Brugada syndrome Unmasked by Fever and Paradoxical lower degree of dromotropic disturbance in the Right Ventricular Outflow Tract

Javier **Garcia-Niebla**[1] **&** Andrés Ricardo **Pérez-Riera M.D. Ph.D.**[2]

1) Profesor colaborador Escuela Universitaria de Enfermería. Hospital Universitario de La Candelaria en Universidad de La Laguna. Valle del Golfo Health Center, Servicio Canario de Salud, El Hierro, Spain.
2) Design of Studies and Scientific Writing Laboratory at the ABC School of Medicine, Santo André, São Paulo, Brazil. Professor de Clinica Media da Universidade Uninove

Case report

Elderly Caucasian male (77 years old) former heavy smoker (50 packs per year) who caused chronic obstructive pulmonary disease. Sick with pneumonia 7 years ago. Mixed dyslipidemia on regular treatment with statin (20mg/day simvastatin) and ezetimibe (10mg daily). Anxiety disorder on regular use of the antidepressant mirtazepine (30mg per day).

Syncopal episodes at rest, without prodromes since the age of 67, **always related to fever** and since April 2014 he has been asymptomatic. As his ECGs showed a type 2 Brugada pattern only during syncopal episodes, he was instructed to use antipyretics as long as they reached 37 degrees Celsius (37º C) and he is given a list of drugs that he should not use following the guidelines of BrugadaDrugs.org(It is a non-profit initiative developed by physicians from the University of Amsterdam Academic Medical Center, department of Cardiology, in collaboration with the panel of world-renowned experts on Brugada syndrome)

Family background. Negative

Physical examination: Absence of: cyanosis, tachypnea, shortness of breath, use of accessory respiratory muscles, paradoxical indrawing of lower intercostal spaces, elevated jugular venous pulse or peripheral edema, decreased vesicular breath sounds and no adventitious sounds. Unremarkable cardiac exam.

Transthoracic echocardiogram was performed, which revealed a normal-sized left ventricle, with minimal concentric hypertrophy and good global and segmental contractility. Straight cavities of normal size and contractility. Mild degenerative mitral and aortic sclerosis without significant stenosis or regurgitation. Considered without structural heart disease.

On December 5, consultation with fever and an ECG is performed (**Figure 1**). A few hours later, with the afebrile patient, the ECG in **figure 2** is performed

We additionally requested exercise stress testing, High-resolution electrocardiography, 24-hour Holter monitoring, and a Computerized Tomography (CT) coronary angiogram (the latter because the patient is elderly, ex-strong smoker and has dyslipidemia). The results of all these exams were unimpressive. Finally, we do not consider necessary to carry out programmed electrical stimulation due to advanced age, absence of electrocardiographic risk markers, and low Shanghai Score System recently validated (1)

Português

Homem Caucasiano idoso (77 anos) ex fumante inveterado (de 50 maços por/ano) que lhe ocasionou doença pulmonar obstrutiva crônica. Acometido de pneumonia há 7 anos atrás. Dislipidêmico misto em tratamento regular com estatina (sinvastatina 20mg/dia) e ezetimibe (10mg por dia). Transtorno de ansiedade em uso regular do antidepressivo mirtazepina (30mg por dia)

Episódios sincopais no repouso, sem pródromos desde os 67 anos sempre relacionados a febre sendo que desde abril de 2014 se encontra assintomático. Como seus ECGs mostravam padrão Brugada tipo 2 apenas durante os episódios febris foi orientado a fazer uso de antitérmicos desde que atingisse os 37 graus Celsius (37º C) e se lhe fornece a lista dos fármacos que não deve usar seguindo as orientações do BrugadaDrugs.org (It is a non-profit initiative developed by physicians from the University of Amsterdam Academic Medical Center, department of Cardiology, in collaboration with a panel of world-renowned experts on Brugada syndrome)

Antecedentes familiares negativos. Exame físico: Ausência de: cianose, taquipnéia, falta de ar, uso de músculos respiratórios acessórios, desenho paradoxal dos espaços intercostais inferiores (o sinal de Hoover), pulso venoso jugular elevado ou edema periférico, ruídos respiratórios vesiculares diminuídos e sem ruídos adventícios. Exame cardíaco normal. Foi realizado ecocardiograma transtorácico, que revelou ventrículo esquerdo de tamanho normal, com hipertrofia concêntrica mínima e boa contratilidade global e segmentar.

Em 10/2020 se realizou Ecocardiograma transtorácico que revelou ventrículo esquerdo de tamanho normal, com mínima hipertrofia concêntrica e boa contratilidade global e segmentar. Cavidades direitas de tamanho e contratilidade normais. Esclerose mitral e aórtica degenerativas leves sem estenose ou regurgitação significativas. Considerado sem cardiopatia estrutural.

Além disso, solicitamos teste ergométrico, eletrocardiografia de alta resolução, Holter de 24 horas e angiografia coronária por tomografia computadorizada (TC) (esta última porque o paciente é idoso, ex-fumante forte e tem dislipidemia). Os resultados de todos esses exames foram inexpressivos. Por fim, não consideramos necessária a realização de estimulação elétrica programada devido à idade avançada, ausência de marcadores de risco eletrocardiográfico e baixo Shanghai Score System recentemente validado (1)

Em December 5, consulta com febre e se realiza um ECG (figura 1).

Castellano

Varón anciano caucásico (77 años) español, exfumador empedernido (50 paquetes por año) que causaba enfermedad pulmonar obstructiva crónica. Neumonía hace 7 años. Dislipémico mixto en tratamiento continuo con estatina (20 mg / día de simvastatina) y ezetimiba (10 mg al día). Trastorno de ansiedad y en uso regular del antidepresivo mirtazepina (30 mg/día).

Episodios sincopales en reposo, sin pródromos desde los 67 años, siempre relacionados con fiebre siendo que desde abril de 2014 está asintomático. Como sus ECG mostraban un patrón de Brugada tipo 2 **solo durante los episodios febriles**, se le indicó antipiréticos siempre que la temperatura corporal alcance los 37 grados Celsius (37°C) y se le entregó una lista de medicamentos que no debería usar siguiendo las pautas de Brugada Drugs .org (Esta es una iniciativa sin fines de lucro desarrollada por médicos del Centro Médico Académico de la Universidad de Ámsterdam, departamento de Cardiología, en colaboración con el panel de expertos de renombre mundial en el síndrome de Brugada),

Antecedentes familiares negativos.

Examen físico: Ausencia de: cianosis, taquipnea, disnea, uso de músculos respiratorios accesorios, diseño paradójico de los espacios intercostales inferiores (signo de Hoover), pulso venoso yugular elevado o edema periférico, disminución de los ruidos respiratorios vesiculares y ausencia de ruidos adventicios. Examen cardíaco normal.

Se realizó un ecocardiograma transtorácico que reveló ventrículo izquierdo de tamaño normal, con mínima hipertrofia concéntrica y buena contractilidad global y segmentaria. Cavidades de tamaño y contractilidad normales. Esclerosis mitral y aórtica degenerativa leve sin estenosis ni regurgitación significativas. Considerado sin cardiopatía estructural.

Se solicitó adicionalmente prueba de esfuerzo, electrocardiograma de alta resolución, monitorización Holter de 24 horas y coronariografía por tomografía computarizada (TC) (esta última por ser anciano, exfumador fuerte y dislipidemia). Los resultados de todos estos exámenes no fueron impresionantes. Finalmente, no consideramos necesario realizar estimulación eléctrica programada por edad avanzada, ausencia de marcadores de riesgo electrocardiográfico y bajo Shanghai Score System recientemente validado (1)

El 5 de diciembre se realiza consulta con fiebre y ECG (figura 1). Unas horas después, con el paciente afebril, se realizó el ECG que se muestra en la figura 2.

