Case report

She is a 74 yo woman. While eating at a restaurant, she went to the bathroom to urinate and on the way back felt light headed. No syncope. EMS brought her to hospital where the first ECG was obtained. She was given 1 mg atropine and HR increased and went into SR; she felt better (ECG 2).
How do you explain CL variability and coupled beats during JR in the initial ECG?
Appreciate your thoughts.

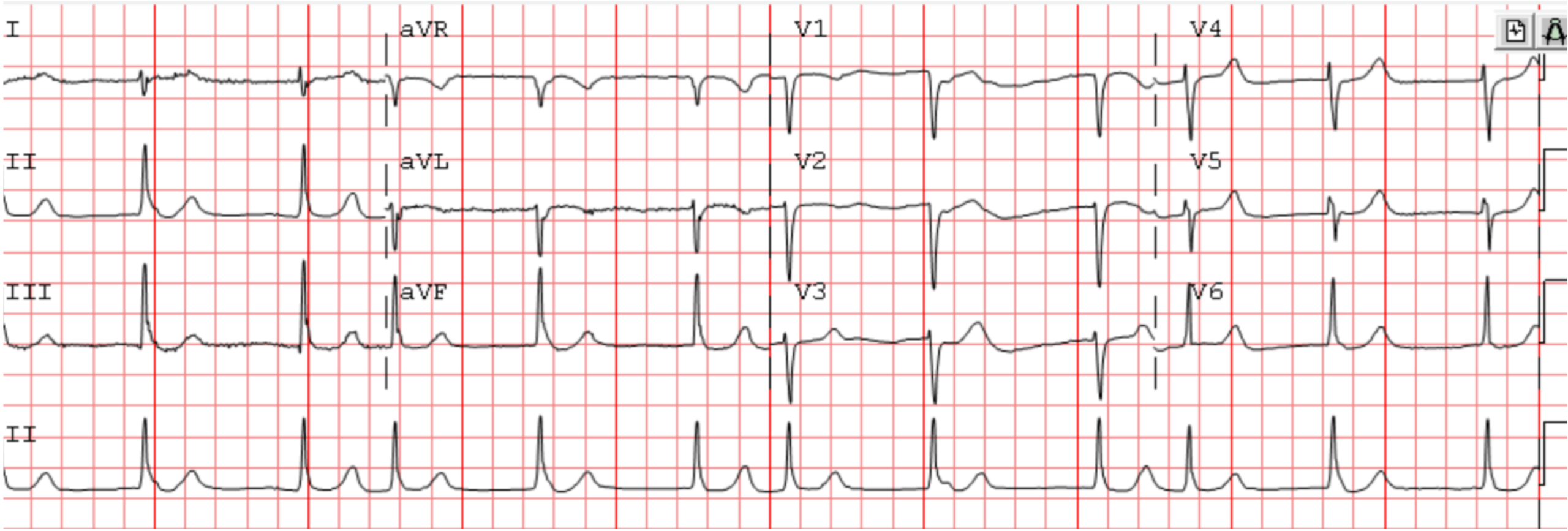
Ranjan
epthakur@gmail.com

Spanish
Se trata de una mujer de 74 años, cual mientras comía en un restaurante, fue al baño a orinar y en el camino de regreso se sintió mareada. Ningún síncope. El servico medico de emergencia EMS ("Emergency Medical Services") la llevó al hospital donde se obtuvo el primer ECG. dado 1 mg de atropina y la frecuencia cardiaca (HR) aumentó entrando en ritmo sinusal (SR); se sintió mejor (ECG 2).
¿Cómo explica la variabilidad de la longitud del ciclo "Cycle lenght" (CL) y los latidos acoplados durante el ritmo juncional (JR) en el ECG inicial?
Apreciaré sus opiniones.

Ranjan

Português:
Trata-se de uma mulher de 74 anos, a qual em quanto almoçava num restaurante, foi a banheiro para urinar. No caminho de regresso sentiu- tontura. Nega síncope. O serviço médico de emergência levou-a a um hospital de emergência onde realizou o ECG-1 e foi medicada com 1 mg de atropina. Então a FC aumentou voltando ao ritmo sinusal com melhora clínica (ECG 2).
Como explicar a variação do comprimento do ciclo e os batimentos acoplamentos durante o ritmo juncional no ECG-1?
Apreciarei suas opiniões.

ECG-1

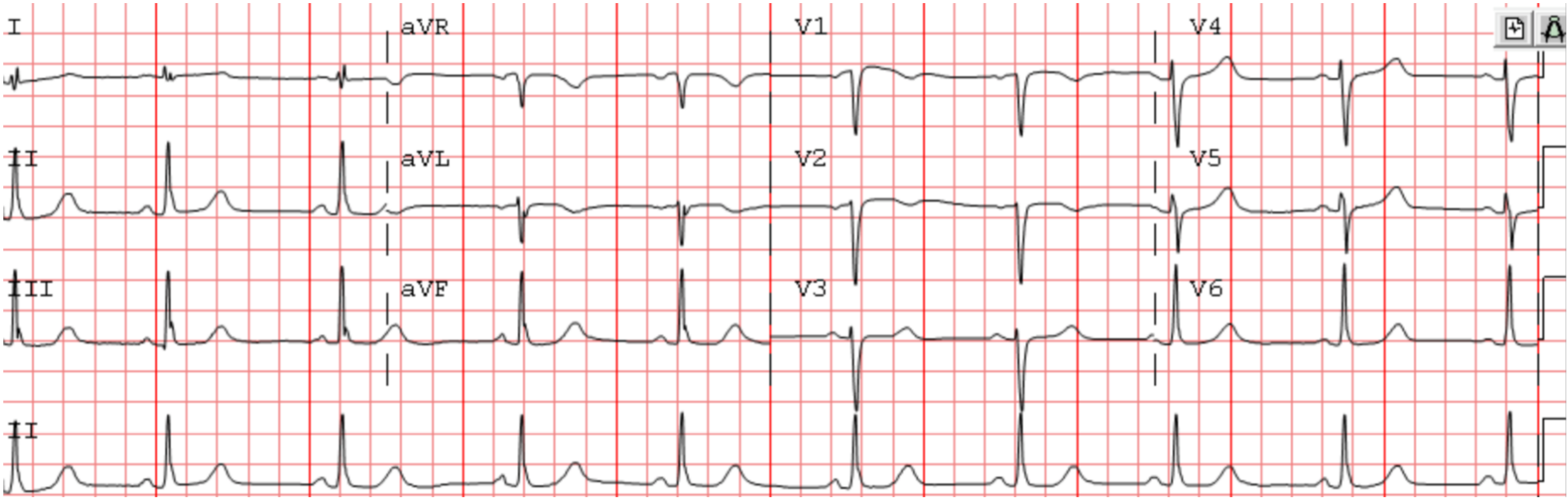


Sinus bradycardia with Junctional rhythm with retrograde VA Conduction suppressing the sinus rate the coupled QRS is due to sinus capture note P waves in V12 and 3 when there is no retrograde conduction

