Mulher de média idade com numerosos fatores de risco e dor de repouso, prolongada dorsal irradiada a região precordial associada a bradiarritmia sinusal com pausas

Middle-aged woman with risk factors and prolonged oppressive back pain at rest irradiated to the precordial region associated to sinus bradychardia with pauses: A new terminology: Atypical Type 1 Brugada ECG pattern

From Raimundo Barbosa Barros M.D.
Coronary Center Hospital de Messejana Dr. Carlos Alberto Studart Gomes Fortaleza-Ceará-Brazil

Finals comments Andrés Ricardo Pérez-Riera M.D. Ph.D.
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HDA: female, 44-year-old patient: hypertensive, diabetic, and dyslipidemic; admitted on February 29th, 2012 due to complaint of dyspnea and posterior oppressive chest pain for 3 h, irradiating to the precordial area, without triggering factor. At the time, she was adynamic, with significant bradyarrhythmia, BP of 130x80 mmHg and lower limbs pain. She mentioned a catheterization 5 years ago, after the episode of pain similar to the current one, not knowing the result of the test. She denies having syncopes or lipothymia episodes.
Medications in use: Glibenclamide 5 mg 1 cp in jejunum and 1 cp before lunch; enalapril 5 mg 1 cp of 12/12 h; simvastatin 40 mg 1 cp after meals; calcium carbonate 500 mg 1 cp at the time of lunch; omeprazol 20 mg.
She denies syncopes or SCD in 1st, 2nd, or 3rd degree relatives.
Laboratory tests (Feb. 29, 2012): Hb: 11.9; Ht: 38.6%; glucemia: 267 mg/dL; Urea: 32 mg/dL; creatinine: 0.8 mg/dL Cl: 100.9 mEq/L; K+: 4.7 mEq/L; Na+: 137 mEq/L GOT: 27 U/L; GPT: 35 U/L; TSH: 2.67 uL U/mL; leukocytes: 6,030/mm 3 rods: 0; segmented: 53% platelets: 227,000/mm3 troponin and CK-MB are normal.
Echocardiogram (March 2, 2012):
heart chambers of normal dimensions and septum and free wall with normal thickness. EF = 56%
LV systolic function: reduced in a mild degree
Mild diastolic dysfunction of the LV
Valves with no significant alterations.
Catheterization (March 3, 2012): normal coronary arteries. Normal LV function.
Initial prescription: ASA, clopidogrel, isordil, losartan, atorvastatin, metformin, glibenclamide, regular insulin according to HGT, omeprazole.

Question: what would you do with this patient? Pharmacological test? EPS? There is 1 ECG showing sinus bradycardia with sinus arrest (later I will send this).
Warm regards,

HDA: Paciente feminina. 44 anos, hipertensa, diabética e dislipidêmica, admitida em 29/02/2012 com queixa de dispnéia e dor torácica posterior, em aperto, durante 3h, irradiando para precórdio, sem fator desencadeante. Na ocasião, encontrava-se adinâmica, com bradiarritmia importante, PA de 130x80mmHg e dor em MMIIA

Refere realização de cateterismo há 5 anos, após episódio de dor semelhante ao atual, não sabendo informar o resultado do exame. Nega episódios de síncope ou lipotimia.

Nega sincopes ou mortes súbitas em parentes de 1º, 2º ou 3º graus

Exames Laboratorias (29/02/12): Hb: 11,9; Ht:38,6%; Glicemia: 267mg/Dl; Uréia: 32mg/dL; Creatinina: 0,8mg/dL; Cl: 100,9mEq/L; K^+: 4,7mEq/L; Na^+: 137mEq/L; TGO: 27U/L; TGP: 35U/L; TSH: 2,67uIU/mL; Leucócitos: 6.030/mm3 Bastonetes: 0; Neutrófilos: 53%; Plaquetas: 227.000/mm3; Troponina e CK-MB normais

ECOCARDIOGRAMA (02/03/12):

- Cavidades cardíacas de dimensões e septo e parede livre de espessuras normais. FE = 56%
- Função sistólica de VE reduzida em grau discreto
- Disfunção diastólica leve do VE

Aparelhos valvares sem alterações significativas.

CATETERISMO (03/03/12) Coronárias normais. FEVE Normal.