Figure 1 ECG performed on December 5, 2021 at 2:03:41 PM. Patient with fever

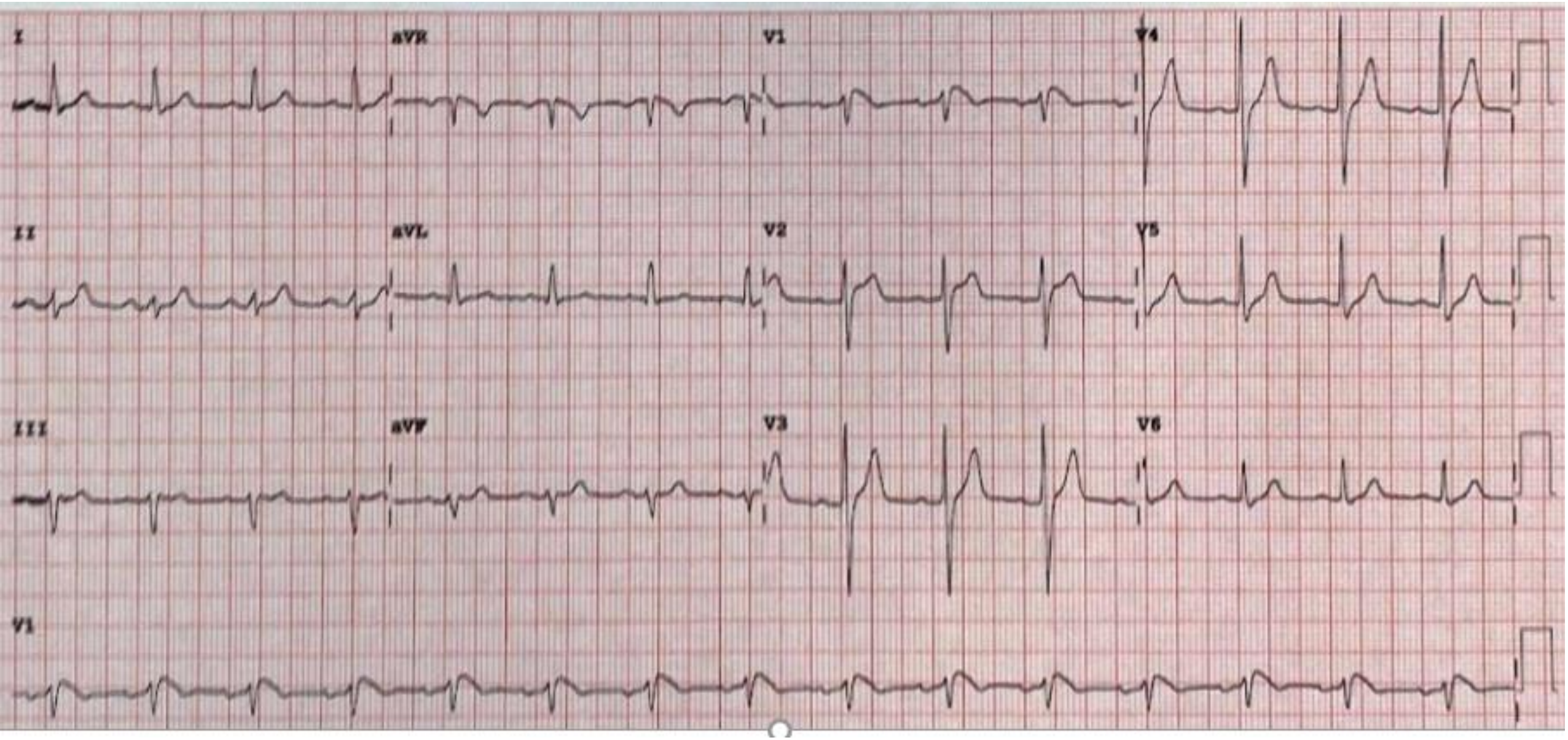
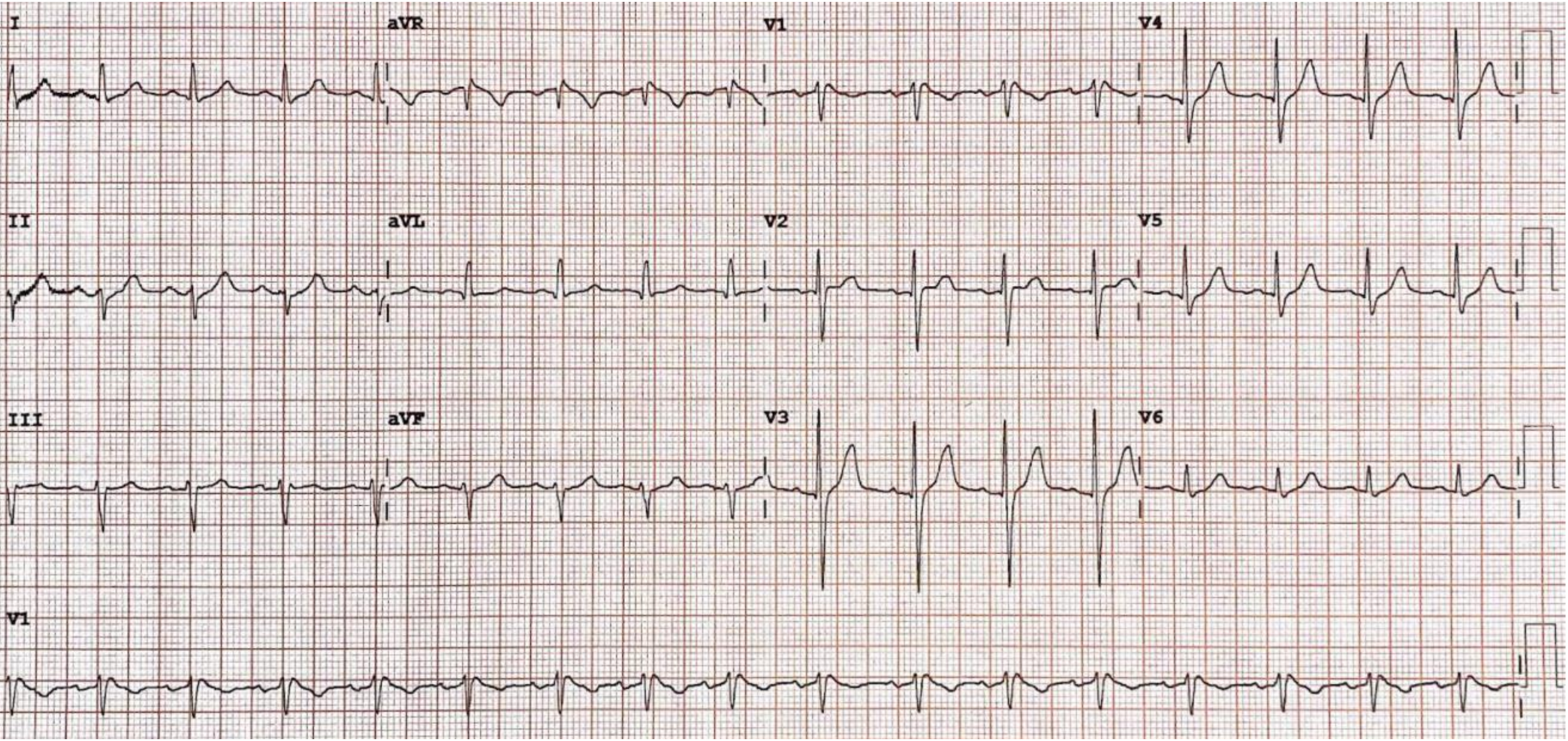
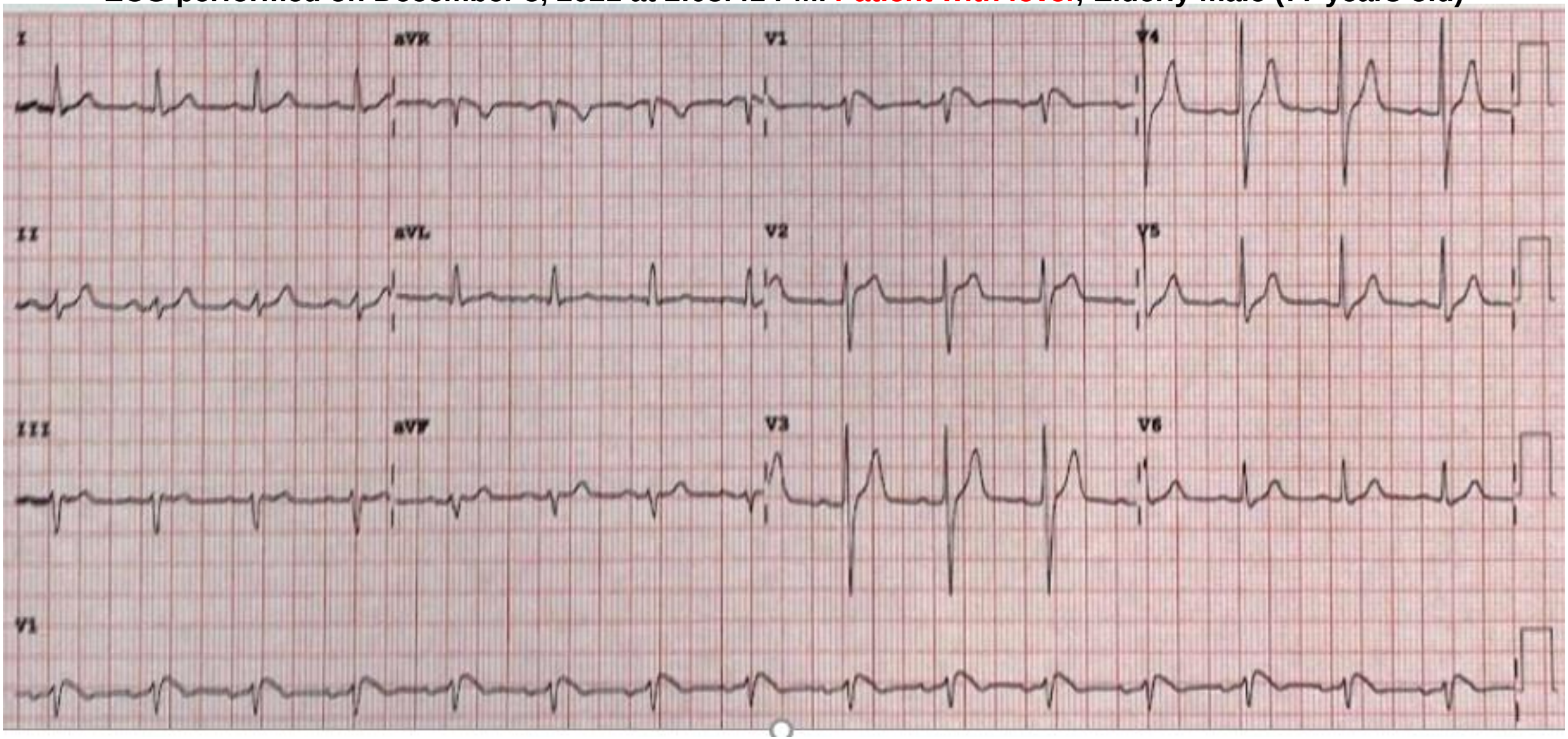


Figure 2: ECG performed with the patient without fever *38.3 graus Celsius*



ECG performed on December 5, 2021 at 2:03:41 PM. Patient with fever, Elderly male (77 years old)

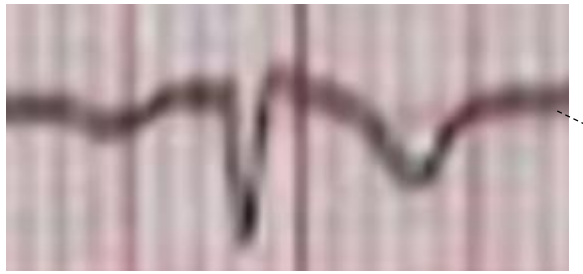


Sinus rhythm, heart rate 91bpm, normal P axis, normal PR interval (180 ms), normal QRS duration (98ms), QRS axis -27°, SIII> SII, prolonged R- Wave Peak Time in aVL (≥ 45 ms), qRs in I and aVL: subtle degree of left anterior fascicular block(LAFB), type 1 ECG Brugada pattern in V1 and normal QT/QTc interval (325-400ms.),

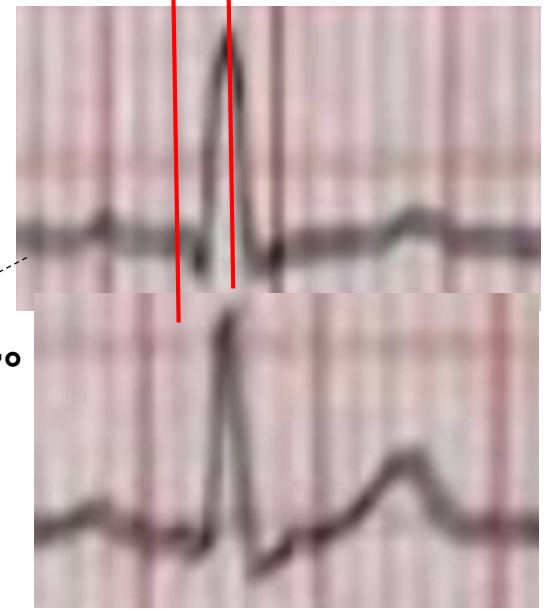
ECG performed on December 5, 2021 at 2:03:41 PM. Patient with fever