Professor Melvin Scheinman´s analysis

Melvin.Scheinman@ucsf.edu

ECG-2



Dear all **How do you explain CL variability and coupled beats during JR in the initial ECG?**

Answer: The heart beat arises rhythmically in the Sino-atrial node (SAN) and then spreads regularly throughout the heart. The molecular mechanism underlying SAN rhythm has been attributed to the interplay between two clocks, one involving the hyperpolarization activated cation current I_f funny current pacemaker current (the membrane clock), and the second attributable to activation of the electrogenic Na^+Ca^{2+} exchanger by spontaneous sarcoplasmic releases of Ca^{2+} (the Ca^{2+} clock). Both mechanisms contain, in principle, sources of beat-to-beat cycle length(CL) variability, which can determine the intrinsic variability of SAN firing and, in turn, contribute to the HRV. The spontaneous beating activity of the heart is characterized by CL variability between consecutive beats, the so called HRV, which is under primary control of the autonomic nervous system(1). In addition to I_f serving as a so-called "membrane clock", rhythmic release of SR calcium also contributes, as a "calcium clock", to SA nodal phase 4 diastolic depolarization (DD)(2). The Ca^{2+} clock mechanism operates by generating spontaneous local subsarcolemmal Ca^{2+} releases (LCRs) during late phase 4 DD, which activate forward Na^+-Ca^{2+} exchange, providing a cyclic source of depolarizing current (3). The stability and flexibility of pacemaker function likely depends on the synergistic interplay between the two clocks (4). Since the very nature of LCRs that sustain the Ca^{2+} clock is stochastic, it has been shown that their beat-to-beat variations sustain spontaneous beat-to-beat variability of CL in single SANCs(5). **Additionally, this old woman has a malignant shape of early repolarization with J-wave notched and slurring with ST segment elevation≥ 2mm in the inferior leads**. See explanation in next slides.

Pacemaker current, I_f or "funny" current: it operates exclusively in the initial portion of phase 4 (it only acts in a potential range from -60/-70 mV to -40 mV) and contributes 20% to determine the heart rate (HR) of P cells of the SA node (4), controlling diastolic depolarization and spontaneous activity of P, pacemaker cells. The molecular determinants of the If channel, belong to a family of channels activated in hyperpolarization known as HCN channels, made up by 4 isoforms (HCN1, HCN2, HCN3, HCN4), with HCN2 (chromosome 19p13.3) and HCN4

being the main ones in the heart (Hyperpolarization-activated Cyclic Nucleotide-gated channels family (HCN)). Based on the sequence of HCN channels, these are classified as members of a superfamily of voltage-gated K+ (Kv) and CNG channels (**6;7**). A research showed that inhibiting the If current could be used to decrease the incidence of coronary artery disease (CAD) in a subset of patients with HR≥70 bpm (**8;9**). The mutations in HCN4 (chromosome 15q24-125.3) and CNBD (S672R) isoforms are associated to familial inherited bradycardia, as they cause an effect similar to parasympathetic stimulus, by reducing If channel activity (9). There are micro-domains of the membrane, rich in cholesterol and sphingolipids in cardiomyocytes, called caveolae. In caveolin-3 (CAV3), several channels have been located, such as L-type Ca2+, INa+ (Na(v)1.5), the If pacemaker channel (HCN4) or the Na+/Ca^{2+} exchanger (NCX1) and others.

Mutations in CAV3 may originate variant 9 of congenital Long QT Syndrome variant 9 (LQT9) and other inherited arrhythmias. In acquired diseases that lead to congestive heart failure, CAV3 may be affected, originating arrhythmias **(11).** The fast Ca^{2+} T type current or T-type Ca^{2+} T type channel, transient I Ca^{2+} T type current or tiny conductance channel, voltage-dependent T-type calcium channel, and low-voltage-activated (T-type) calcium channels are responsible for the entrance of Ca^{2+} in the final part of phase 4 in the SA Node, in the N region of the AV node and in the His-Purkinje System. The rapid type Ca^{2+} channel is blocked in a selective way by the Ca^{2+} antagonist mibefradil (mibefradil-sensitive component), and other drugs such as bepridil, flunarizine, and pimozide, which bind to the receptor channel in a concentration-dependent fashion, thus blocking the Ca^{2+} cation entrance.

Mibefradil decreases HR, not affecting contractility **(12).** The great efficacy of bepridil to end with atrial fibrillation or flutter, is due in part to the block of this rapid type Ca^{2+} channel **(13).** ICa-T is not sensitive to dihydropyridine. ICa-T has its function increased with noradrenaline, the α adrenergic agonist phenylephrine, the ratio of extracellular ATP and endothelin-1 (ET-1).

Phase 4 of Diastolic Depolarization, rhythmicity, or automatism: It corresponds in surface ECG, to inconstant U wave. In it, energetic output occurs due to the action by the Na^+/K^+-A_{TPase} pump (**14**). The Na^+/K^+-A_{TPase} pump, acting in phase 4 by energetic output, reintroduces K^+ and "expels" Na^+. Note that intracellular K^+ concentration is much greater (150 mEq/L) than the extracellular one (5 mEq/L). On the contrary, Na^+ predominates in the extracellular milieu (142 mEq/L) than in the intracellular one (10 mEq/L). Also in phase 4, the following channels act:

I) I_f channel or pacemaker channel in the initial part of phase 4. The I_f channel is a current activated by hyperpolarization, that acts on the SA node, AV node, and the His-Purkinje system in phase 4 of depolarization. It causes increase in the rate of impulses (pacemaker current), so it has a predominant role during more negative potentials or hyperpolarization (initial portion of phase 4). The I_f channel contributes only with $^1/_5$ of the SA node pacemaker activity.

II) Fast T type Ca^{2+} channel, transient Ca^{2+} current, or tiny conductance Ca^{2+} current: it acts causing inward Ca^{2+} in the final portion of phase 4 in the SA node, N region of the AV node, and His-Purkinje system. Blocked selectively by the Ca^{2+} antagonist, mibefradil. Insensitive to dihydropyridine agents. ICa^{+2}-T channel function is increased with noradrenaline, the α adrenergic agonist phenylephrine (**15**), increase of extracellular ATP and endothelin-1. Cardiomyocytes where ICa^{+2}-T is plentiful, are those with less extensive transverse T tubules. shows the three main types of ICa^{+2}-T.

