudicessi, J. R., et al 2011**.)

Gene/ OMIM	BrS	ERS	Protein /Locus	Functional effect/author
CACNA2D1	Brs 10		Cavα2δ−1/Locus on chromosome 7q21-22	Loss-of-function LOF
RANGRF	BrS11		MOGI/17p13.1	Loss-of-function LOF Rare (Olesen MS, et al, 2011)
KCNE5(*KCNE1L*)	BrS12		MiRP4/Locus on chromosome Xq22.3	Kv4.3, I_{to} Gain-of-function (GOF) (Ohno S, et al, 2011)
KCND3	BrS13? Or BrS9		Potassium Voltage-gated Channel, Shal-related Subfamily, Member 3/Locus on chromosome: 1p13.2	↑I_{to} Gain-of-function (GOF) (Postma,A.V 2000) (Giudicessi, J. R et al 2012)
HCN4	BrS14		Hyperpolarization-activated Cyclic Nucleotide-gated Potassium Channel 4 /Locus on chromosome 15q24.1	GOF ↑IK^+Rare (Crotti, L, et al 2012)
SLMAP	BrS15 and Cerebral Cavernous Malformations, 3		Sarcolemma Menbrane Associated Protein /Locus on chromosome 3p21.2-p14.3	↓INa^+modulating the intracell, ular trafficking of hNav1.5 channel. (Ishikawa T, et al. 2012)
TRPM4	Br16		NSCCa/Locus on chromosome 19q13.33	Abnormal resting potential. Rare (Hui Liu, et al 2013)

Gene/ OMIM	BrS	ERS	Protein /Locus	Functional effect/author
SCN2B * 601327	BrS17		Sodium Voltage-gated Channel, Beta Subunit 2Navβ3/Locus on chromosome 11q23.3	Loss-of-function(LOF)↓INa^+ Rare (Riuro, H et al 2013)
SCN10A * 604427	BrS18		Sodium Voltage-gated Channel, Alpha Subunit 10Nav1.8/Locus on chromosome 3p22.2	↓INa^+ Loss-of-function(LOF) Rare (Fukuyama M 2016)
HEY2 * 604674	Yes BrS19	No	Hes related family bHLH transcription factor with YRPW motif 2Nav1.5/Locus on chromosome 6q22.31	Loss-of-function(LOF) (Christiaan C Veerman, et al 2017)
PKP2	Yes BrS20	No ARV C9	Plakophilin-2 PKP2/Locus on chromosome 12p11.21 12p13	Loss-of-function (LOF) ↓INa^+ (**Cerrone M et al, 2013, 2014**)
ABCC9 * 601439	Yes Brs 21	Yes	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9 *SUR2A* (sulfonylurea receptor subunit 2 A), IK-ATP)/ /Locus on chromosome *12p12.1*	Gain-of-function GOF/ (**Hu D et al 2014**)

Differences between the ERS and BrS

1) The region of the heart most affected (right ventricular outflow tract in BrS vs. left ventricular inferior region in ERS
2) Leads affected:
   A. BrS: right precordial leads
   B. ER syndrome II, III a, VF, V4, V5, V6; I, aVL, Both: inferolateral

3) The presence of (discrete) structural abnormalities in BrS and not perhaps in ERS;
4) Higher incidence of late potentials in signal-averaged ECGs in BrS vs. ERS,
5) Effect of sodium channel blockers on surface ECG: Increased J-wave manifestation in BrS and Reduced J-wave manifestation in ER syndrome. The reduction of J wave in the setting of ER syndrome is thought to be due largely to prolongation of QRS. Accentuation of repolarization defects predominates in BrS, whereas accentuation of depolarization defects predominates in ERS.
6) Higher prevalence of atrial fibrillation in BrS vs. ERS.
7) Structural changes, including mild fibrosis and reduced expression of Cx43 in RVOT or fibrofatty infiltration in cases of AC. Imaging studies have also revealed wall motion abnormalities and mild dilation in the region of the RVOT in BrS. On the other hands in ER syndrome structural changes are unknow.

Differences between Brugada and early repolarization syndromes and possible underlying mechanisms

	Brugada Syndrome	Early Repolarization Syndrome	Possible Mechanism(s)
Region most involved	RVOT wall	Inferior LV R	Higher levels of Ito and/or differences in conduction
Leads affected	V1–V3	II, III a, VF, V4, V5, V6; I, aVL, Both: inferolateral	
Incidence of late potential in signal averaged ECG	Higher	Lower	
Prevalence of atrial fibrillation	Higher	Lower	
Effect of sodium channel blockers on surface ECG	Increased J-wave manifestation	Reduced J-wave manifestation	Reduction of J wave in the setting of ER is thought to be due largely to prolongation of QRS. Accentuation of repolarization defects predominates in BrS, whereas accentuation of depolarization defects predominates in ERS.
Structural changes, including mild fibrosis and reduced expression of Cx43 in RVOT or fibrofatty infiltration in cases of AC. Imaging studies have also revealed wall motion abnormalities and mild dilation in the region of the RVOT.	Higher in some forms of the syndrome	Unknown	Some investigators have hypothesized that some of these changes may be the result of, rather than the cause of the BrS substrate, which may create a hibernation-like state due to loss of contractility in the RVOT secondary to loss of the AP dome.

AP = action potential; APD = action potential duration; BrS = Brugada syndrome; ERS = early repolarization syndrome; RVOT =right ventricular outflow tract; PVC=premature ventricular contraction; pVT=polymorphic ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Genetic basis of Brugada syndrome

Gene	Frequency	Functional abnormalities
INa^+channel dysfunction		
SCN5A	20-30%	LOF $\downarrow INa^+$
SCN10A	Rare	LOF $\downarrow INa^+$
SCN1B	Rare	LOF $\downarrow INa^+$
SCN2B	Rare	LOF $\downarrow INa^+$
SCN3B	Rare	LOF $\downarrow INa^+$
GPD1L	Rare	LOF $\downarrow INa^+$
MOGI1	Rare	LOF $\downarrow INa^+$
SLMAP	Rare	LOF $\downarrow INa^+$
PKP2	Rare	LOF $\downarrow INa^+$

Gene	Frequency	Functional abnormalities
INa^+channel dysfunction		
SCN5A	20-30%	LOF $\downarrow INa^+$
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SCN2B	Rare	LOF $\downarrow INa^+$
SCN3B	Rare	LOF $\downarrow INa^+$
GPD1L	Rare	LOF $\downarrow INa^+$
MOGI1	Rare	LOF $\downarrow INa^+$
SLMAP	Rare	LOF $\downarrow INa^+$
PKP2	Rare	LOF $\downarrow INa^+$

Gene	Yes	No	Protein/lLocus	Functional deffect
KCNH2	Yes	No	Rapid component of the cardiac delayed rectifier current	Increased repolarizing current (gain of function)
KCNJ8	Yes	Yes	Acetylcholine-dependent potassium current / 12p11.23	Incomplete closing of the ATP-sensitive potassium channels
CACNA2D1	Yes	No	L-type calcium channel delta 2 subunit	Loss of function, reduced Ca21 current
RANGRF	Yes	No	RAN protein GTP releasing factor	Unknown (possible effect on sodium current)
KCNE5	Yes	No	Potassium channel β 5 subunit transient outward current	Gain of function, increased K1 Ito current
KCND3	Yes	No	SHAL potassium channel isoform 3-transient outward current	Gain of function, increased K1 Ito current
HCN4	Yes	No	Hyperpolarization activated potassium channel (If)	No functional studies available
SLMAP	Yes **BrS 12**	No	Sarcolemmal membrane–associated protein	Reduced Na^+current (impaired NaV 1.5 trafficking) **↓INa. Rare** Ishikawa T,et al. 2012)
TRPM4	Yes	No	Calcium-activated cationic channel subfamily M isoform 4	Reduced sodium current
SCN2B	Yes	No	Cardiac sodium channel Beta 2 subunit	Loss of function, reduced Na1 current
SCN10A	Yes	Yes	Voltage-gated sodium channel alpha subunit 10	Reduced NaV1.8 current
MOG1	Yes **BrS 11**	No	Guanine nucleotide release factor, control of NaV1.5 trafficking Locus **17p13.1**	Loss of function, **↓INa^+** reduced Na current (**Olsen MS, et al. 2011**) Rare.
TRPM4	Yes	No	Calcium-activated cationic channel subfamily M isoform 4	Reduced sodium current
SCN2B	Yes	No	Cardiac sodium channel Beta 2 subunit	Loss of function, reduced Na1 current