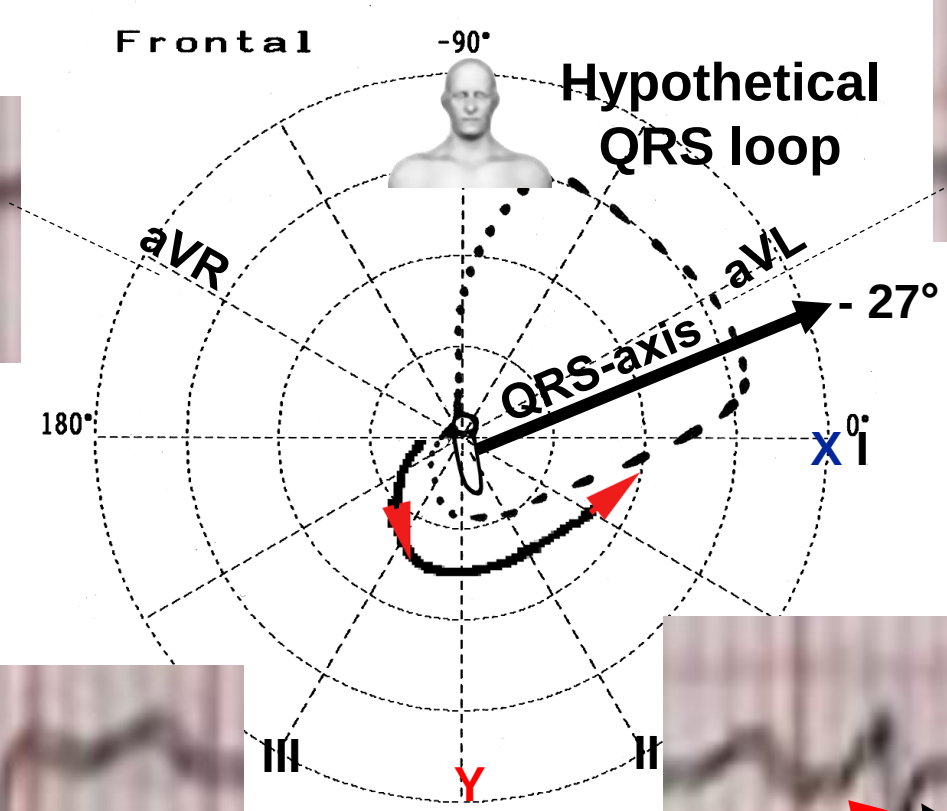
I+ II+III : Some degree of Left Anterior Fascicular Block

R- Wave Peak Time in aVL ≥ 45 ms

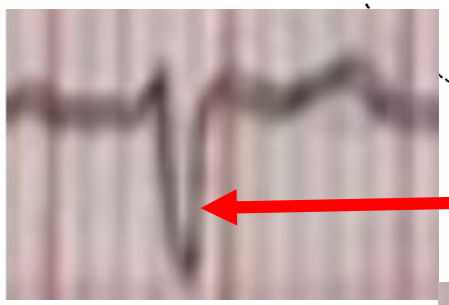


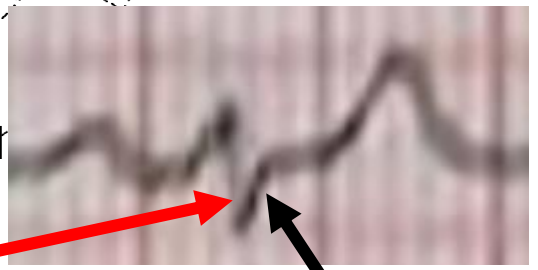
QS





II) qRs pattern in I and aVL

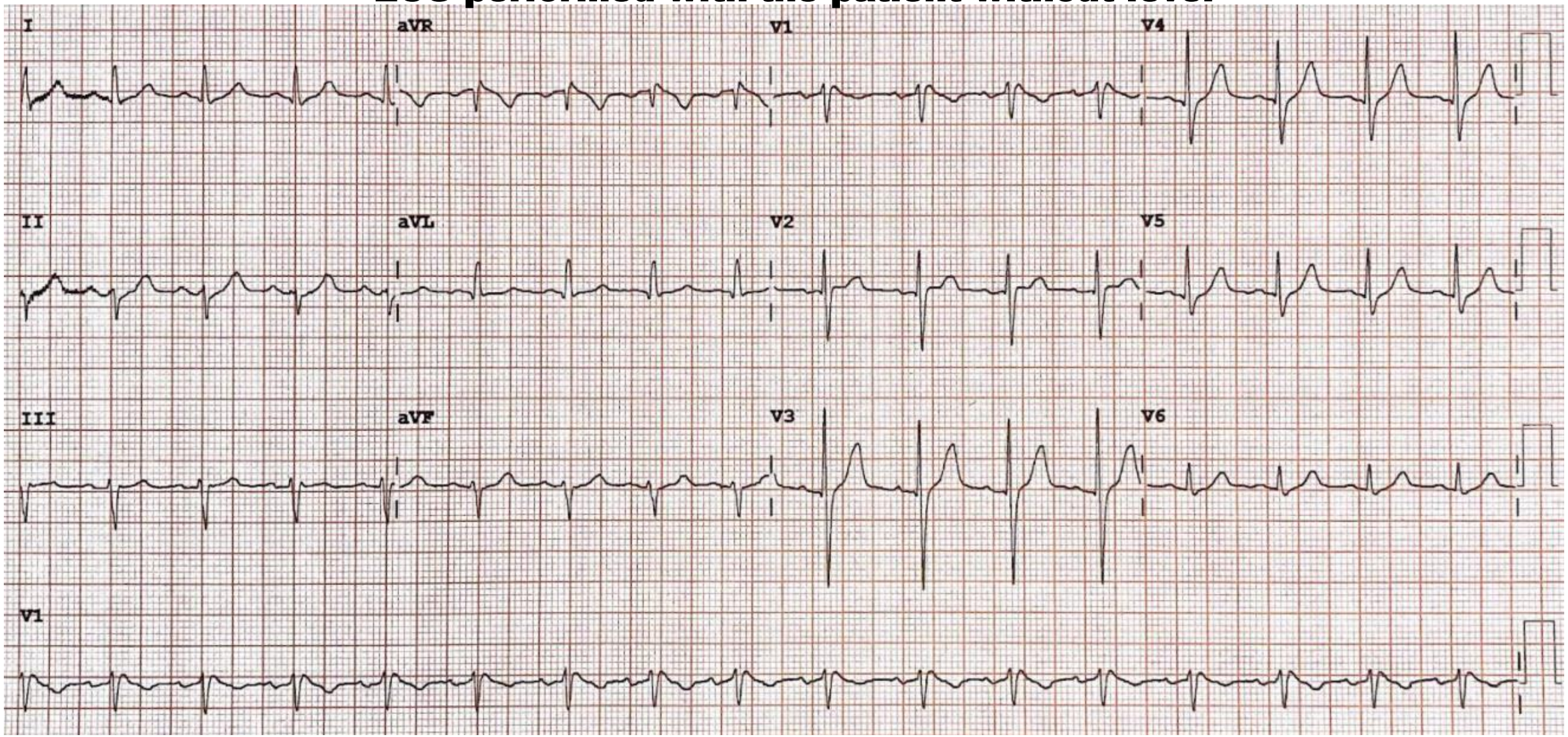




SIII > SII
aVF

r >s

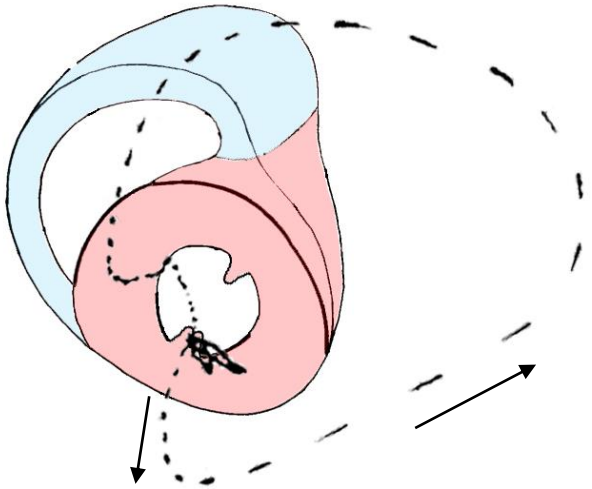
ECG performed with the patient without fever