Type-T calcium channels or I_{Ca}^{+2}-T

Isoform	Name of Gene	Name of Channel	Tissue
α_{1G}	**CACNA1G**	**$Ca_n3.1$**	Neurons, Purkinje.
α_{1H}	**CACNA1H**	**$Ca_n3.2$**	Heart, kidneys, liver
α_{1I}	**CACNA1I**	**$Ca_n3.3$**	Neurons.

3. Acetylcholine-activated inward rectifying current ($I_{k(ACH)}$), which produces hyperpolarization and stimulated bradycardia. This channel is strongly inhibited by dronedarone, an analog to amiodarone in the SA node and the atrial tissue. This also inhibits I_{k1}, L-Ca^{2+}, I_{kr} and to a lesser degree I_{ks}. This drug is an α and β antagonist of adrenoreceptors, and unlike amiodarone, it has little effect on thyroid receptors (**16**). By the characteristics of phase 4, heart cells are classified into automatic and nonautomatic.

A. Automatic: They display unstable, ascending phase 4, or with diastolic, automatic, or rhythmic depolarization. This is the characteristic of cardiac cells, of spontaneously starting an impulse, in the absence of external stimulus. Phase 4 of diastolic depolarization originates by the inward current of the so-called pacemaker or If channel, that is the main mechanism by which the autonomic nervous system regulates automaticity. Thus, catecholamines open the If channel, increasing heart rate by making the phase 4 slope steeper. If, pacemaker subunit, or funny current is a current activated in hyperpolarization, present in the SA node, AV node, and His-Purkinje system cells, causing increase in shock rate of automatic or pacemaker cells (**17**). Phase 4 of SA node is the one with greatest automaticity by a mechanism known as overdrive suppression; a phenomenon that consists of inhibiting subsidiary pacemakers by a faster pacemaker with spontaneous shocks.

A. Nonautomatic: characterized by presenting a stable phase 4; i.e. without spontanous ascending slope. This characteristic is mainly due to the presence of the rectifier inward Ik1 channel, closed during depolarization. This channel, voltage-dependent and blocked by Ba2+, is responsible for keeping the resting potential in atrial and ventricular muscle cells (ordinary working muscle cells). Phase 4 corresponds to transmembrane resting potential or just membrane resting potential, which in the SA node cells is ≈ than -50 to -60 mV, in atrial muscle cells -80 to -90 mV, in AV node cells -55 to -70 mV, in Purkinje fibers -90 to -95 mV, and finally, in ventricular muscle cells -80 to -90 mV.

Cardiac cellular types according to AP & Electro-pharmacologic behavior

A) **Automatic: ascending phase 4**

1) Sinoatrial node cells: SA-N
2) Atrioventricular node cells : AV-N

} Slow

3) His-Purkinje System cells : HP-S } Fast

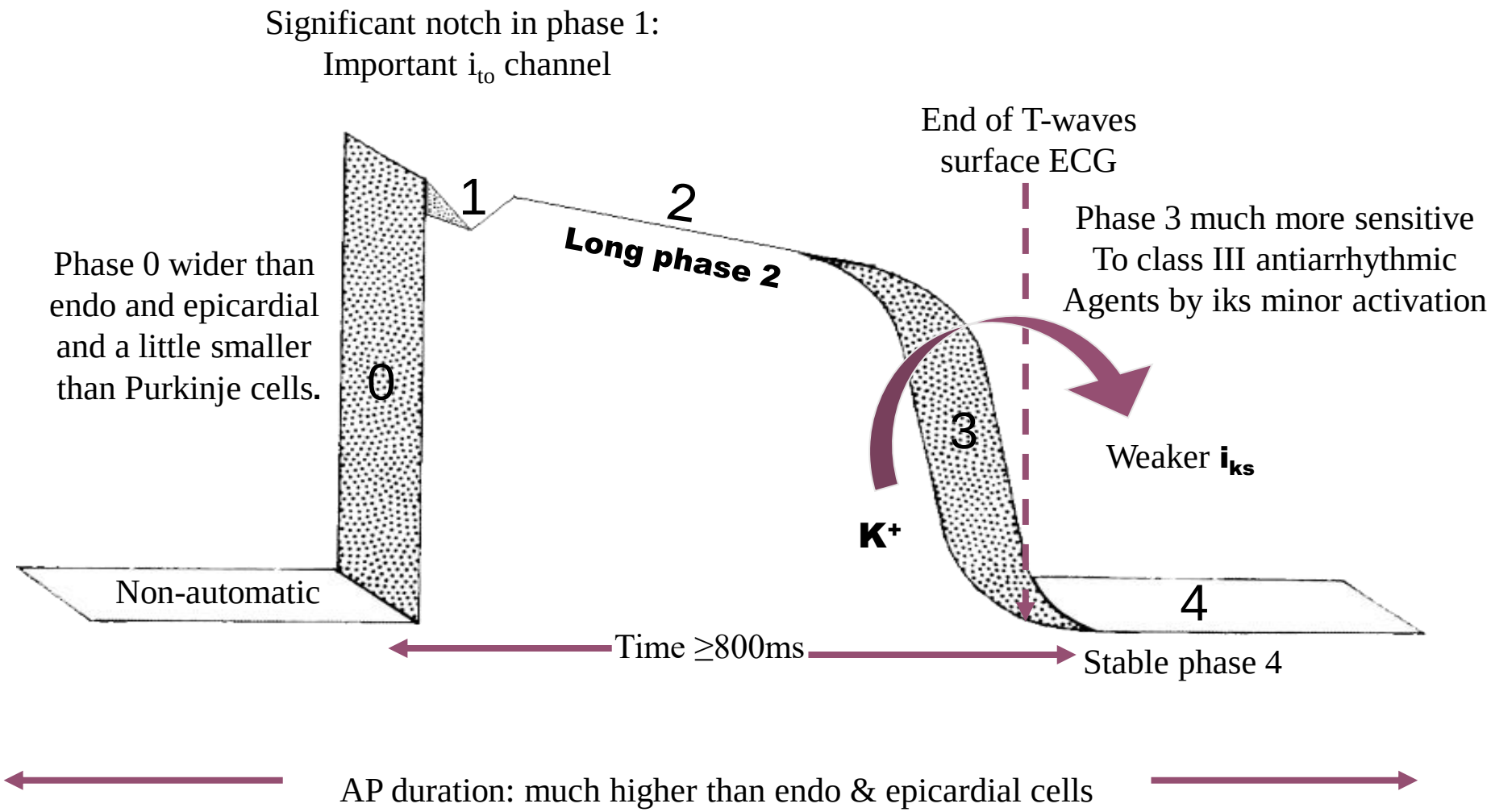
B) **Non-automatic contractile: stable phase 4**

4) Atrial contractile myocardial cells

5) Ventricular contractile myocardial cells :
- Epicardial
- Midmyocardium
  - a) Contractile
  - b) "M" cells? Polemic
- Endocardial

We show how cardiac cells are divided from the point of view of rhythmicity, diastolic depolarization or automatism. When phase 4 is horizontal (muscular, atrial and ventricular cells), we say that the cell is not automatic (it does not have the capacity of self-stimulation). When phase 4 is spontaneously ascending, as it occurs with sinus node, AV node and His-Purkinje cells, we say that the cell is automatic or with diastolic depolarization.