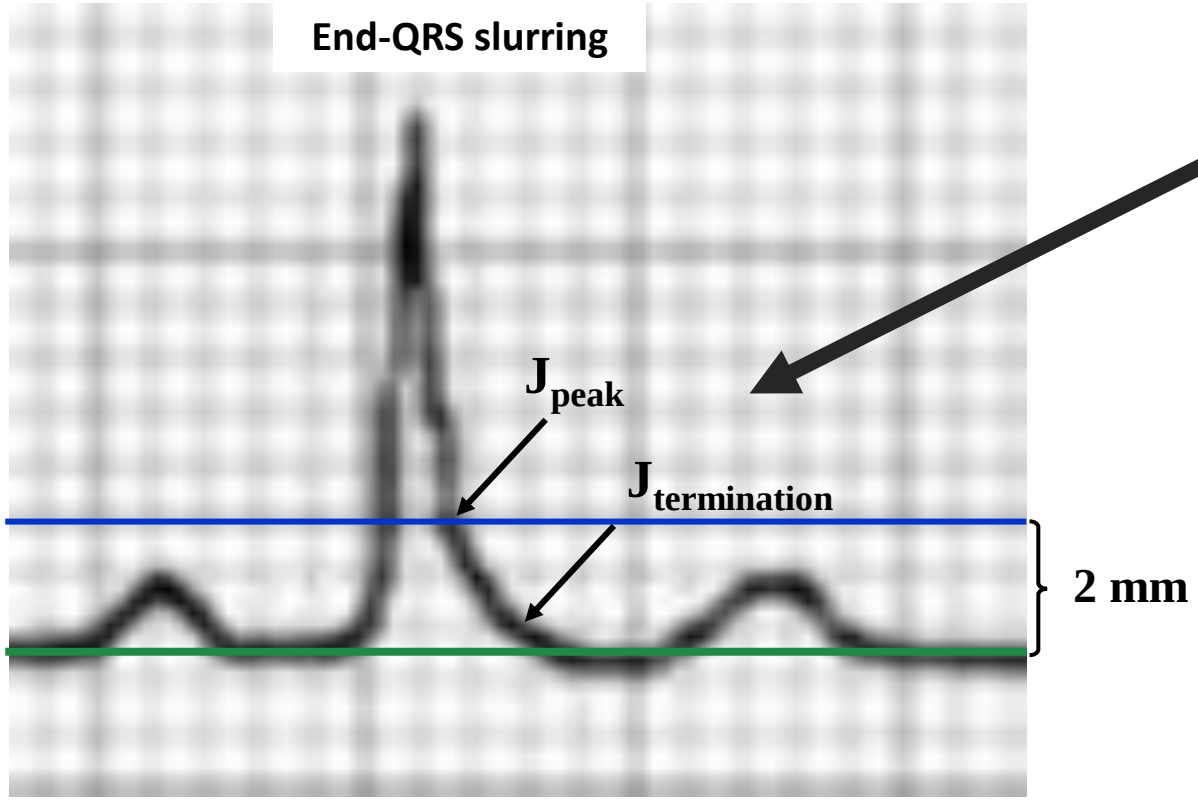
The cardiac potassium K^+ channels (Crotti L et al 2020)

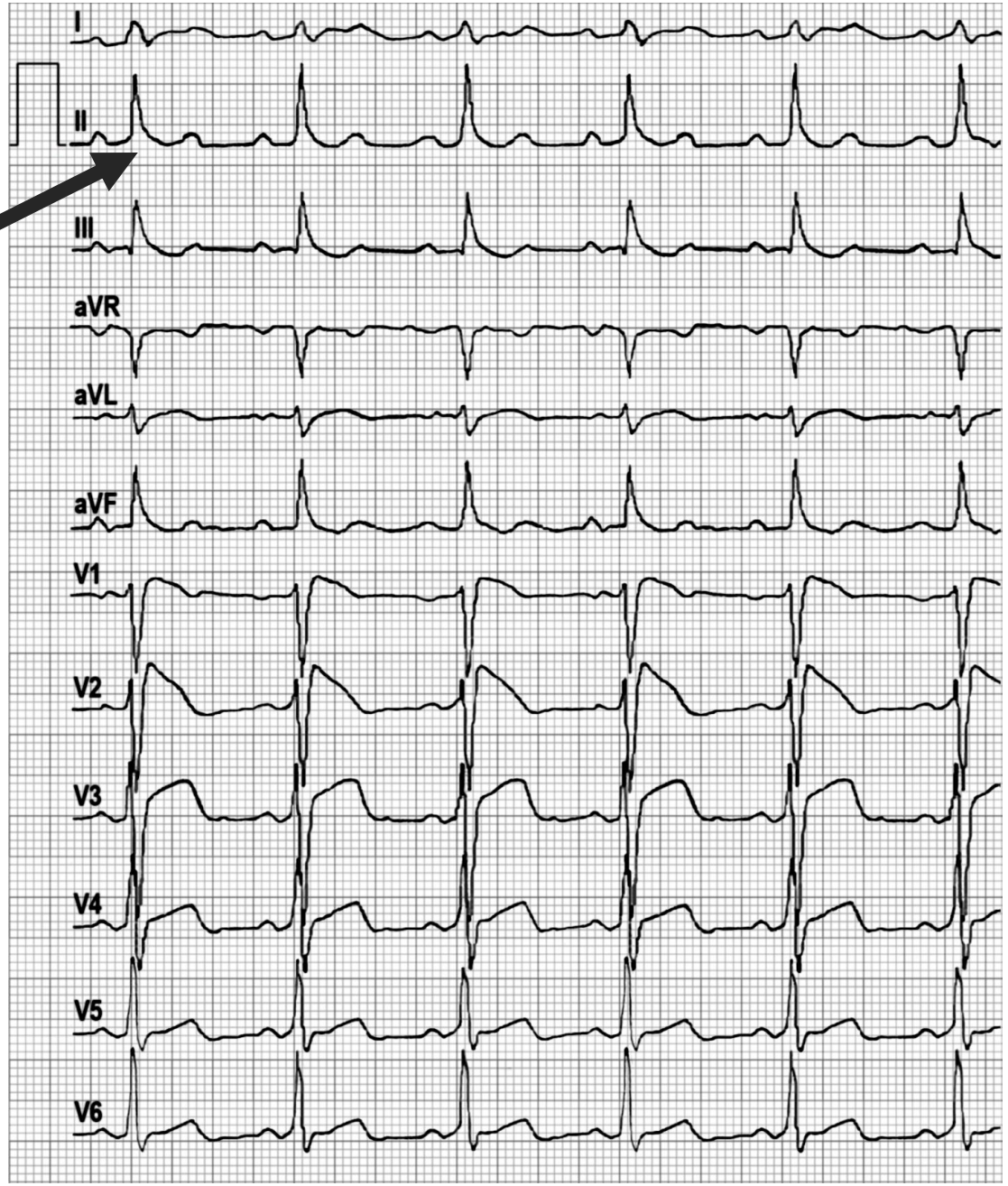
Cardiac K^+ channels are membrane-spanning proteins that allow the passive movement of K^+ ions across the cell membrane along its electrochemical gradient. They regulate the resting membrane potential, the frequency of pacemaker cells and the shape and duration of the cardiac action potential. Normal K^+ channel function is essential to maintain electrical stability in the heart. Gene mutations that alter the assembly, trafficking, turnover or gating of cardiac K^+ channels can cause LQTS, SQTS, J-wave syndromes and AF.

1. **Delayed Rectifier Potassium(K^+) Currents/Channels**
   a) The rapidly activating component of the delayed rectifier K^+ current, I_{Kr}, rapid-rates of activation onset. Name: Kv11.1 (HERG), Gene:KCNH2, Human Crhomosomal location:7q35–36
   b) The slowly activating component of the delayed rectifier K^+ current, I_{Ks} , slow-rates of activation onset: Name: Kv7.1 (KVLQT1), Gene: KCNQ1. Human Crhomosomal location 11p15.5
   c) The ultrarapid (I_{Kur}) ultra-rapid rates of activation onset. Name:KCNA5, Gene:12p13.3, Human Crhomosomal location: 12p13.3
2. **Inward rectifying K^+ channels**
   a) I_{K1}, "The transient outward current". Name: Kir2.1 (IRK1), Gene: KCNJ2, Human Crhomosomal location: 17q23.1–24.2
   b) I_{KATP} ATP-sensitive K^+ channels, K_{ATP} Name: Kir6.2 (BIR), Gene:KCNJ11, Human Crhomosomal location:11p15.1
   c) I_{KAch} The acetylcholine-activated K^+ current, I_{KAch} Name: Kir3.1 (GIRK1), Gene: KCNJ3, Human Crhomosomal location: 2q24.1 11p15.1