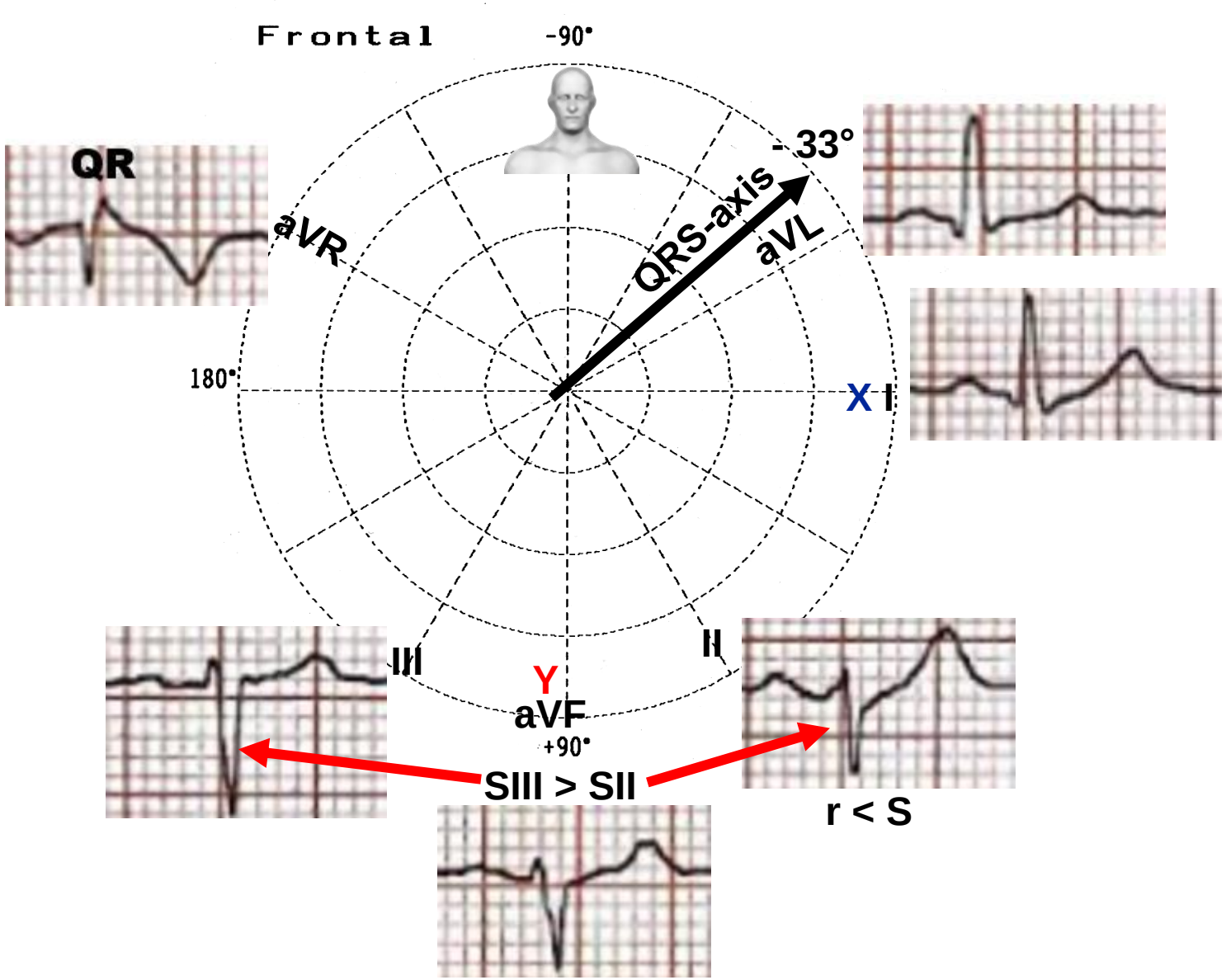


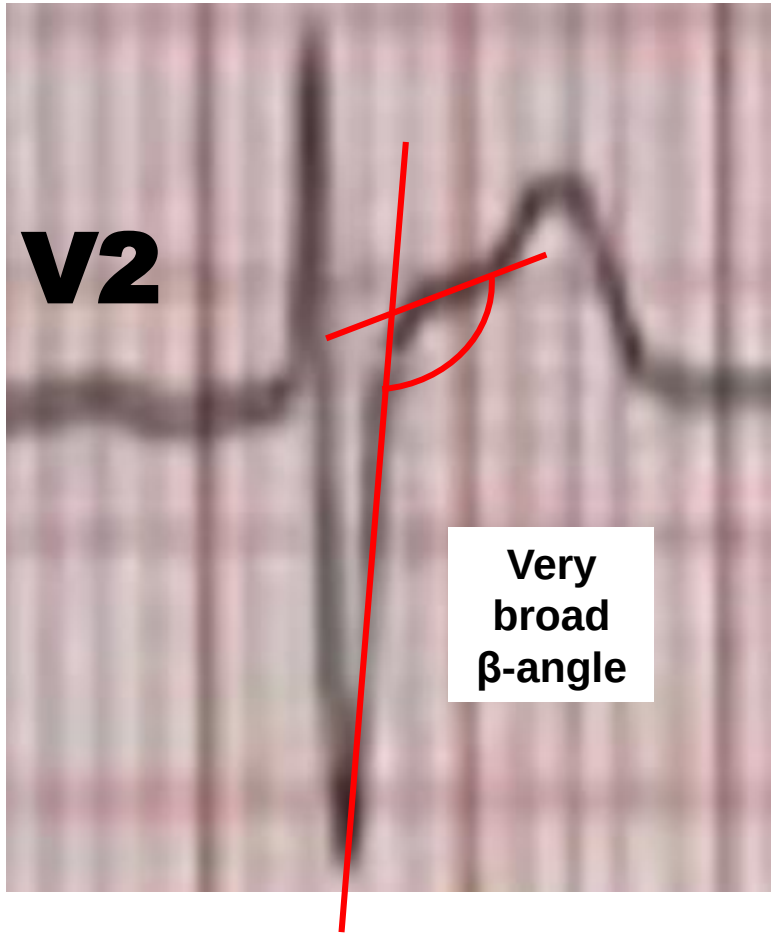
Sinus rhythm, heart rate 100 bpm, normal P axis, normal PR interval (180 ms), normal QRS duration (98ms), abnormal -left axis deviation (QRS axis between −30° to −90°) (- 33°), Qr pattern in aVR, triphasic pattern rSr´ in V1 and normal QT/QTc.

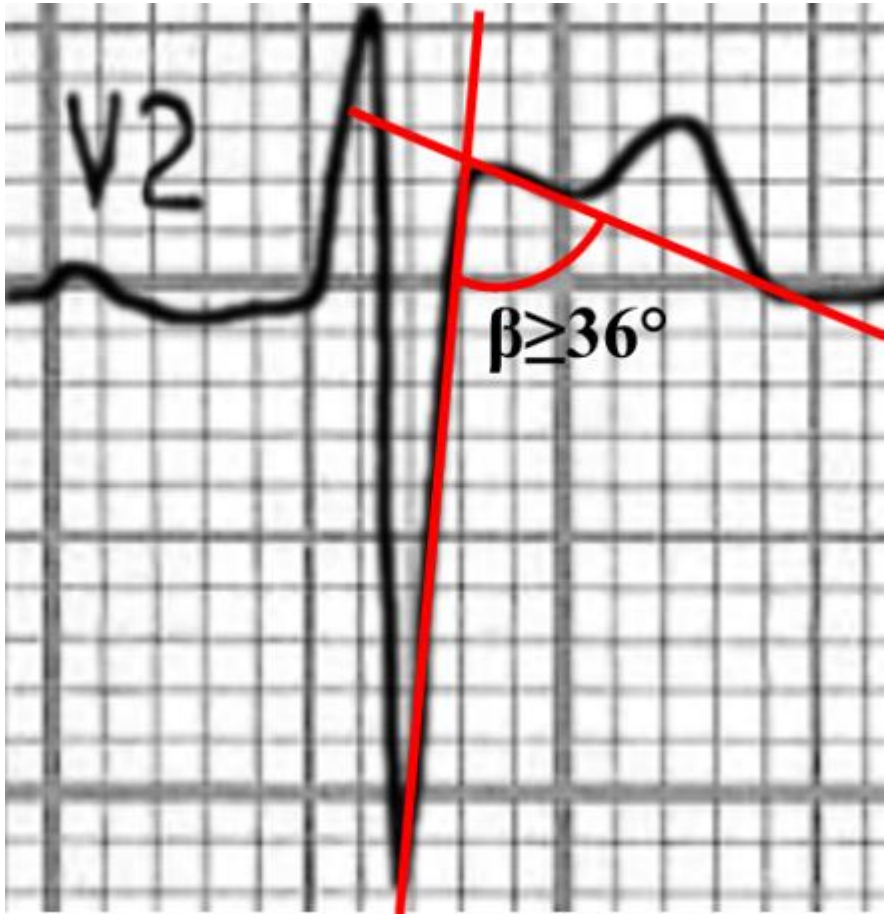
Frontal Plane: ECG performed with the patient without fever

Hypothetical mode of ventricular activation

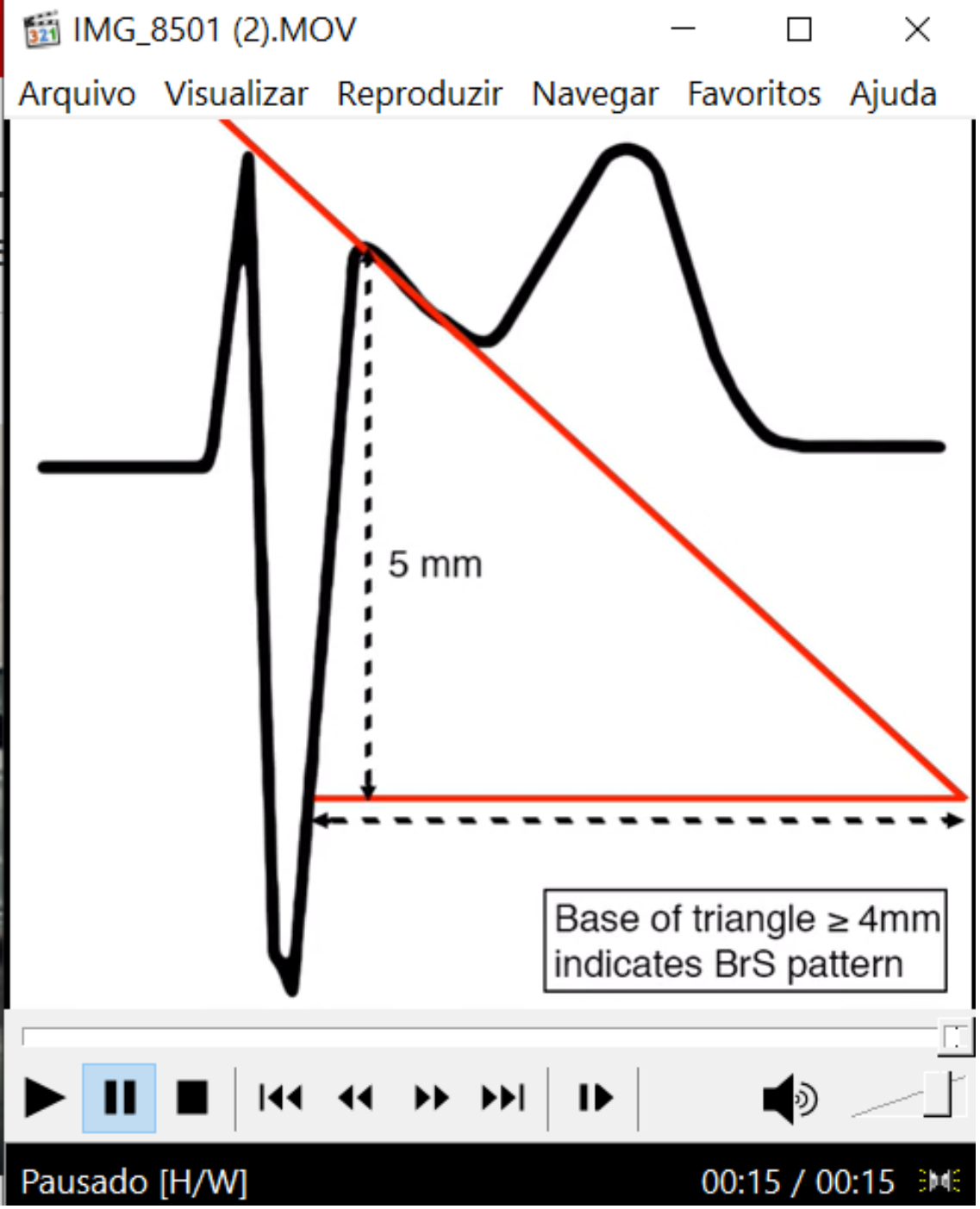








Typical type 2 Brugada pattern in the precordial lead V2. Note the ST with saddleback appearance and followed by positive T wave in V2. The angle formed by the ascending and descending ramp of the final R' wave with blunt contours and the so-called β angle always is ≥36.8°. In the present case > 90° The β angle is formed by the ascending and descending ramp of R'/r' wave. This angle has a mean value of 36.8°. Additionally, the peak of r' wave is broad.