Action Potential characteristics of the mid-myocardium "M cells"



Characteristics of action potential of M cells. It is a fast and non-automatic fiber; therefore, we could say that it is a mixture between Purkinje cells and contractile ventricular myocardium. It is very sensitive to bradycardia and class III antiarrhythmic drugs, such as amiodarone and sotalol.

In brief, cardiac cells are divided into two groups from the point of view of rhythmicity, diastolic depolarization or automaticity. When phase 4 is horizontal (atrial and ventricular muscle cells), we say that cells are nonautomatic (it does not have the capacity to self-stimulate). When phase 4 is spontaneously ascending, as it happens with SA node, AV node, and His-Purkinje system cells, we say that cells are automatic or with diastolic depolarization.

Table below shows the main channels acting in phase 4.

Main channels acting in phase 4

Cation	Channel	α subunit protein	Subunit of the gene	Phase / responsibility
K^+	I_{K1}	K_{ir}2.1/2.2/2.3	KCNJ2KCNJ12KCNJ4	3,4
I_f pacemaker channel			HAC1	4. It contributes 20% of pacemaker function in the SA node.
Ca^{2+} T($I_{Ca\text{-}T}$); T-type Ca^{2+} channel		**Cav3.2**		Final portion of phase 4 in SA node, N region of AV node, and His-Purkinje system cells.
Na^+/ K^+ ATP_{ase} pump.				

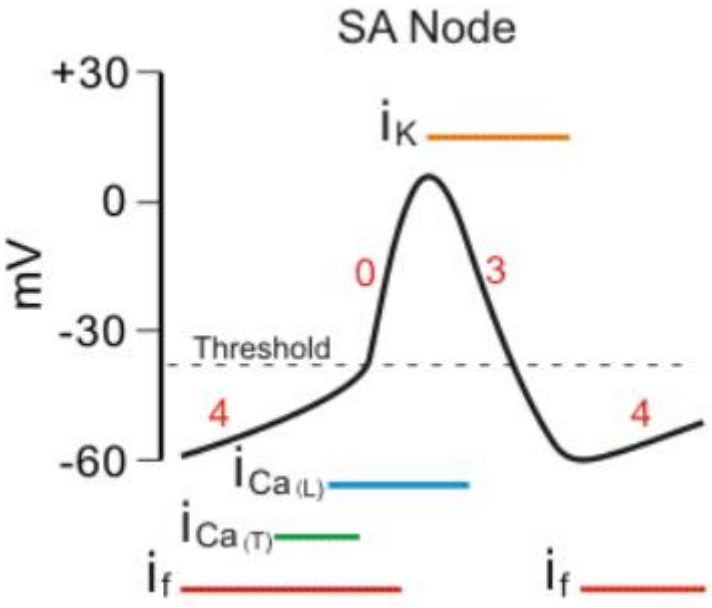
Phase 4 of the SA node depends on the following channels:

I. I_f, channel, pacemaker current or funny current: activated by hyperpolarization or pacemaker channel, increases impulse rate. It has a preponderant role in the initial phase. I_f, channel

II. $I_{K(ACH)}$ acetylcholine-activated inward rectifying current, which produces hyperpolarization and stimulated bradycardia

III. $I_{ca\text{-}L}$ channel.

IV. T-type calcium channels Fast T type channels ($I_{Ca\text{-}T}$): transient current or tiny conductance: these are low-voltage activated calcium channels that open during membrane depolarization. These channels aid in mediating Ca^{2+} influx into cells after an action potential or depolarizing signal. The T-type channels are much different from the L-type Ca^{2+} channels due to their ability to be activated by more negative membrane potential



Phase 4 is the spontaneous depolarization (pacemaker potential) that triggers the action potential once the membrane potential reaches threshold between -40 and -30 mV).

Phase 0 is the depolarization phase of the action potential. This is followed by

Phase 3 repolarization. Once the cell is completely repolarized at about -60 mV, the cycle is spontaneously repeated. The changes in membrane potential during the different phases are brought about by changes in the movement of ions (principally $Ca^{2+}$and K^+, and to a lesser extent Na+) across the membrane through ion channels that open and close at different times during the action potential. When a channel is opened, there is increased electrical conductance (g) of specific ions through that ion channel. Closure of ion channels causes ion conductance to decrease.

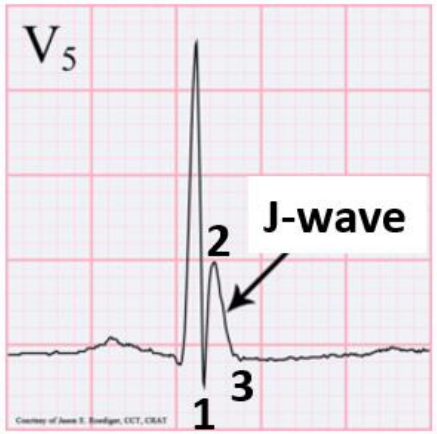
References

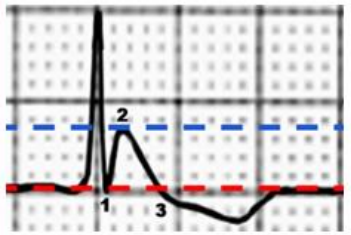
1. Posokhova E, Ng D, Opel A, Masuho I, Tinker A, et al. (2013) Essential Role of the m2R-RGS6-IKACh Pathway in Controlling Intrinsic Heart Rate Variability. PLoS One 8: e76973.
2. Maltsev VA, Lakatta EG (2009) Synergism of coupled subsarcolemmal Ca2+ clocks and sarcolemmal voltage clocks confers robust and flexible pacemaker function in a novel pacemaker cell model. Am J Physiol Heart Circ Physiol 296: H594–615.
3. Bogdanov KY, Vinogradova TM, Lakatta EG (2001) Sinoatrial nodal cell ryanodine receptor and Na(+)-Ca(2+) exchanger: molecular partners in pacemaker regulation. Circ Res 88: 1254–1258.
4. Maltsev VA, Lakatta EG (2009) Synergism of coupled subsarcolemmal Ca2+ clocks and sarcolemmal voltage clocks confers robust and flexible pacemaker function in a novel pacemaker cell model. Am J Physiol Heart Circ Physiol 296: H594–615.
5. Monfredi O, Maltseva LA, Spurgeon HA, Boyett MR, Lakatta EG, et al. (2013) Beat-to-Beat Variation in Periodicity of Local Calcium Releases Contributes to Intrinsic Variations of Spontaneous Cycle Length in Isolated Single Sinoatrial Node Cells. PLoS One 8: e67247.
6. Baruscotti, M., Bucchi, A., DiFrancesco, D. (2005). Physiology and pharmacology of the cardiac pacemaker ("funny") current. Pharmacology & Therapeutics, 107, 59-79.
7. Barbuti A, Baruscotti M, DiFrancesco D. The pacemaker current: from basics to the clinics. J Cardiovasc Electrophysiol. 2007 Mar; 18: 342-347.
8. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; BEAUTIFUL Investigators Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 372:807-816.
9. Ferrari R, Ford I, Fox K, Steg PG, Tendera M. The BEAUTIFUL Study Group,: randomized trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction – baseline characteristics of the study population. Cardiology. 2008; 110: 271-282.