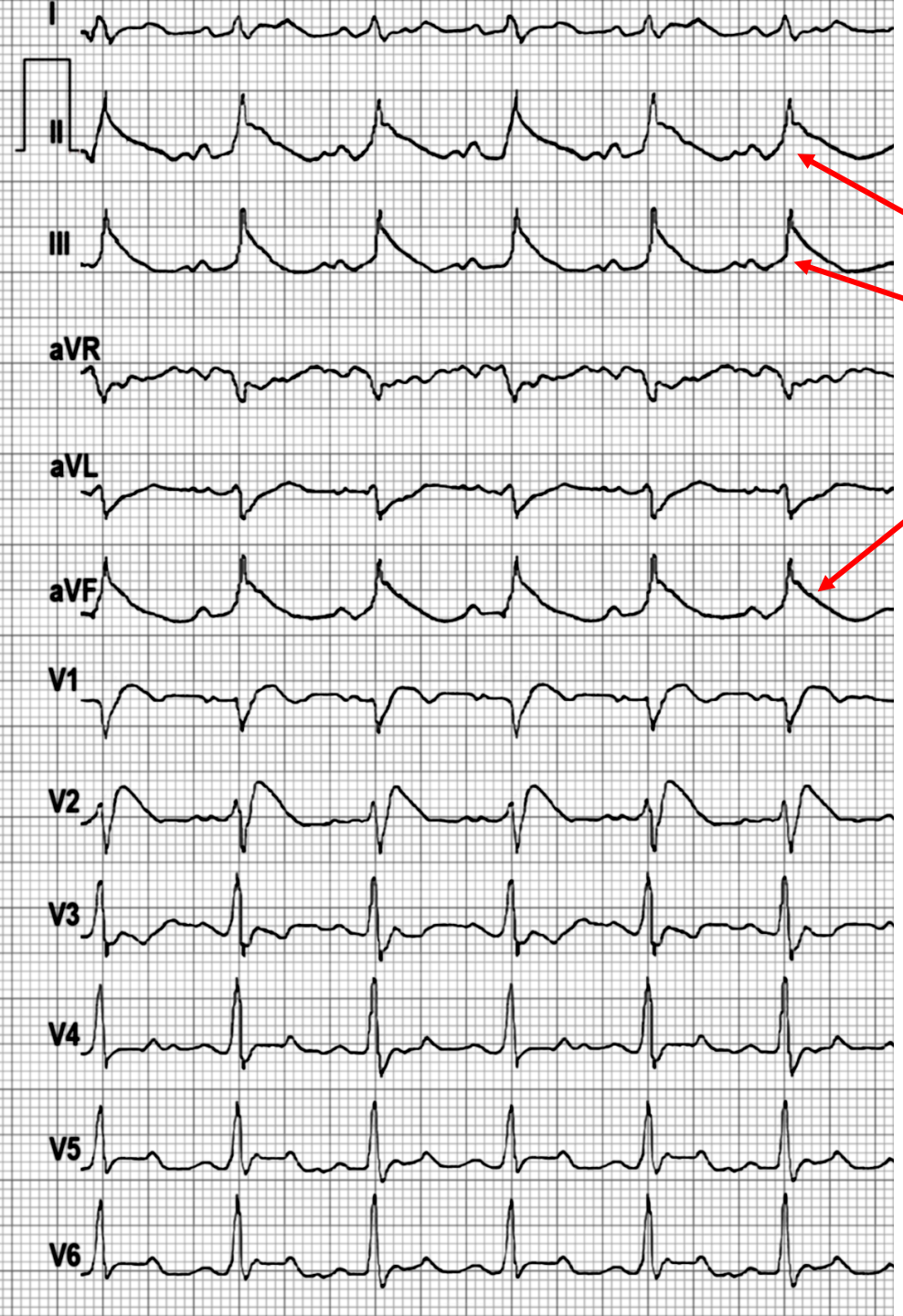
3. **Transient outward currents**
   - ***I***$_{tof}$ ***I***$_{to1}$ 4-aminopyridine (4-AP)-sensitive, calcium-independent K^+ current (I_{to1}) is rapidly activated and inactivated in response to depolarization
   - I_{to2} ***I***$_{to2}$ 4-AP-insensitive, Ca^{2+}-activated Cl^- or K^+ current (I_{to2})
4. **Intracellular cation activated currents**
   - IKNa,
   - IKCa) and at least one
   - “background leak” current (IKleak)