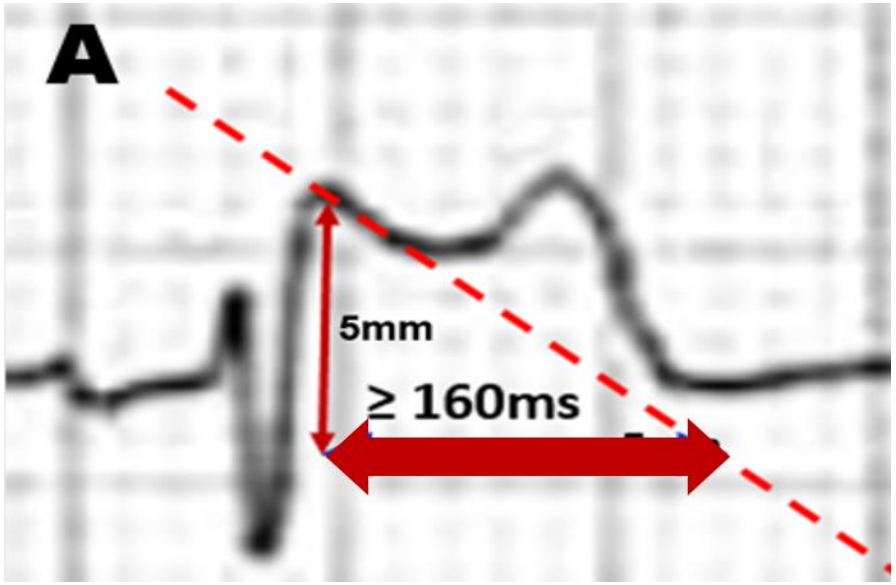
Using triangle base measurement methodologies for the differential diagnosis between truly type 2 Brugada pattern and “ordinary” IRBBB

Triangle base measurement for the differential diagnosis between truly Brugada pattern and “ordinary” IRBBB (Garcia-Niebla J, Elosua R, Brugada R, Brugada P. Base of the triangle to determine a Brugada electrocardiogram pattern. Europace. 2015 Mar;17(3):505. doi: 10.1093/europace/euu359; García-Niebla J, Baranchuk A, Bayés de Luna A. Measuring the base of the triangle is a useful tool to differentiate between electrocardiographic patterns of healthy athletes and Brugada syndrome. Am J Cardiol. 2015 Apr 1;115(7):1001. doi: 10.1016/j.amjcard.2015.01.006)

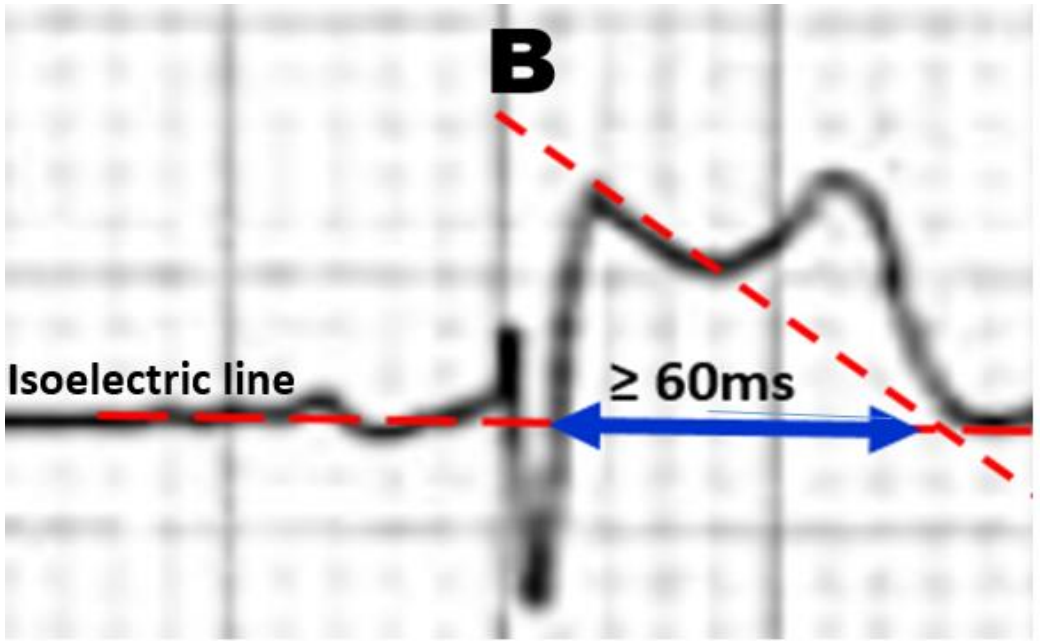
Aditionally the type 2 Brugada ECG pattern has the following characteristics:

Triangle base measured at 5mm (0.5 mV) from the peak of the r´ wave e ≥160 ms (three large squares or 15 small ones)

A. Triangle base measured at 5mm (0.5 mV) from the peak of the r´ wave e ≥160 ms (three large squares or 15 small ones)



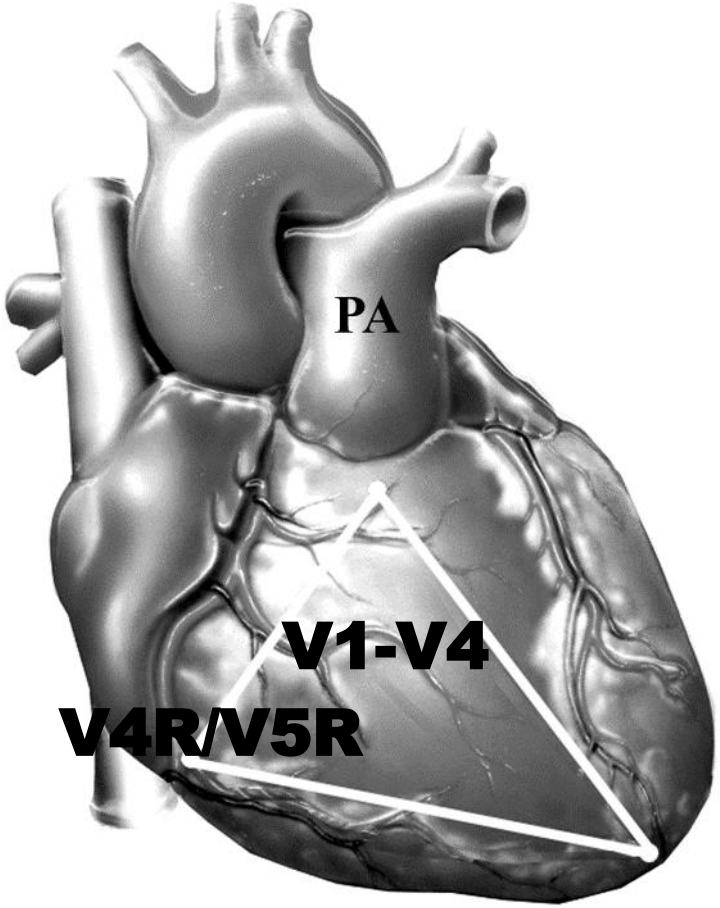
B, Triangle base measured from the peak of the r´ wave at the isoelectric line level ≥60 ms.

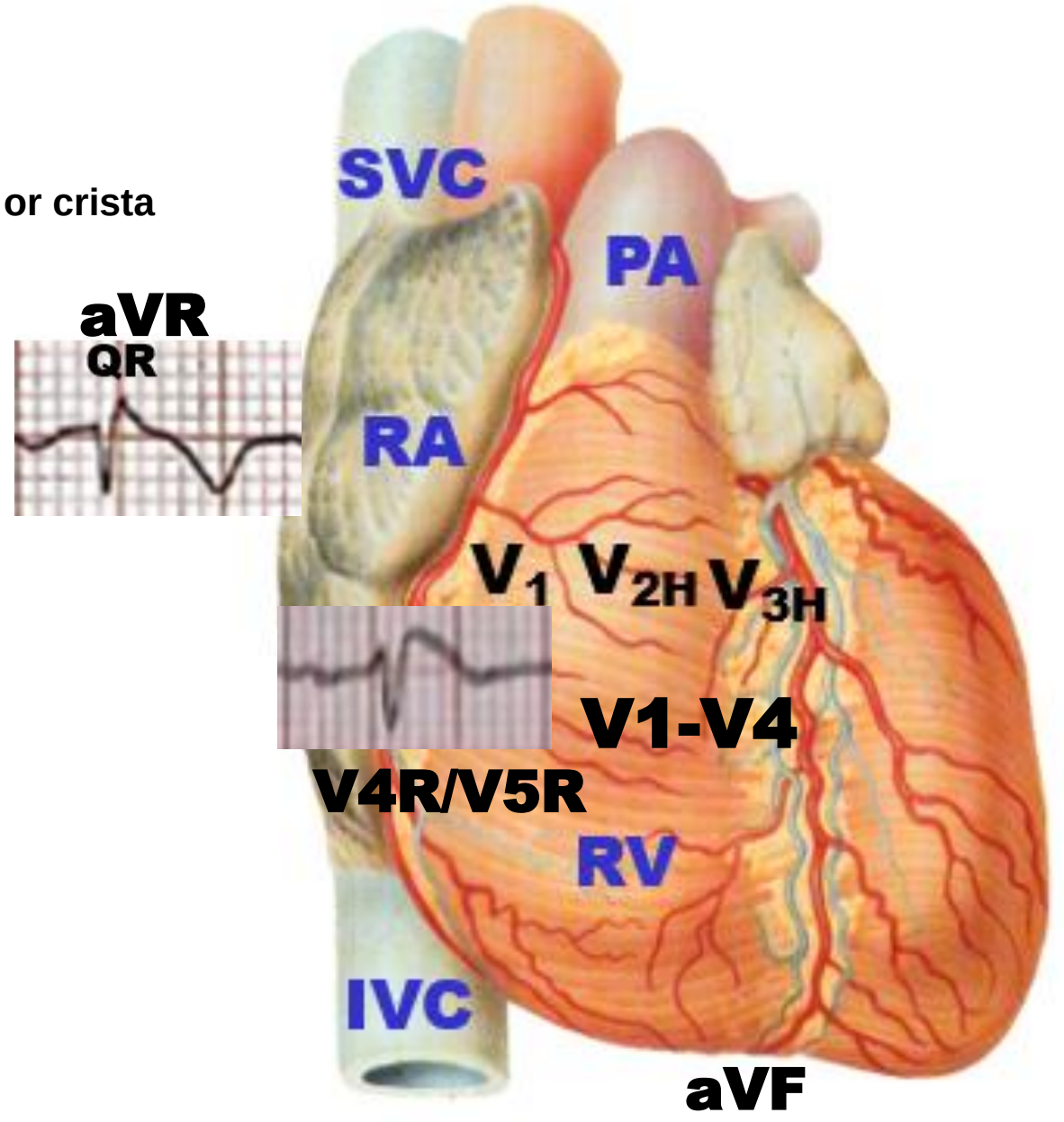


High right precordial leads V_{1H}, V_{2H} and V_{3H} and unipolar aVR face the RVOT (A)