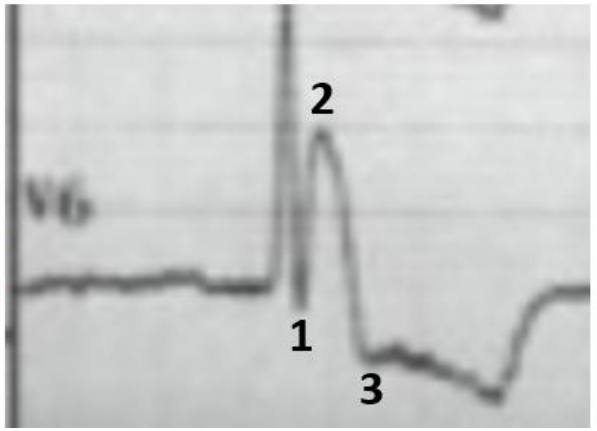
10. Milanesi, R., Baruscotti, M., Gnecchi-Ruscone, T, DiFrancesco, D. Familial sinus bradycardia associated with a mutation in the cardiac pacemaker channel. The New England Journal of Medicine, 2006; 354,151-157.
11. Balijepalli RC, Kamp TJ. Caveolae, ion channels and cardiac arrhythmias. Prog Biophys Mol Biol. 2008 Oct-Nov; 98:149-160.
12. Palatini P. Heart rate as a risk factor for atherosclerosis and cardiovascular mortality: the effect of antihypertensive drugs. Drugs 1999 May; 57: 713-724.
13. Uchino T, Lee TS, Kaku T, Yamashita N, Noguchi T, Ono K. Voltage-dependent and frequency-independent inhibition of recombinant Cav3.2 T-type Ca2+ channel by bepridil. Pharmacology. 2005 Jul; 74:174-181.
14. Friedrich T, Bamberg E, Nagel G Na+,K(+)-ATPase pump currents in giant excised patches activated by an ATP concentration jump. Biophys J 1996 Nov;71(5): 2486-2500.
15. Liu QY, Karpinski E, Pang PK. The L-type calcium channel current is increased by alpha-1 adrenoceptor activation in neonatal rat ventricular cells. J Pharmacol Exp Ther. 1994 Nov;271(2):935-943.
16. Doggrell SA, Hancox JC.Dronedarone: an amiodarone analogue. Expert Opin Investig Drugs. 2004 Apr; 13(4): 415-426.
17. Yeh YH, Burstein B, Qi XY, Sakabe M, Chartier D, Comtois P, Wang Z, Kuo CT, Nattel S. Funny current downregulation and sinus node dysfunction associated with atrial tachyarrhythmia: a molecular basis for tachycardia-bradycardia syndrome. Circulation. 2009 Mar 31;119(12):1576-85.

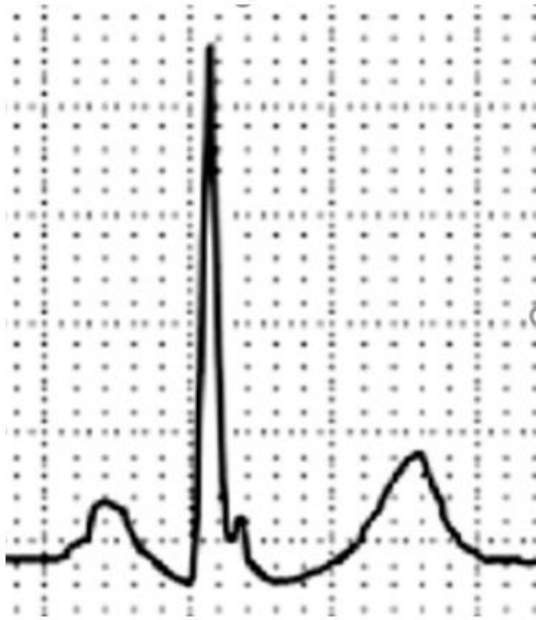
Andrés Ricardo Pérez-Riera MD PhD.