Before ajmaline test

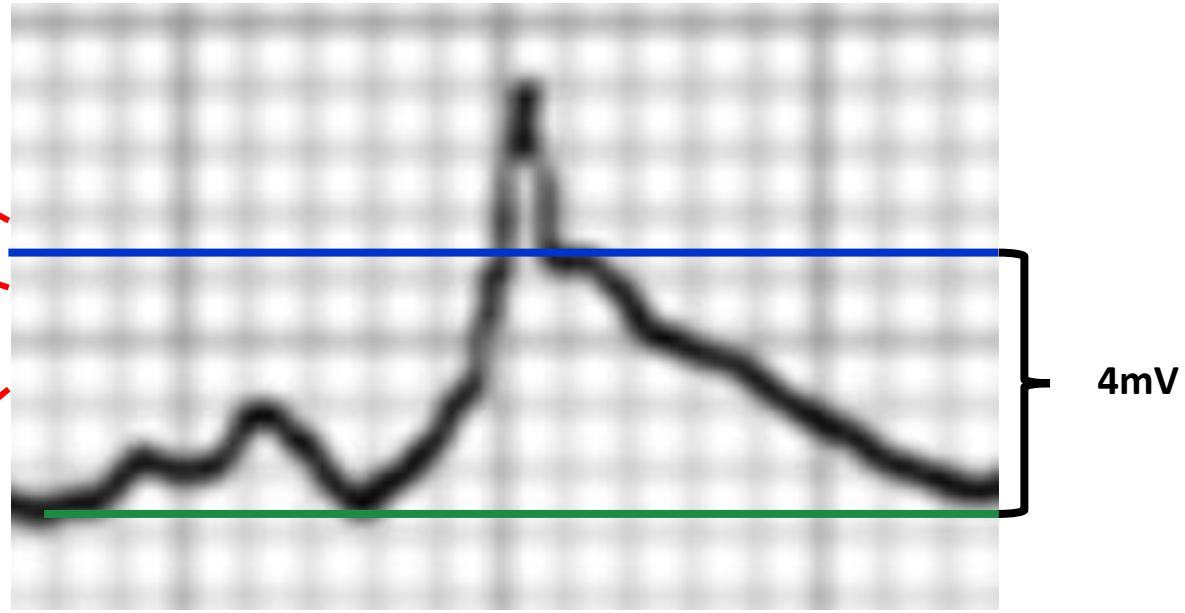


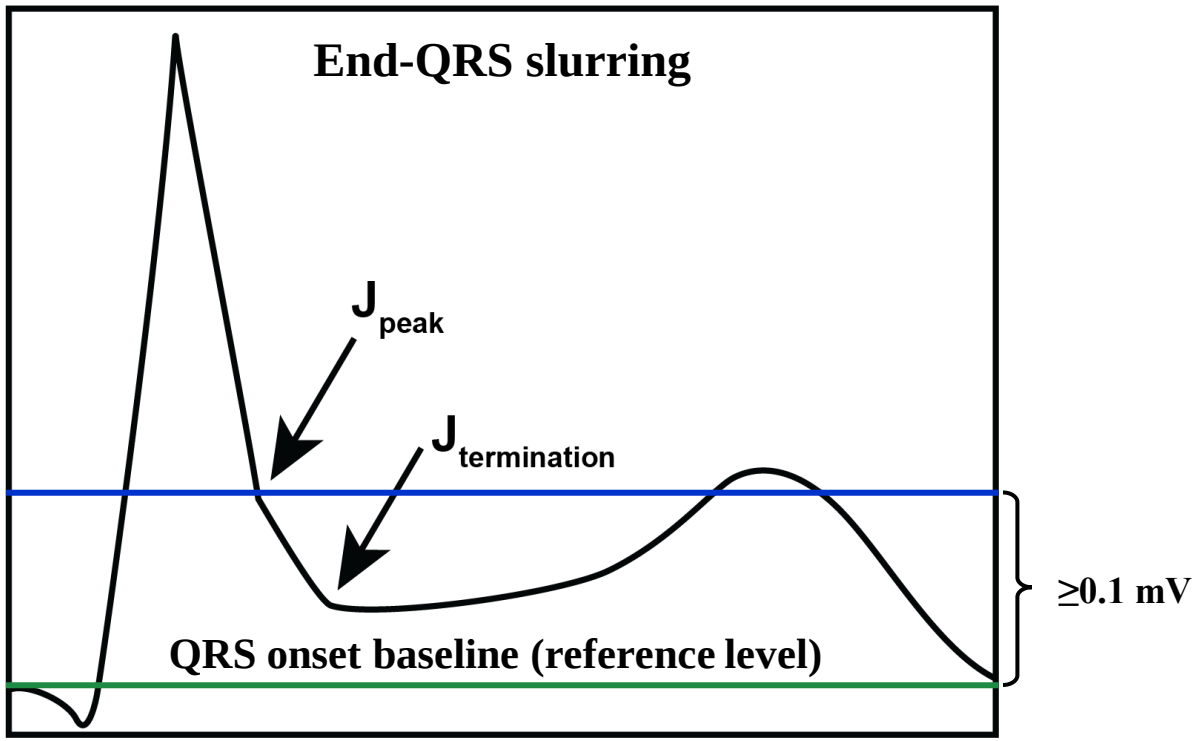


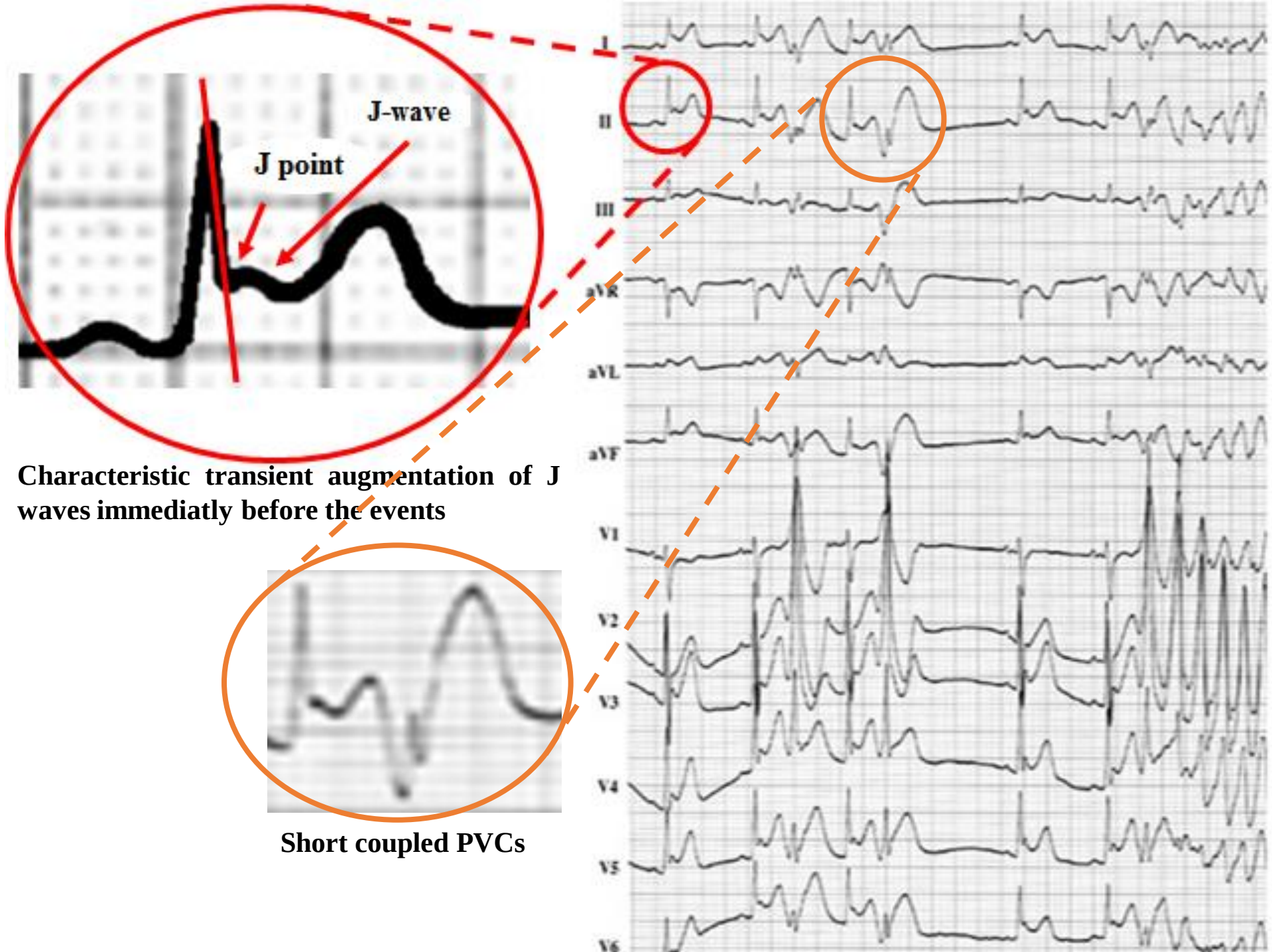
Type 1 Brugada pattern and slurring J-wave insinuation in the inferior leads (before ajmaline injection).