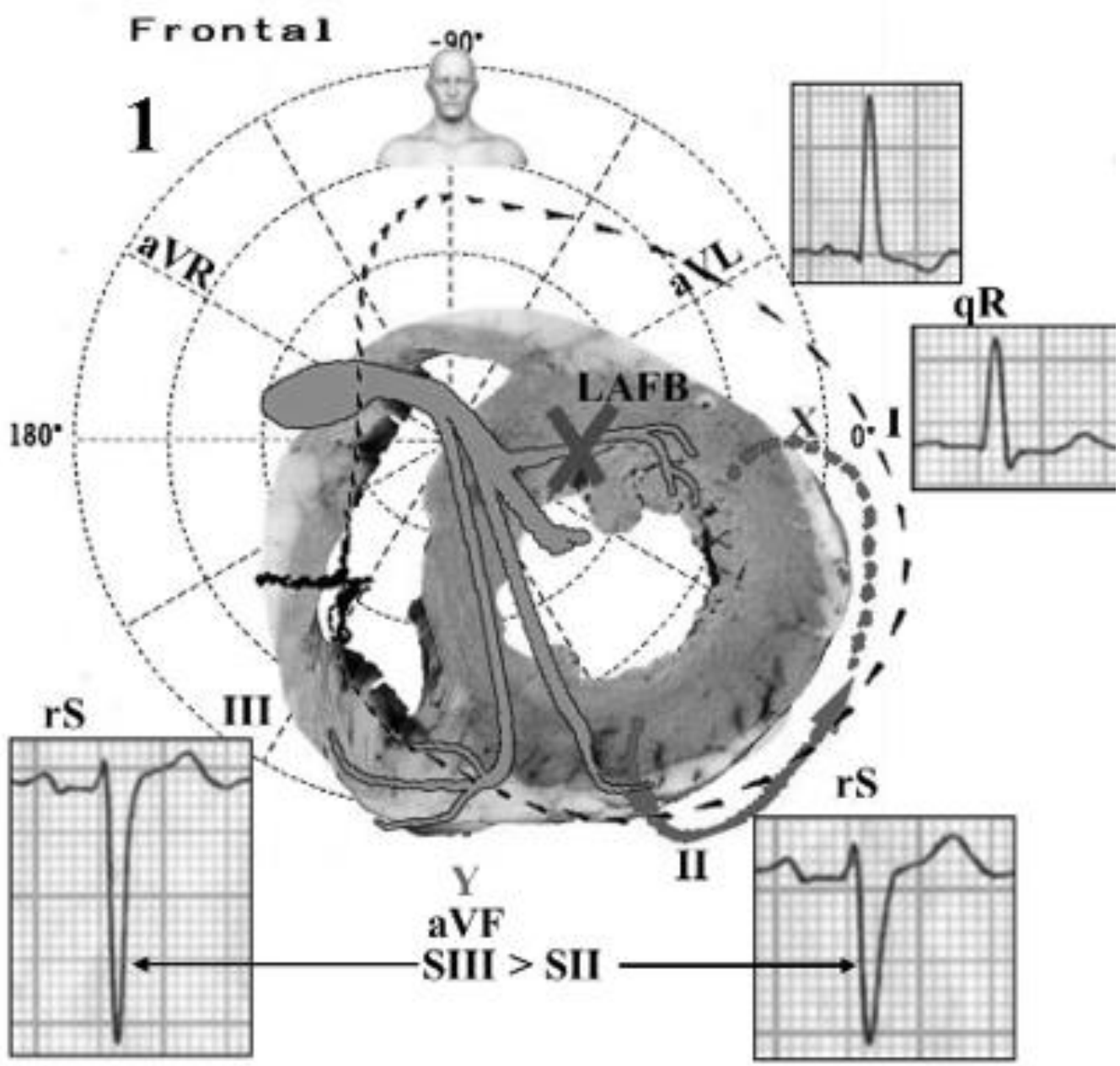
Right ventricular regions and its respective lead

- ❑ Right ventricular trabecular region: V2 and V3.
- ❑ Inferior right paraseptal region: V3 and V4.
- ❑ Right ventricular free wall: from V1 to V4.
- ❑ Basal infundibular region, right ventricular outflow tract (RVOT) or crista supraventricularis: aVR, V1H, V2H and V3H
- ❑ Right Ventricular Inflow Tract (RVIT): V4R, V5R and aVF.