1: J-onset; 2: J-peak (Jp); 3: J-termination

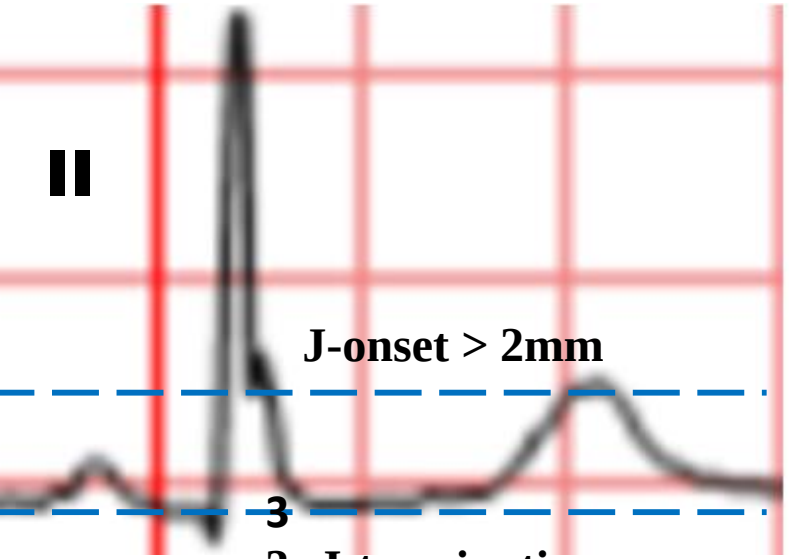


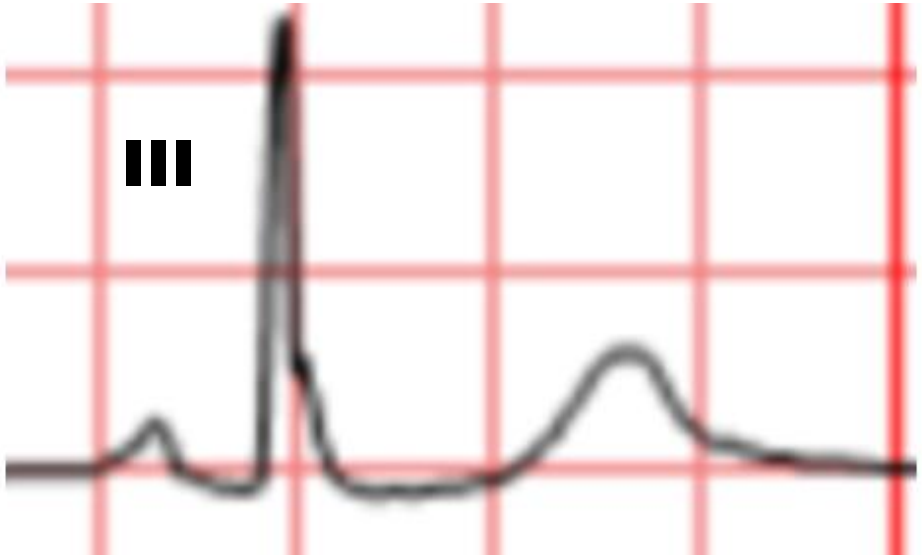


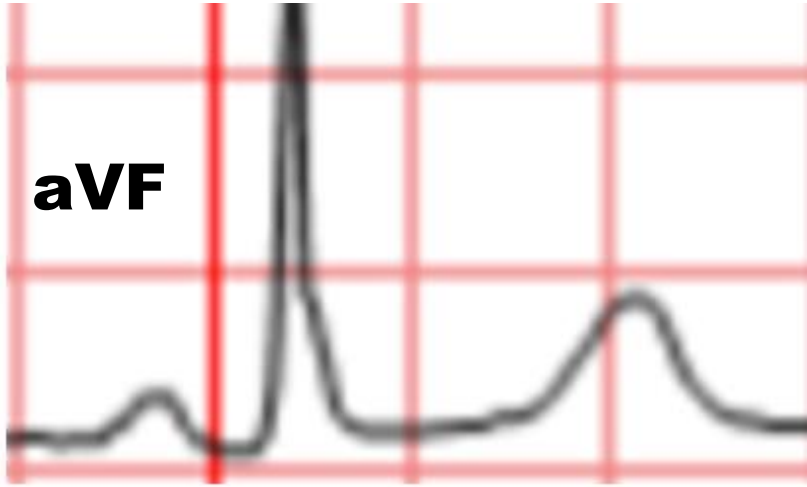




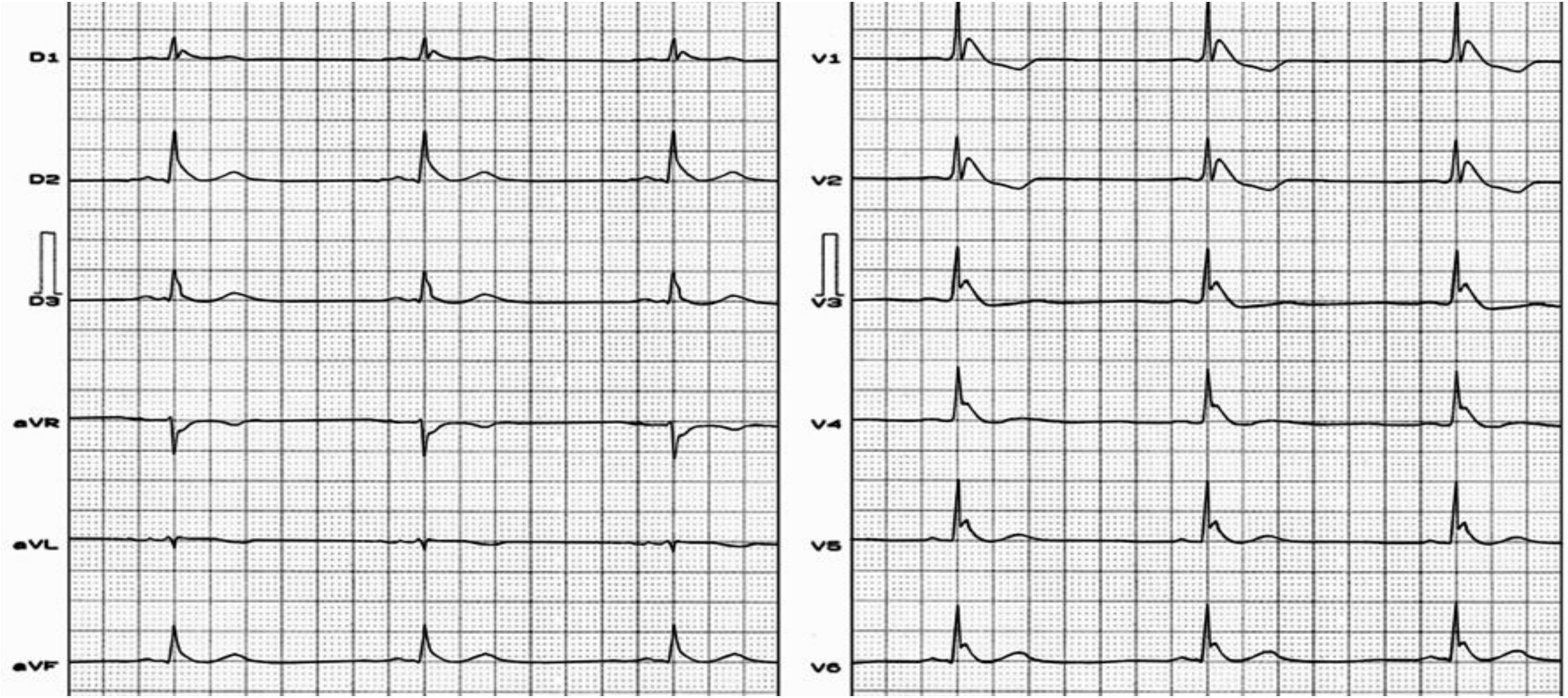
The present case: II and III "end-QRS notch" and aVF "end-QRS Sluring"