After ajmaline test

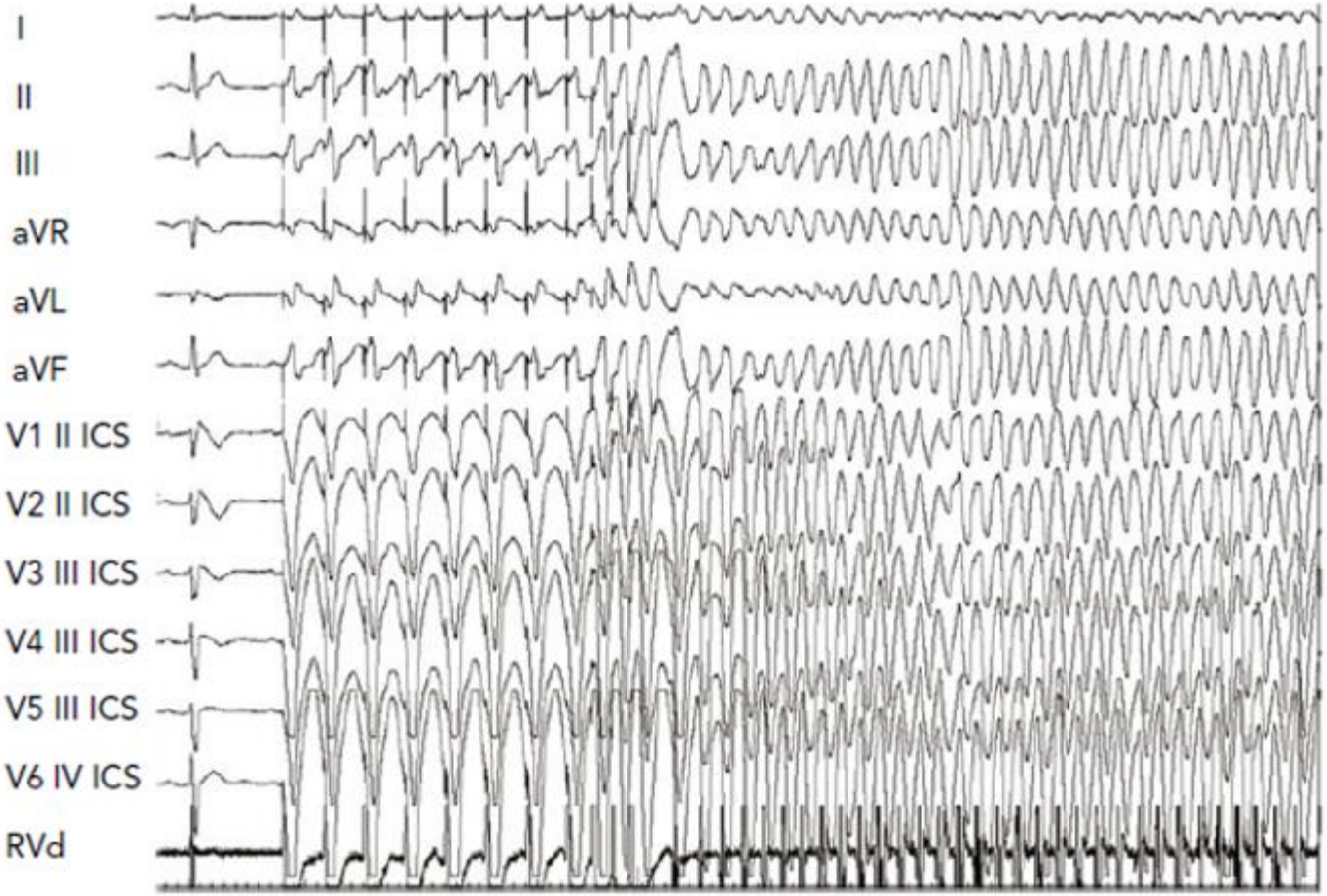


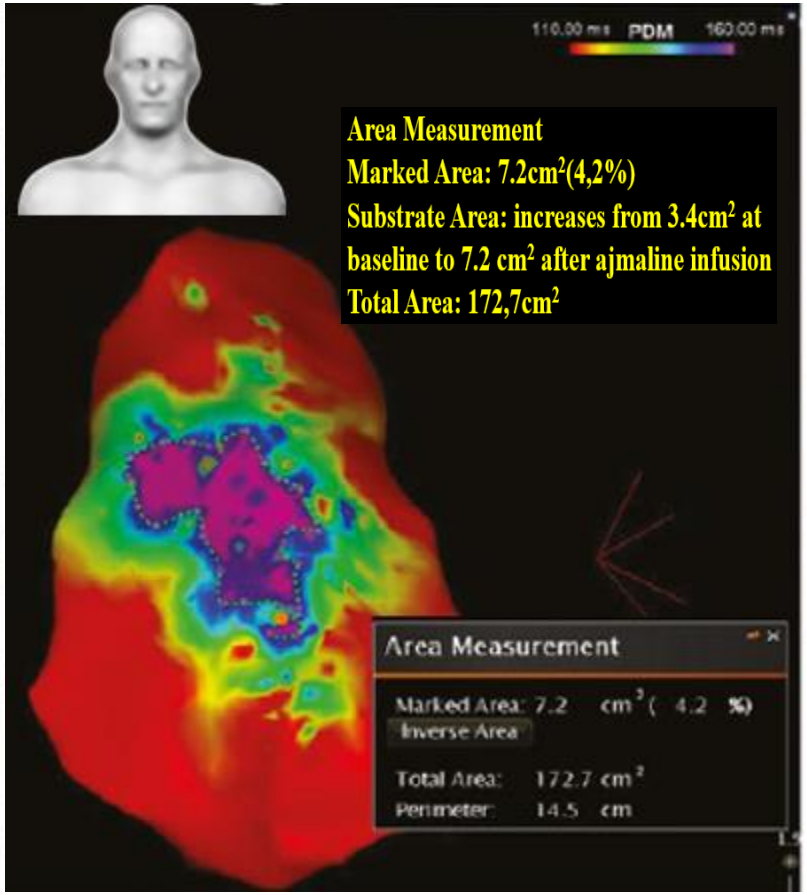


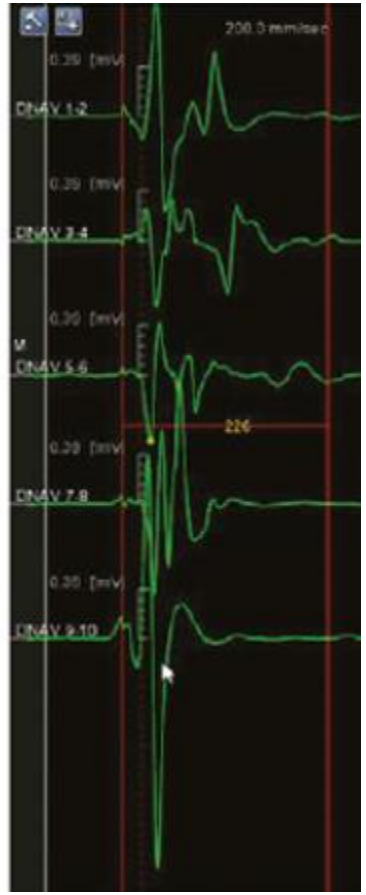


Characteristic transient augmentation of J waves immediatly before the events

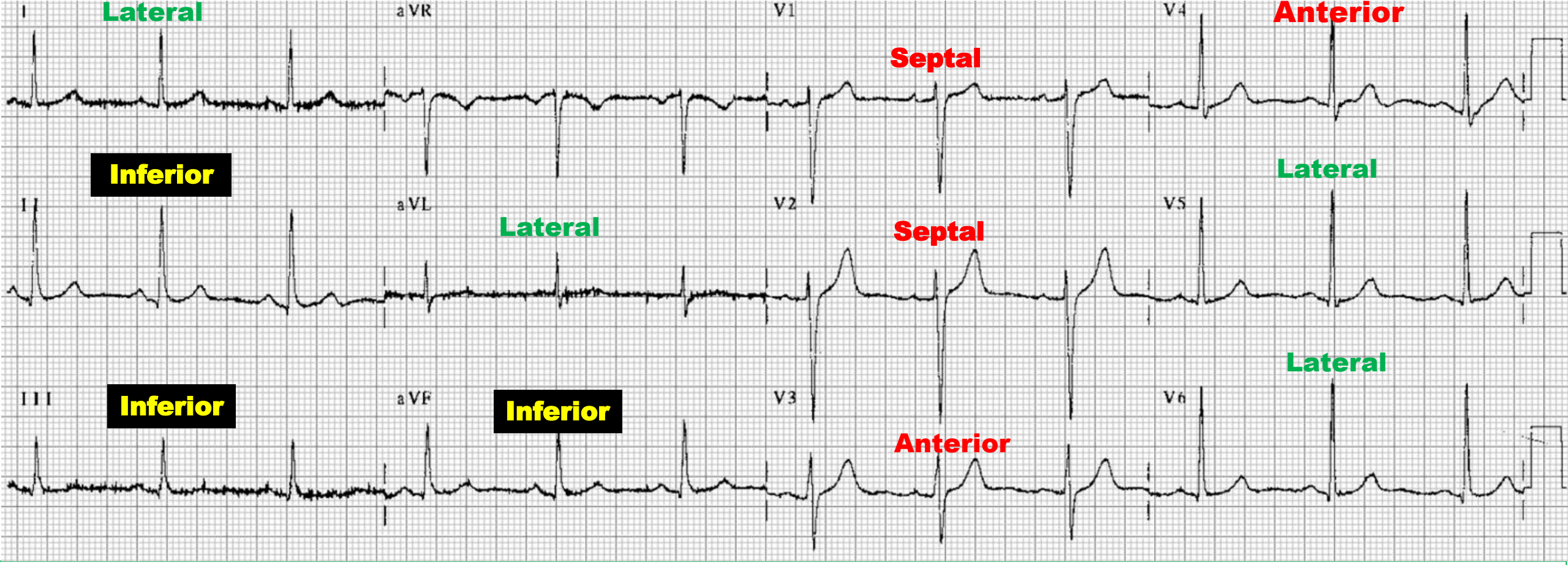
Short coupled PVCs







Type 1 Brugada ECG pattern followed by sustained polymorphic VT degenerating to VF induced by ajmaline. Concomitantly, substrate increases from 3.4 cm^2 at baseline to 7.2 cm^2 after ajmaline infusion Additionally, the duration of prolonged fragmented potentials also increased form 145-226 ms.



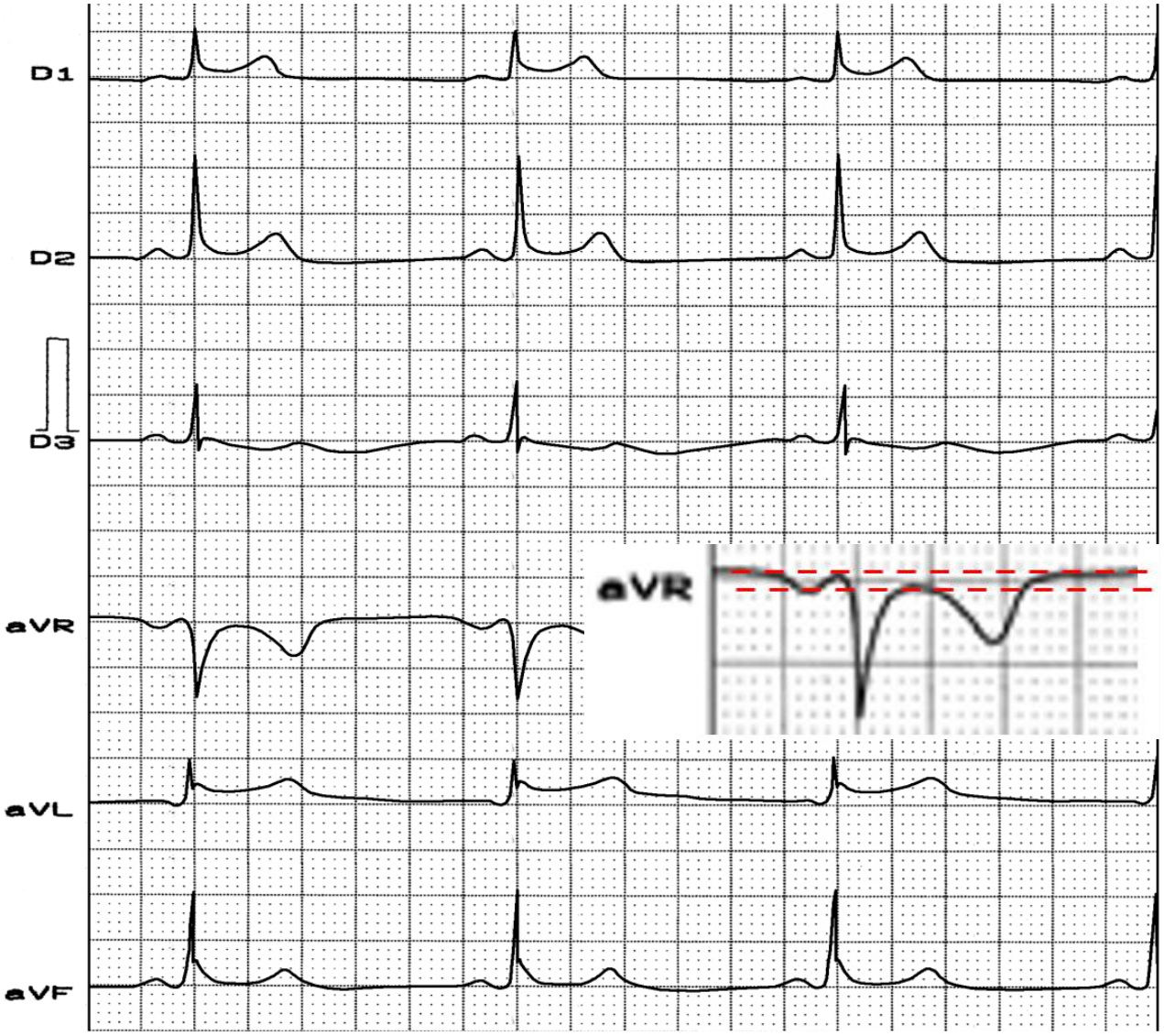
1) **Type 1:** which displays an early repolarization pattern(ERP) predominantly in the lateral precordial leads, is prevalent among healthy young male athletes
2) **Type 2:** An ERP in **inferior** and **lateral** leads: It is associated with **moderate** level of risk
3) **Type 3:** An ERP in **inferior**, **lateral** and **right precordial leads (Anteroseptal)**: Type 3 **highest** risk