Mode of ventricular activation in Left Anterior Fascicular Block

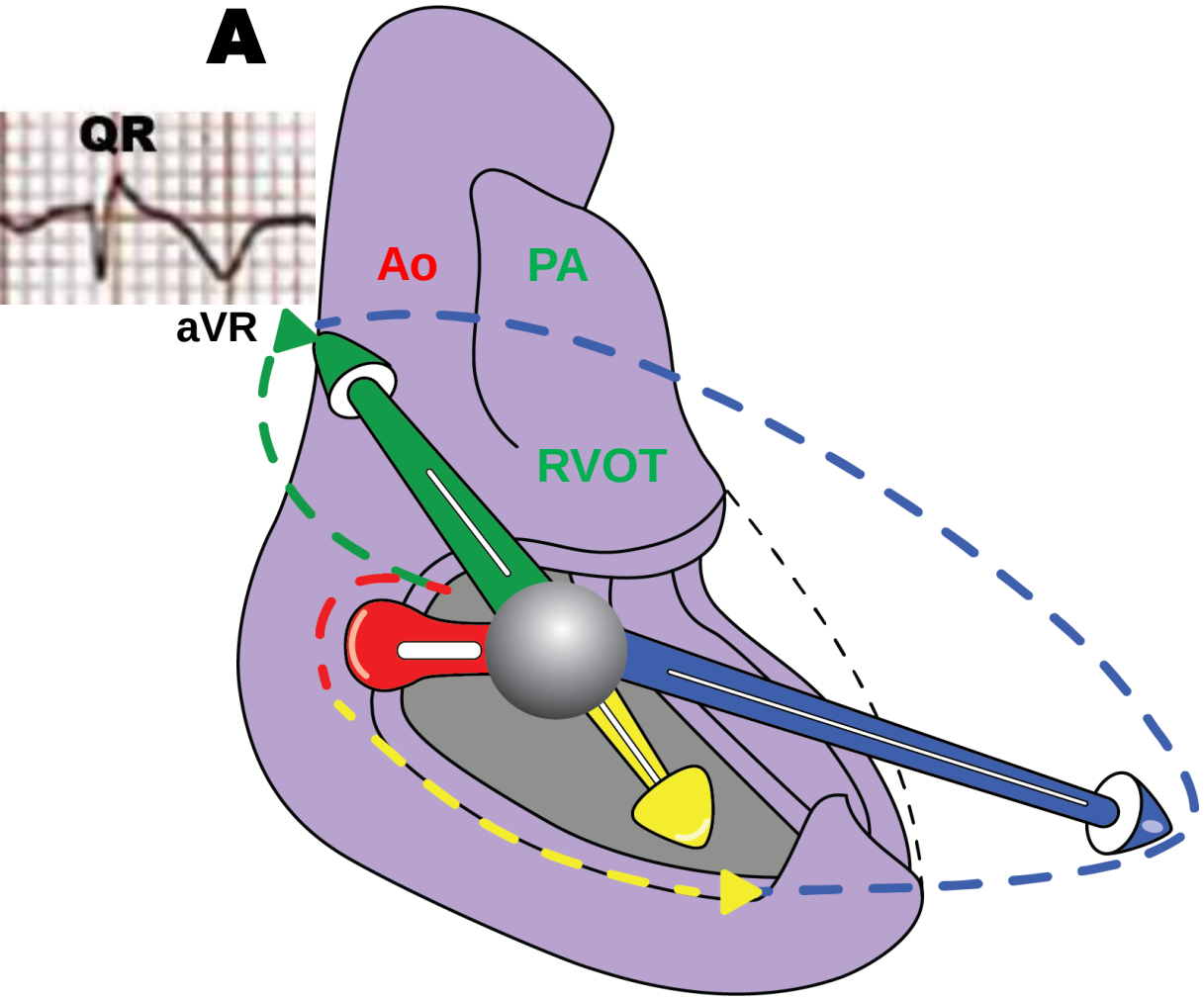


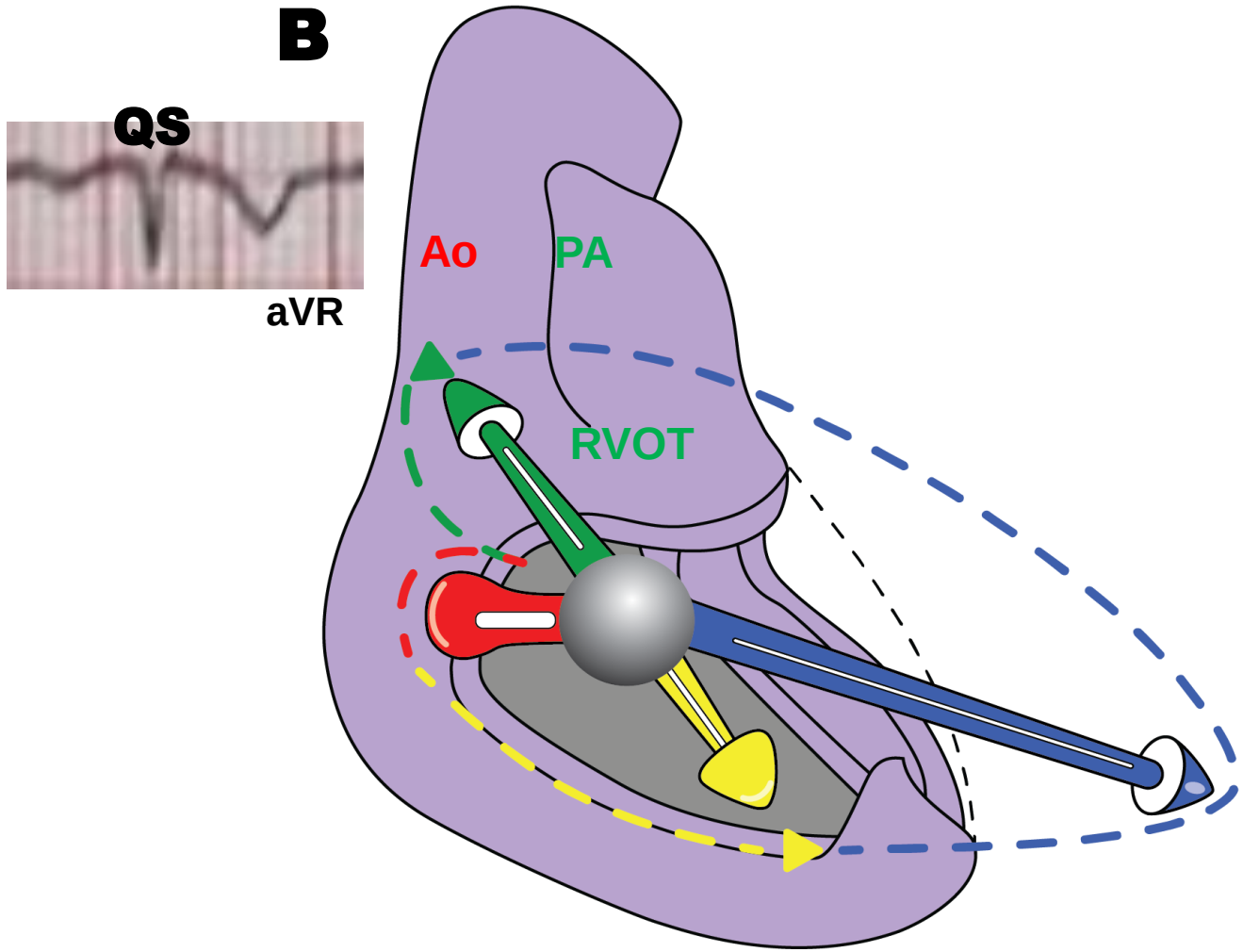
ECG differences between ECG performed with a without fever in the FP

	ECG performed with fever	ECG performed without fever
QRS-axis	- 27°: Normal	- 33° : Abnormal QRS-left axis deviation (QRS axis between −30° to −90°)
QRS-pattern in II lead	R>s	r<S
QRS-pattern in aVR lead	QS	Qr
RVOT Dromotropic disturbance	Paradoxical lower degree of dromotropic disturbance in the RVOT during hyperpyrexia	Paradoxical greater degree of dromotropic disturbance in the RVOT.
Type 1 Brugada patter	Yes	No

Any physiopatological explanation for this apparent paradox??

Theoretical magnitude of the 4th vector (green) with (A) and without (B) fever in the BrS

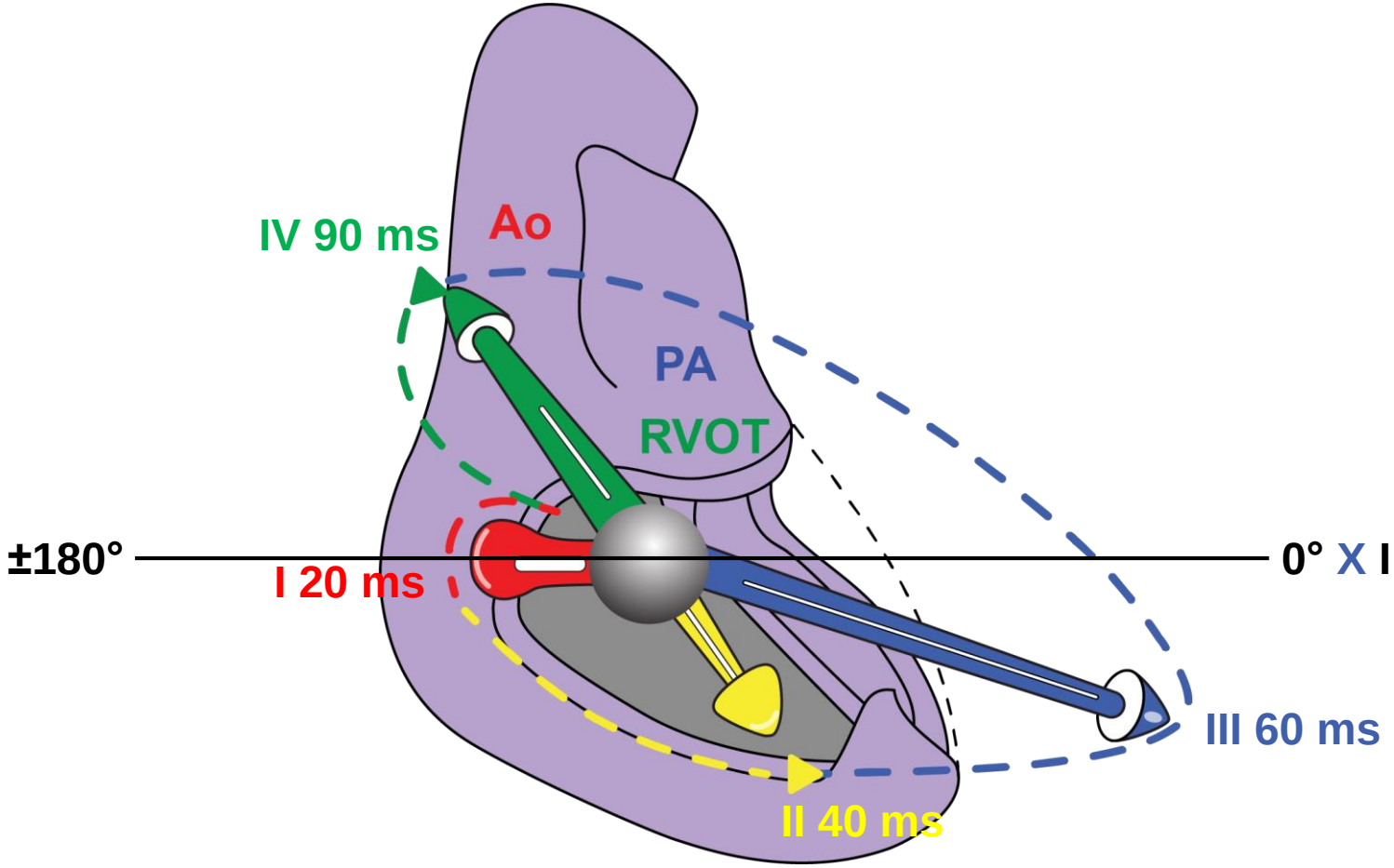




The present case has paradoxical lower degree of dromotropic disturbance in the RVOT. We do not have reasonable explanation.

RVOT Dromotropic disturbance	Paradoxical lower degree of dromotropic disturbance in the Right Ventricular Outflow Tract (RVOT) during hyperpyrexia	Paradoxical greater degree of dromotropic disturbance in the Right Ventricular Outflow Tract (RVOT)

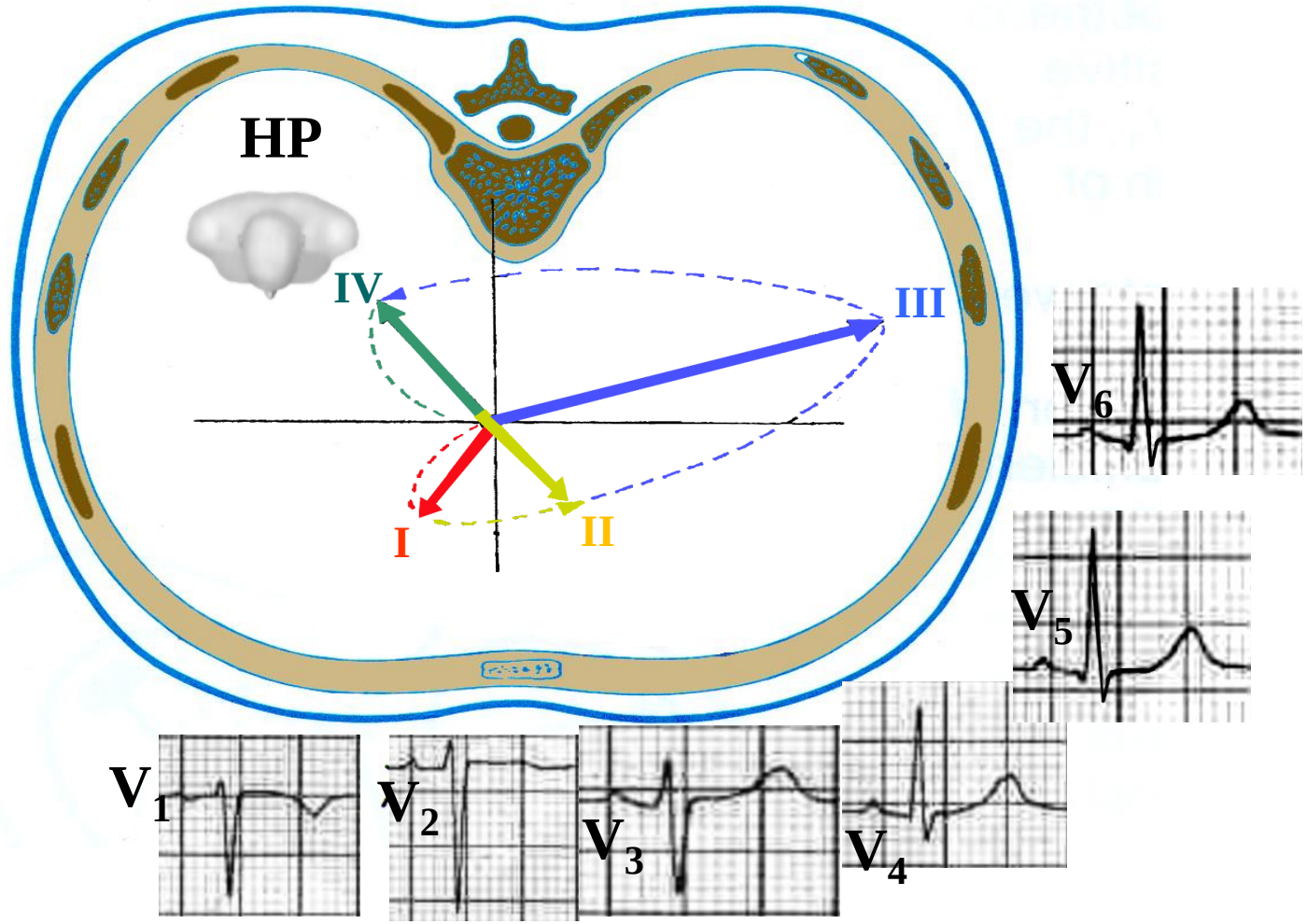
Normal VCG-Loop of Ventricular Activation (QRS) represented by four vectors



Representation of ventricular activation with four vectors. In red, vector I (septal) from the initial 10 ms to 20 ms. In yellow, vector II from 20 ms to 40 ms of the low region of the septum. In blue, vector III from 40 ms to 60 ms, representing activation of free walls of both ventricles. In green, the basal vector or IV from 60 ms to 90 ms or 100 ms representing activation of the basal portion of both ventricles.