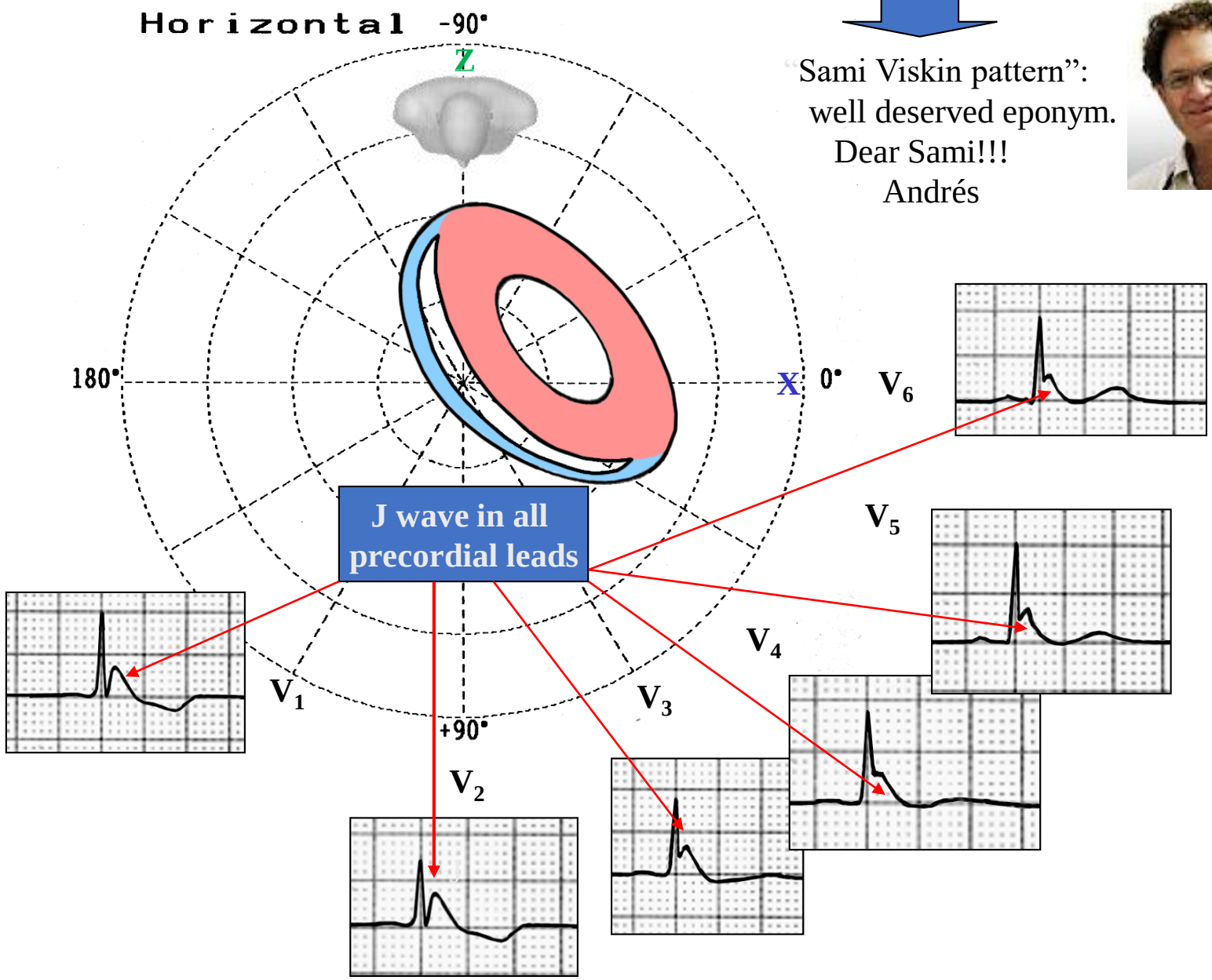
Example of Malignant Early Repolarization Pathological J or malignant waves of idiopathic ventricular fibrillation associated with early repolarization pattern (*ERP): the "Haïssaguerre pattern"*



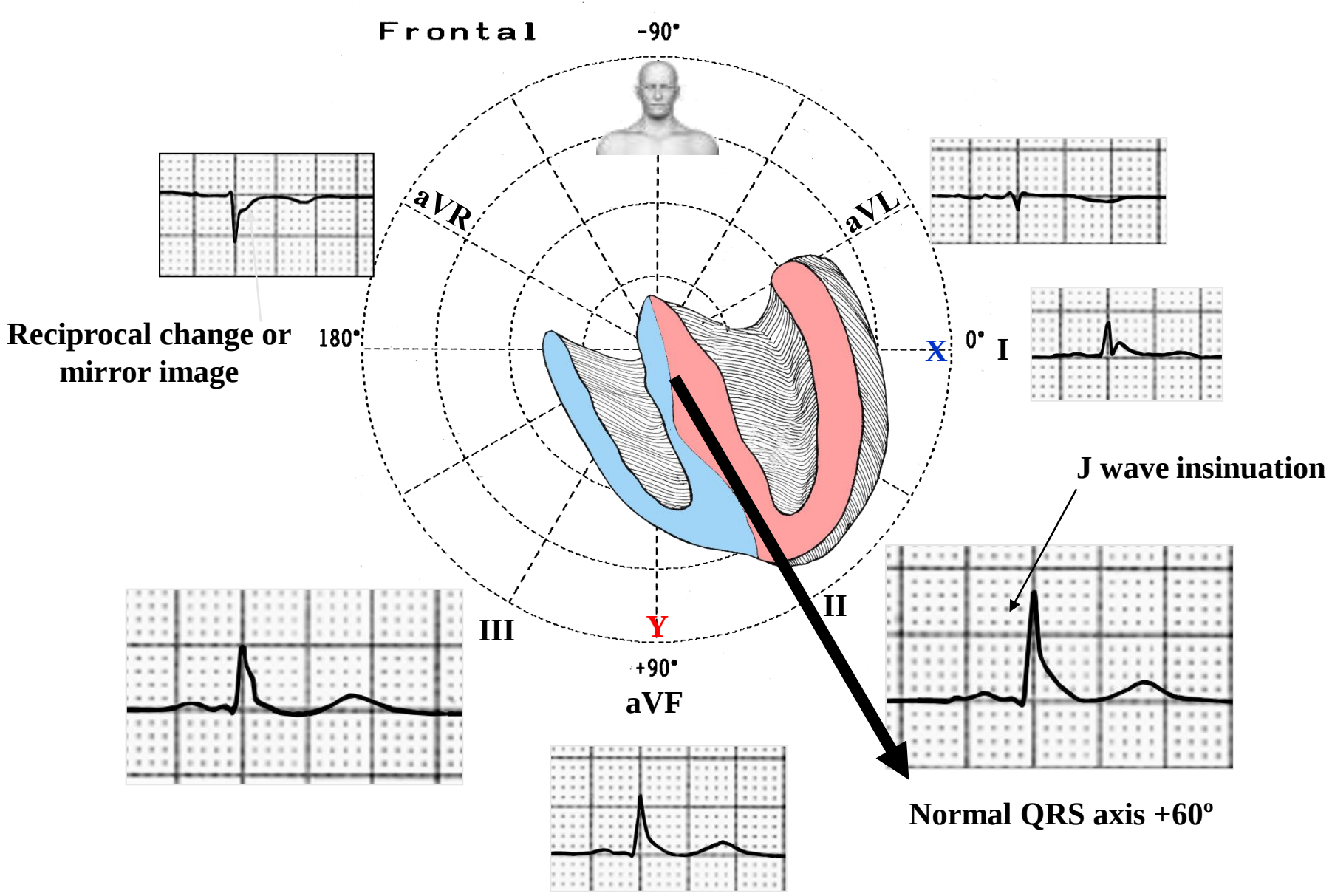
Subtype 3 shows an ER pattern registered globally in the inferior, lateral and right precordial leads. This variant is associated with the highest level of risk for the development of VF storms (**Nam 2008**). In subtype 3, the Brugada waves may be seen together with giant J waves in other ECG leads.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