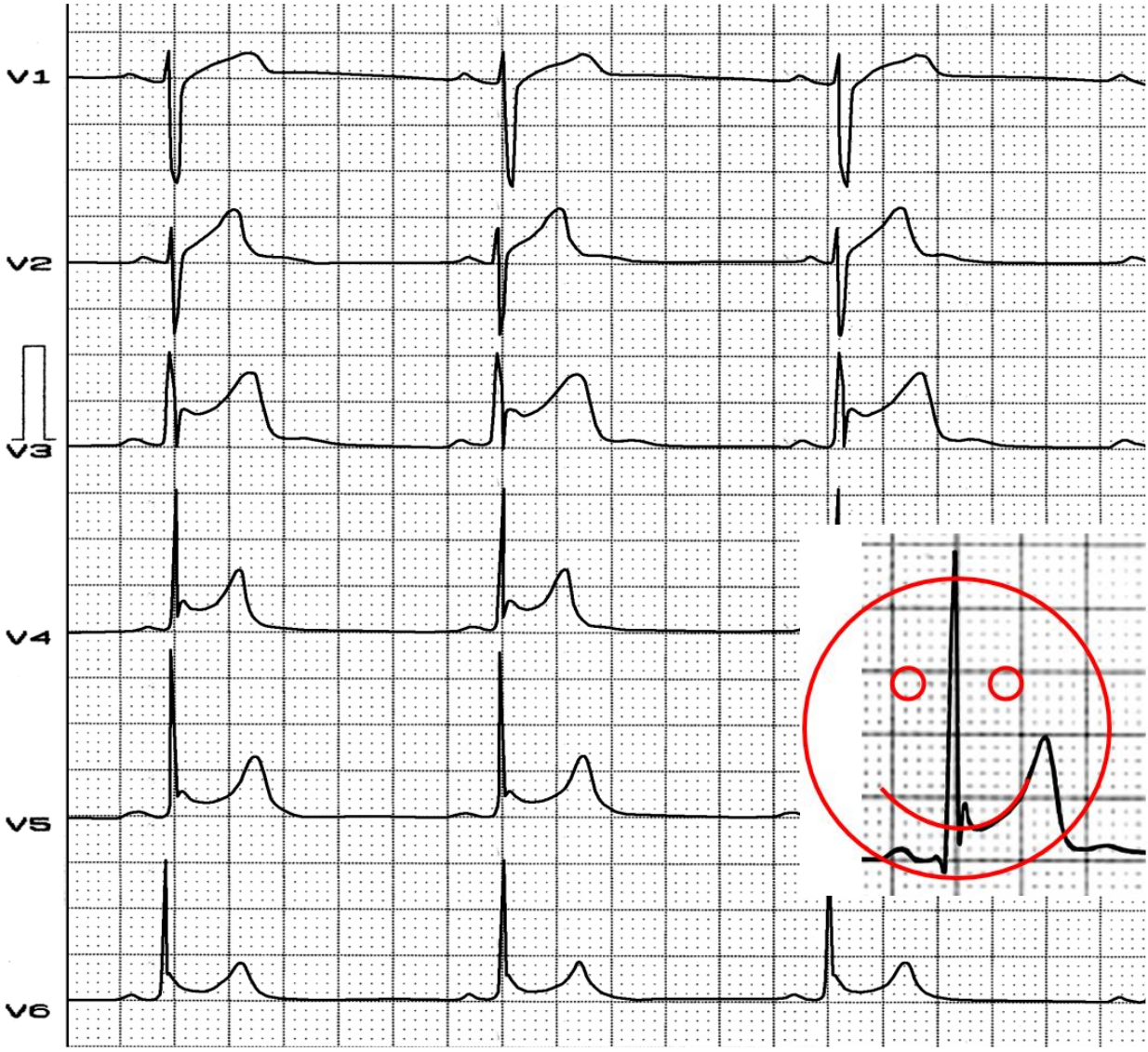
I Lateral	aVR	V1 Septal	V4 Anterior
II Inferior	aVL Lateral	V2 Septal	V5 Lateral
III Inferior	aVF Inferior	V3 Anterior	V6 Lateral

Similarities between early repolarization pattern and Brugada syndrome

- Both are much more frequent in the male gender.
- Both are predominantly observed in young adults.
- Both do not present apparent structural heart disease.
- Both frequently present conduction disorder patterns in the right His system.
- Both may present discrete QRS interval widening. In the ERP of athletes' hearts, a mild increase in QRS duration is observed (100 ms to 110 ms); in 15% of the cases caused by physiological hypertrophy of the RVOT, which is translated in the ECG into the appearance of final r' wave that does not exceed 5 mm and that is lower than the preceding S in the same lead: rSr'(196). In BrS, as we have already mentioned, there may be a selective increase of QRS duration in the right precordial leads (Pitzalis 2003).
- Both may display saddleback pattern quite frequently.
- Both may reverse ventricular repolarization pattern during stress test.
- Both improve ventricular repolarization with endovenous isoproterenol, probably because the drug reduces repolarization dispersion which triggers VF events (Hiss 1962).
- Both have a shortening of phase 2 action potential due to electrophysiological substrate, in the ventricular epicardium thickness by intensification of the notch in phase 1, mediated by the *I*to channel (Yan 1996).
- Both may have modification in the *I*to and $I_{Ca}{}^{++}{}_{-L}$ channels by electrophysiological substrate, which explains the J point and ST segment elevation causing intensification of the notch in phase 1 and decrease in phase 2 duration in the ventricular epicardium thickness (Antzelevitch 2000).
- Both may affect in different degrees, ventricular repolarization in the right precordial leads (Bianco 2001) as well as in the lateral wall (V4-V6) and inferior leads I, II, and III (atypical forms of BrS).

Name: DAS**; Age:** 24y**; Sex:** Male; **Race:** Black; **Weight:** 82 kg; **Height:** 1.91 m**; Biotype:** Athletic; **Profession:** professional basketball player





ECG diagnosis: sinus bradycardia, (HR 50 bpm). J point and ST segment with elevation > 4 mm in precordial leads from V_3-v_5 of superior concavity. Notch or slurring of terminal portion of the QRS complex (J point). ST segment elevation > 4 mm in precordial leads V_3, V_4 and V_5.
Conclusion: sinus bradycardia, early repolarization pattern. Typical ECG of early repolarization pattered in an athlete with bradycardia.