Right Ventricular Outflow Tract (RVOT)

Representation of Ventricular Activation with Four Vectors in the HP



Representation of ventricular activation with four vectors in the horizontal plane.

Discussion

In BrS, fever is associated with a greater chance of tachyarrhythmia events; this suggests that the increase in temperature affects the Na^+ channel conductance. Mutations in a cardiac sodium channel gene is linked to BrS and some experimental data suggest that the dysfunction of the mutated channel can be temperature sensitive. Since temperature affects permeability, temperature change forces the Na^+ channel and other channels to modify their functional state, consequently, INa^+ kinetics depends strongly on temperature.

Dumaine et al was the first to illustrate a cardiac sodium channel mutation of which the arrhythmogenicity suggested that patients are more at risk during febrile states. (**2**) Thus, an increase of 10ºC increment the voltage or width by a factor of 1.3 to 1.6 and increases the time of opening and the number of times that the channel is opened by a factor of three. Activation and inactivation kinetics for early INa^+ are two fold faster at higher temperature, and shift activation and steady-state inactivation (**3**). Then, the fever is considered triggers to PVT/VF in the BrS jointly with other factors capable to get worse the ventricular repolarização in BrS patients are: antimalarial agents, tricyclic antidepressants, sodium channel blockers Class Ia (Ajmaline and Procainamide), Class 1c (Flecainide, Pilsicainide), cocaine, α-agonist, β-blockers, nitrates, cholinergic stimulation, hyperglycemia, nocturnal bradycardia consequence of vagal predominance, alcohol consumption, mental stress, ischemia, hypokalemia, hypothermia and post direct current cardioversion.

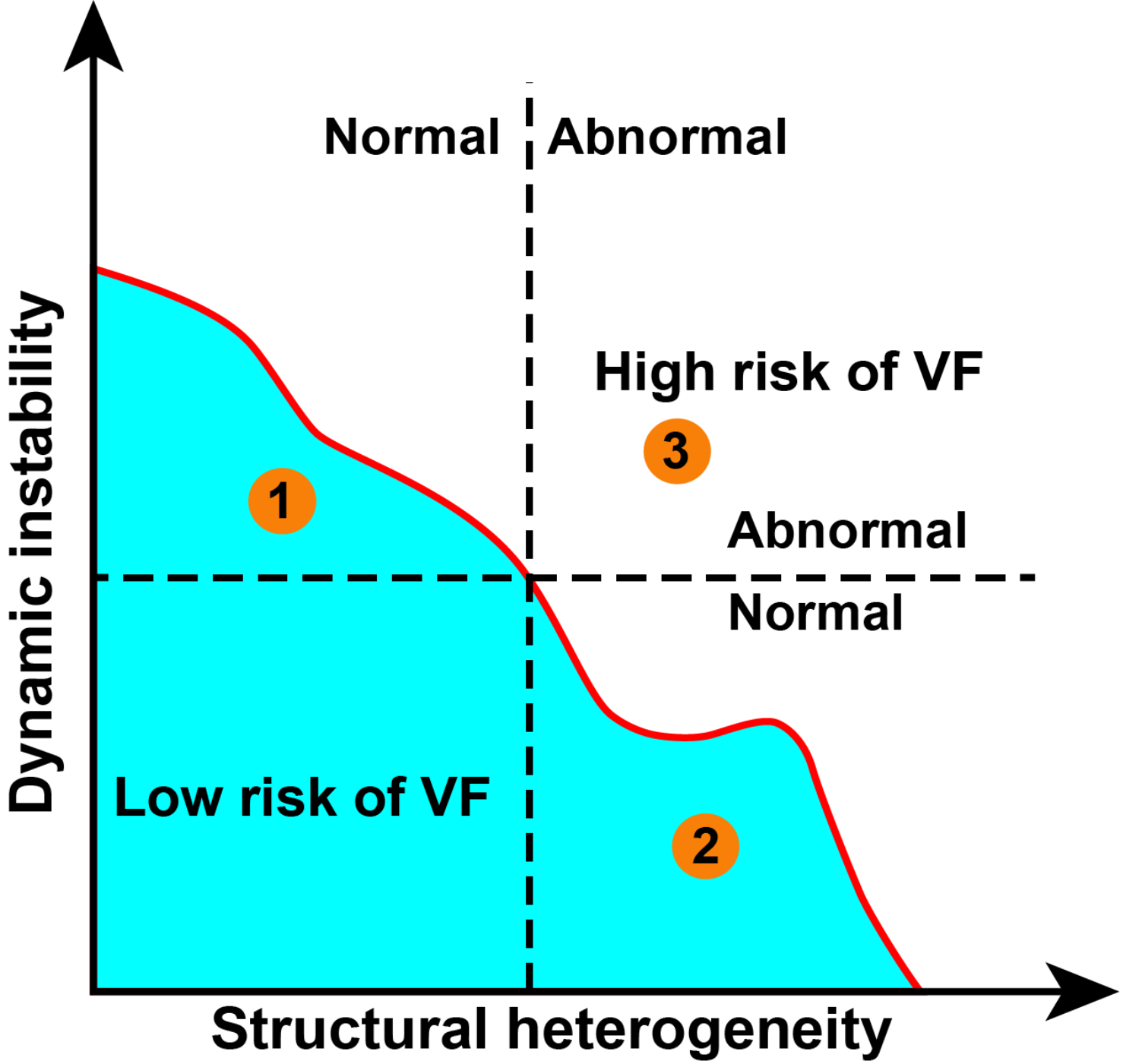
The repolarization versus repolarization hypothesis and eclectic possibility

The “repolarization” hypothesis postulate a gradient of expression of the Ito current across the RVOT myocardium and reduced sodium current facilitates the occurrence of afterdepolarizations originating from the RVOT epicardium and of Phase2 reentry (P2R) polymorphic VT/VF. P2R is a local arrhythmogenic phenomenon where electrotonic current propagates from a spike-and-dome action potential region to re-excite a loss-of-dome action potential region. Reduced I_{Na} may lead to the formation of an arrhythmogenic substrate due to drotropic disturbance, but may also result in a propensity for P2R-induced premature ventricular contractions (PVCs) by decreasing the inward current available to counteract I_{to}. P2R is not the sole arrhythmogenic pathway in BrS and/or I_{to}-induced AP divergence. The dispersion in repolarization due to I_{to} heterogeneity in itself forms an arrhythmogenic substrate with an increased propensity for unidirectional conduction block by a closely coupled PVC not necessarily P2R-induced.

The “depolarization” hypothesis points to slowed and delayed areas of conduction in the RVOT as the substrate for BrS arrhythmias. This latter hypothesis challenges the definition of BrS as a pure electrical heart disease, and is supported by microscopic SHD with lesser expression of connexine 45-gap junction and fibrotic infiltrates localized at the RVOT in series of patients (**Catalano O, Antonaci S, Moro G, Mussida M, Frascaroli M, Baldi M, et al. Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. Eur Heart J . 2009 Sep;30(18):2241-8. doi: 10.1093/eurheartj/ehp252.)(Marina Cerrone 1Editorial commentary: Non-invasive tools for risk stratification and treatment in Brugada syndrome: Less is more? Trends Cardiovasc Med. 2021 Jul;31(5):330-331. doi: 10.1016/j.tcm.2020.06.01**0.).

We carefully analyzed an extensive series of 121 ECGs/VCGs from BrS patients with spontaneous or induced by provocative test type 1 Brugada ECG pattern from the total sample, 102 ECGs/VCGs came from the Department of Clinical and Experimental Cardiology, Academic Medical Center, Amsterdam, The Netherlands; and 19 ECG/VCGs came from our series (total of 121 ECG/VCGs). We demonstrate that the ECG/VCG in the BrS with type 1 Brugada ECG pattern monotonously in all cases we observe terminal conduction delay located on the upper right quadrant of the frontal plane near the aVR lead.(**http://cardiolatina.com/wp-content/uploads/2019/04/Andres.pdf Second "Dr. Cosme Argerich" Internatiotal Symposium of Cardiology on Internet**)(**Pérez-Riera AR, Barbosa-Barros R, Thomaz de Andrade A, Pontes Rodrigues R, Yanowitz F, Daminello Raimundo R, de Abreu LC, Nikus K, Brugada P.J Relevance of the vectorcardiogram in the Brugada syndrome with "northwest QRS axis".Electrocardiol. 2021 May-Jun; 66:125-128. doi: 10.1016/j.jelectrocard.2021.04.009**.) (**Pérez-Riera AR, Yanowitz F, Barbosa-Barros R, Daminello-Raimundo R, de Abreu LC, Nikus K, Brugada P. Electrocardiographic "Northwest QRS Axis" in the Brugada Syndrome: A Potential Marker to Predict Poor Outcome. JACC Case Rep. 2020 Oct 7;2(14):2230-2234. doi: 10.1016/j.jaccas.2020.07.037**.)

Currently, predominant opinions about physiopatological hypotheses admit the coexistence of both mechanisms as we show in the figure of the next slide



Hypothetical **point 1:** represents the repolarization hypothesis alone (abnormal early repolarization without SHD); **point 2**: represents the depolarization hypothesis alone (structural heterogeneity due to fibrosis, lesser gap junction expression (connexin-43), dromotropic disturbance without ER). Whereas neither factor alone places the patient in the high VF risk zone, their combination (**point 3)** does. Modified from **Weiss JN. Arrhythmias in Brugada Syndrome: Defective Depolarization, Repolarization or Both? JACC Clin Electrophysiol. 2021 Feb;7(2):271-272. doi: 10.1016/j.jacep.2020.12.020**,

Conclusion

In the present case, only ECG-2 without the diagnostic Brugada type 1 electrocardiographic pattern shows the paradox of presenting only final r in aVR hinting at a slight final conduction delay during the febrile state y being absent in the ECG of figure 1 with type 1 Brugada pattern with the patient having fever with QS pattern in aVR signaling absence of terminal QRS conduction delay in RVOT territory as expected. Consequently, we have to admit the possibility that in the present case the predominant operative mechanism is that of the repolarization hypothesis.