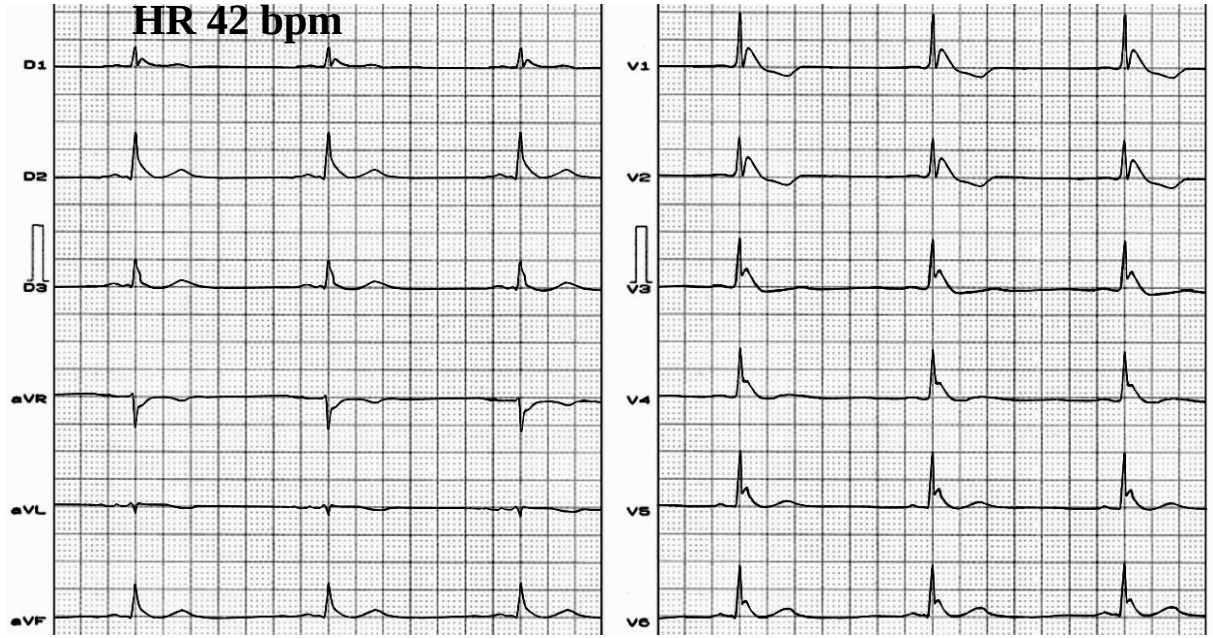
MER "Monstrous Early Repolarization," or

"Sami Viskin pattern":
well deserved eponym.
Dear Sami!!!
Andrés



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

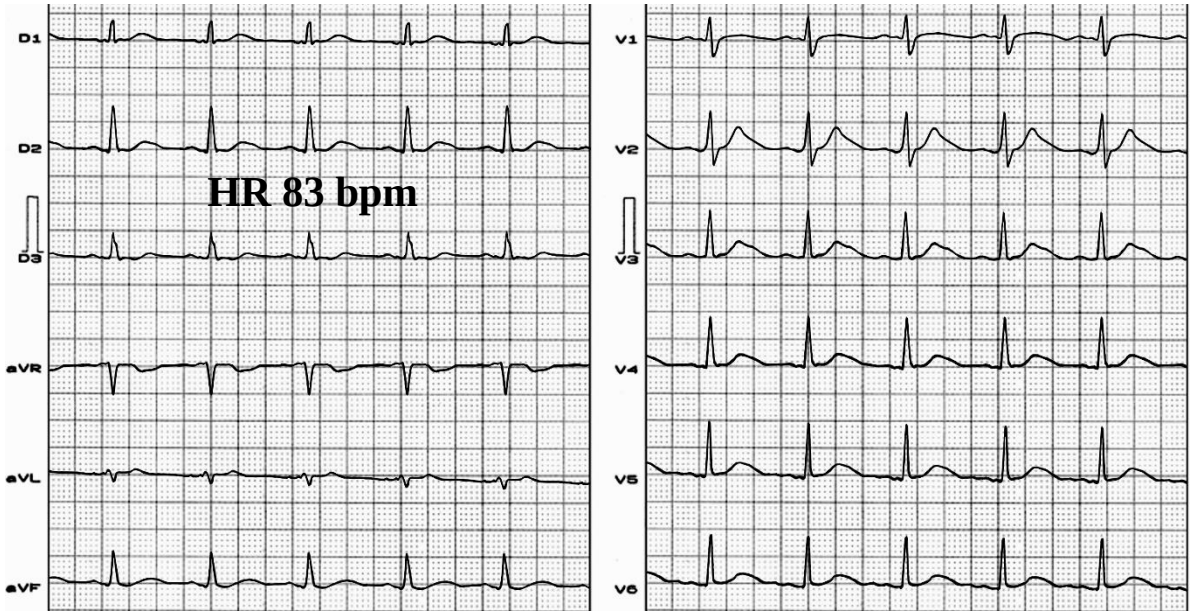

Frontal
-90°
aVR
aVL
180°
0°
I
X
Y
III
II
+90°
aVF
Reciprocal change or mirror image
J wave insinuation
Normal QRS axis +60°



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.



Malignant versus benign early repolarization

	Malignant ERS	Benign ERP
Resuscitation from cardiac arrest or documented VF	Yes, very suggestive	Asymptomatic
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 BrS, ERS, 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	**Suggestive**	Possible
J waves in lateral leads, tall R waves, rapidly ascending ST segments	No	Characteristic