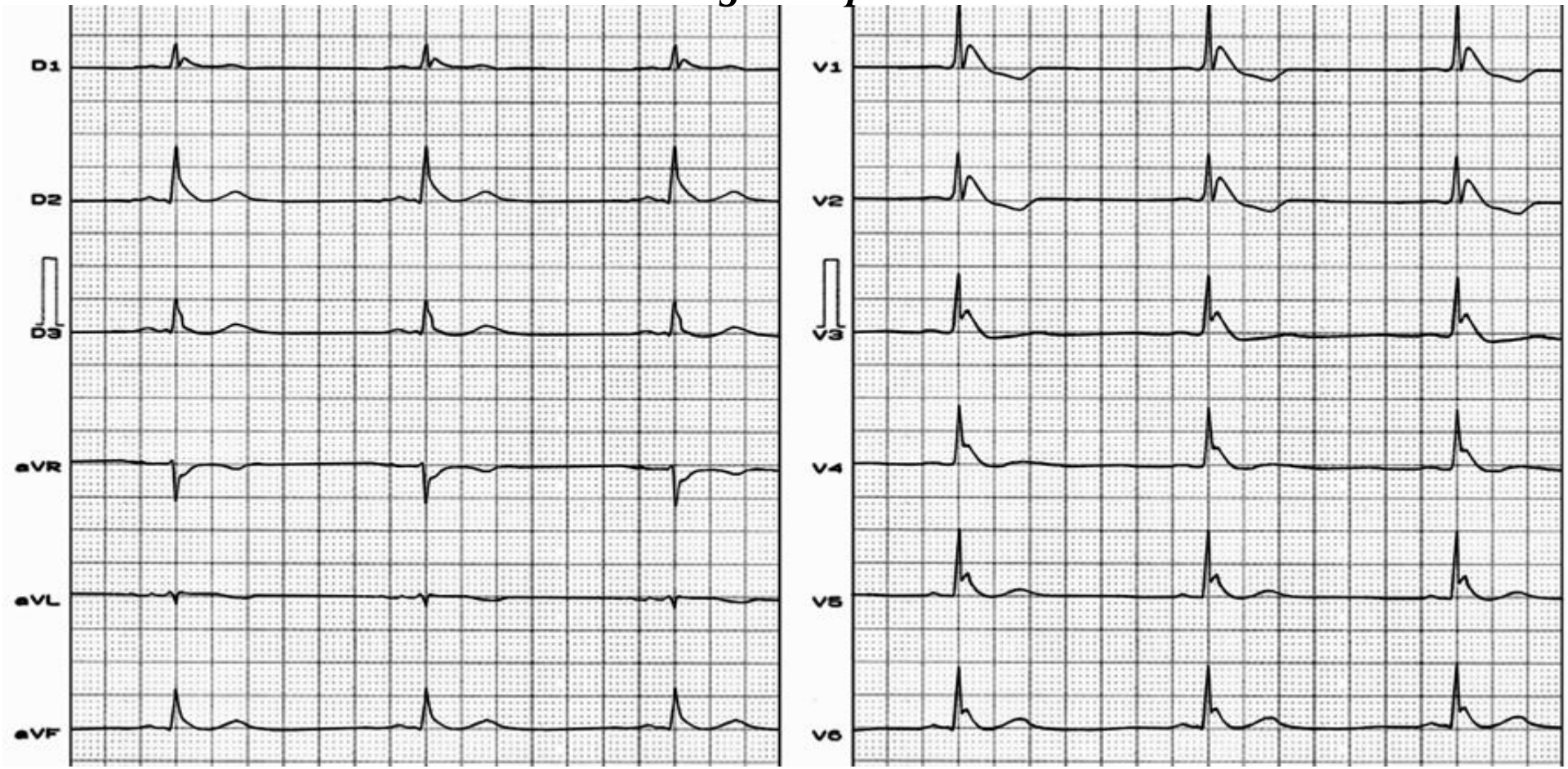
Malignant versus benign early repolarization

	Malignant ERS	Benign ERP
Resuscitation from cardiac arrest or documented VF	Yes, very suggestive	Assymptomatic
Positive family history for SCD in young relative	Possible	Absent
Sinus bradycardia	No	It is the rule
Axes of QRS, ST segment and T wave	Frequently discordant	Oriented to the same direction
Mirror or reciprocal image	Frequently in several leads	Only aVR
Transient augmentation of J waves	Characteristic	Absent
Short coupled PVCs	Frequently	Absent
Co-existing channelopaties such as BsS, SQTS, idiopathic VF	Frequently	No
ST segment elevation	Frequently > 2 mm	Usually < 2 mm
Widespread J waves in inferior and lateral leads and/or globally across leads	Strong signal	No
J waves convex upward or lambda wave pattern	It is the rule	ST concave upward followed by T waves of great voltage and polarity matching QRS
J waves in the inferior leads	Also present	Possible
J waves in lateral leads, tall R waves, rapidly ascending ST segments	No	Characteristic

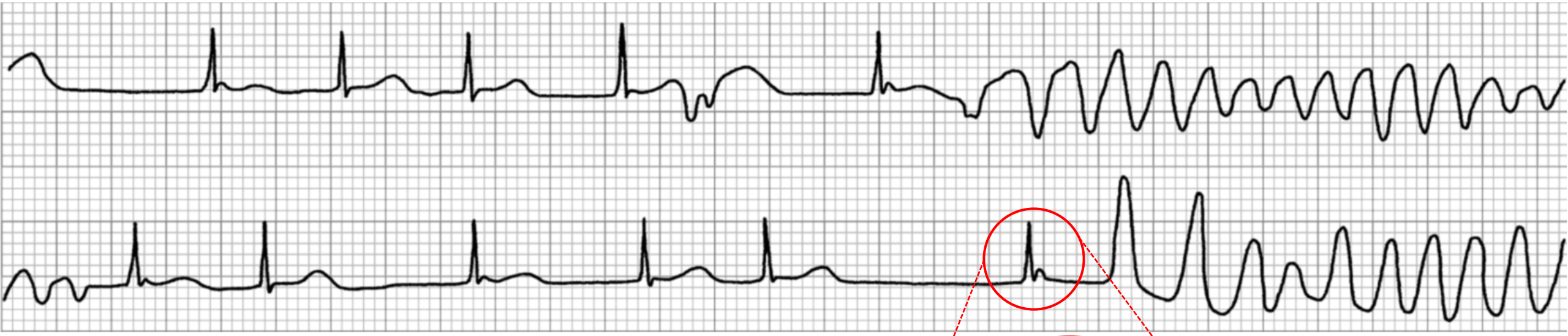
Expert Recommendations for the Diagnosis of ER Pattern and Syndrome Modified from (Priori S.G et al. (2013) HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 10:1932–1963. DOI: 10.1016/j.hrthm.2013.05.014)

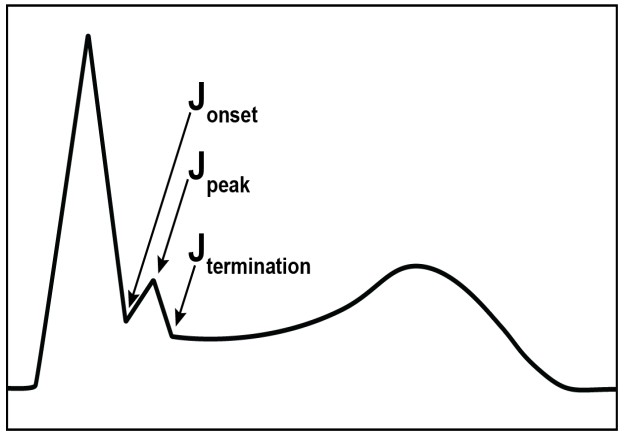
1. Early Repolarization syndrome (ERS) is diagnosed in the presence of J-point elevation ≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated form otherwise unexplained polymorphic/VF
2. ERS can be diagnosed in a SCD victim with a negative autopsy and medical chart review, with a previous ECG demonstrating J-point elevation ≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
3. ERP can be diagnosed in the presence of J-point elevation≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
4. ER Pattern or better inferolateral J waves is defined as elevation of the J point in ≥2 contiguous leads evaluated at baseline using 12-lead ECG.(**Haïssaguerre M, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med Overseas Ed 2008;358:2016–23**.) with an amplitude of the inferolateral J-point elevation of ≥0.1mV above the baseline level, either as QRS slurring or notching in any of the inferior (II, III and aVF), lateral (V4 , V5, V6, I and aVL leads.(**Macfarlane PW, et al. The early repolarization pattern: a consensus paper. J Am Coll Cardiol 2015;66:470–7**.) and slurring or notching they have to happen in the final 50% of the R-wave downslope. The QRS interval in patients with inferolateral J waves had to be <120ms. . J-point amplitude is evaluated at the peak of the notch or at the onset of slur. A greater amplitude of the ST segment 100 ms after the end of the J wave (ie, the end of notch or slur) versus that observed at the end of the J wave indicated an ascending ST segment. A lower or equal amplitude of the ST segment 100 ms after the end of the J wave versus that observed at the end of the J wave indicated a horizontal or descending ST segment.(**Macfarlane PW, et al. 2015**)

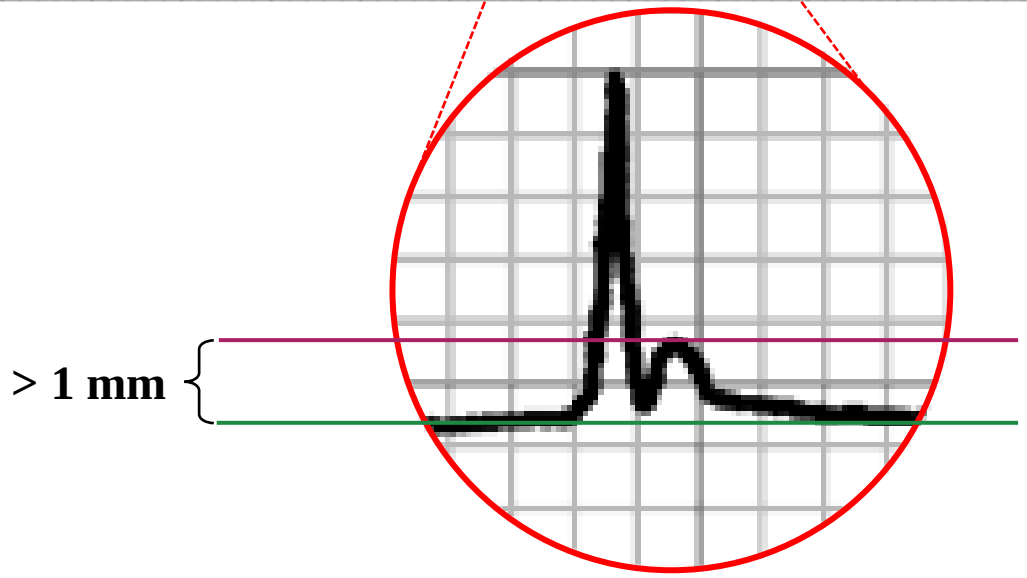
Malignant Early Repolarization Pathological J or malignant waves of idiopathic ventricular fibrillation associated with early repolarization pattern (*ERP): the "Haïssaguerre pattern"*



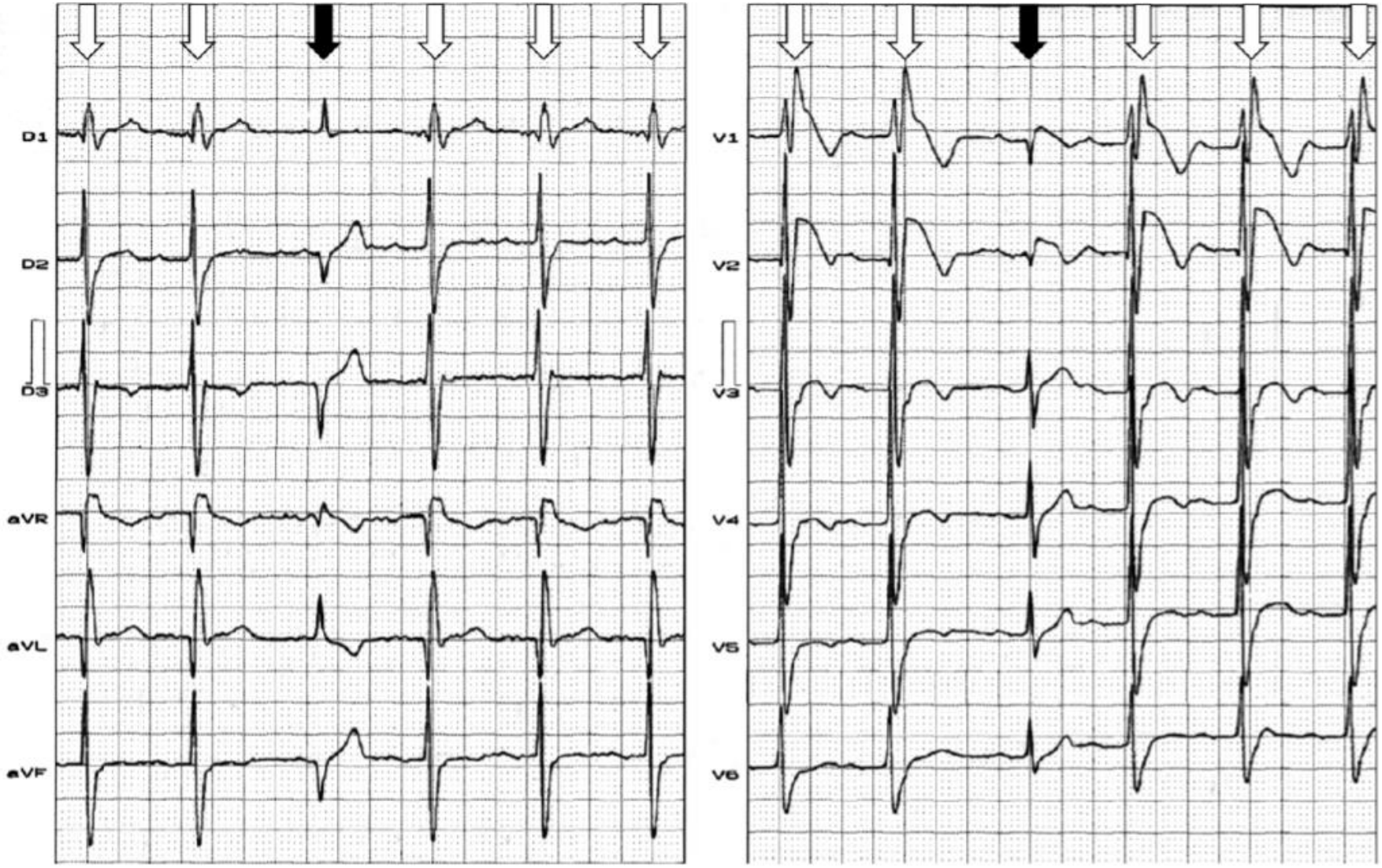
Subtype 3 shows an ER pattern registered globally in the inferior, lateral and right precordial leads. This variant is associated with the highest level of risk for the development of VF storms (**Nam 2008**). In subtype 3, the Brugada waves may be seen together with giant J waves in other ECG leads. Although the Brugada waves are not called ER, their underlying mechanism is identical to that of the ER patterns





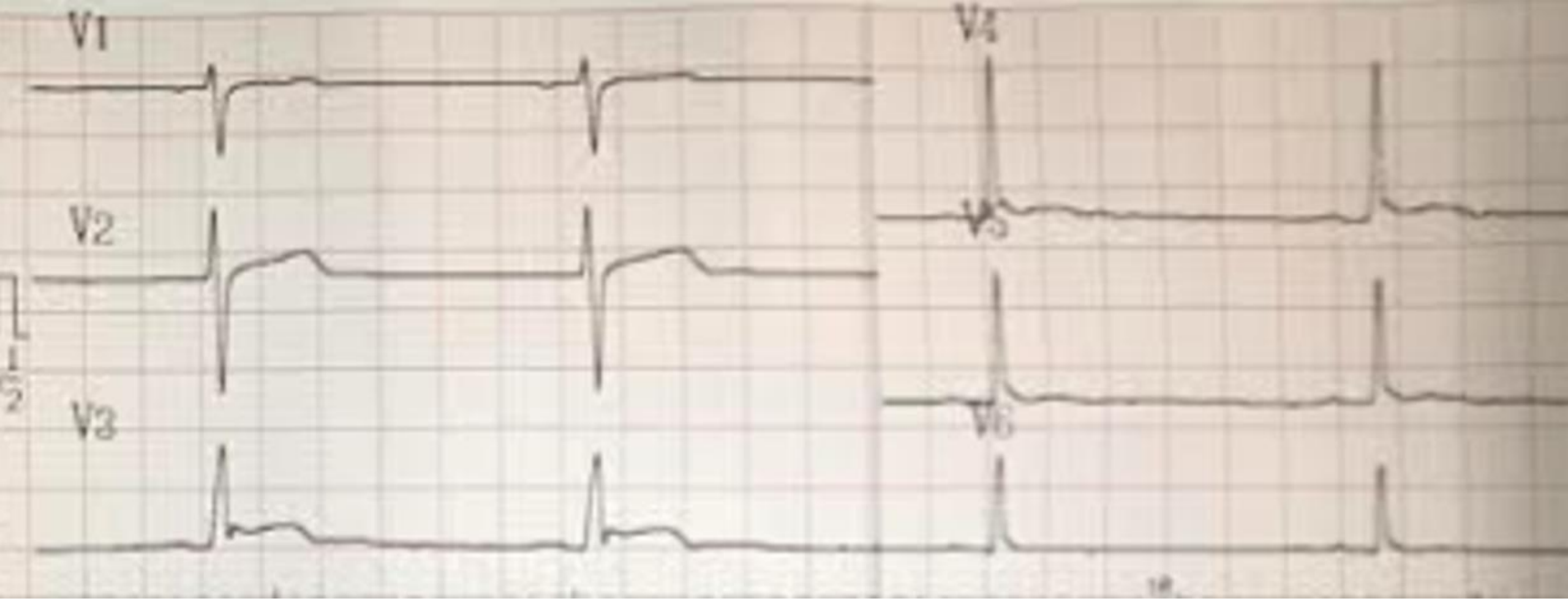


J-point elevation is dynamic as (↑) increases during atrial fibrillation with long R-R intervals. In the present case, the value is > 1 mm. We consider this case an ERS because the ERP is associated with unexplained polymorphic VT.



All beats (white arrows) except the 3rd one in each panel show first degree AVB with CRBBB. The 3rd beat in each panel shows a fusion beat with a narrow QRS which is resulted from the “Chiale’s maneuver” by right apical ventricular pacing with appropriately timed A-V intervals. Third beat (black arrows) shows first degree AVB and typical LAFB and type 1 Brugada pattern (1).

1. **Peréz-Riera AR, et al. International VCG Investigators Group.Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study.Europace. 2012 Jun;14(6):889-97.**


V1
V2
V3
V4
V5
V6