Prescrição inicial: AAS, Clopidogrel, Isordil, Losartana, Atorvastatina, Metformina, Glibenclamida, Insulina Regular conforme HGT, Omeprazol

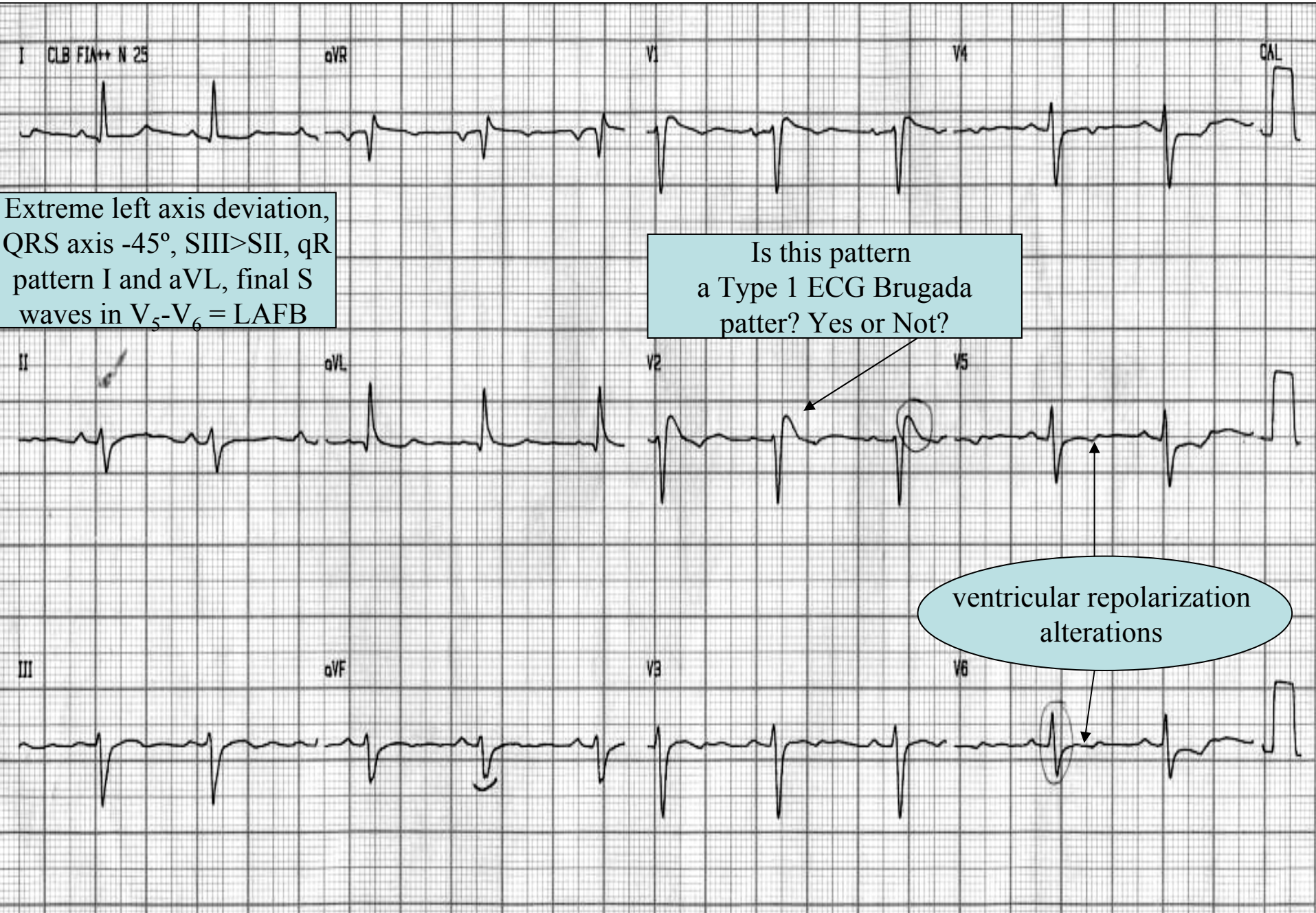
Medicações em uso: Glibenclamida 5mg 1cp em jejum e 1cp antes do almoço; Enalapril 5mg 1cp de 12/12h; Sivastatina 40mg 1cp após jantar; Carbonato de Cálcio 500mg 1cp na hora do almoço; Omeprazol 20mg

Pergunta: o que os colegas fariam com esta paciente? Teste farmacológico?EEI? Há 1 ECG mostrando bradicardia sinusal com paradas sinusais(depois em mando este)

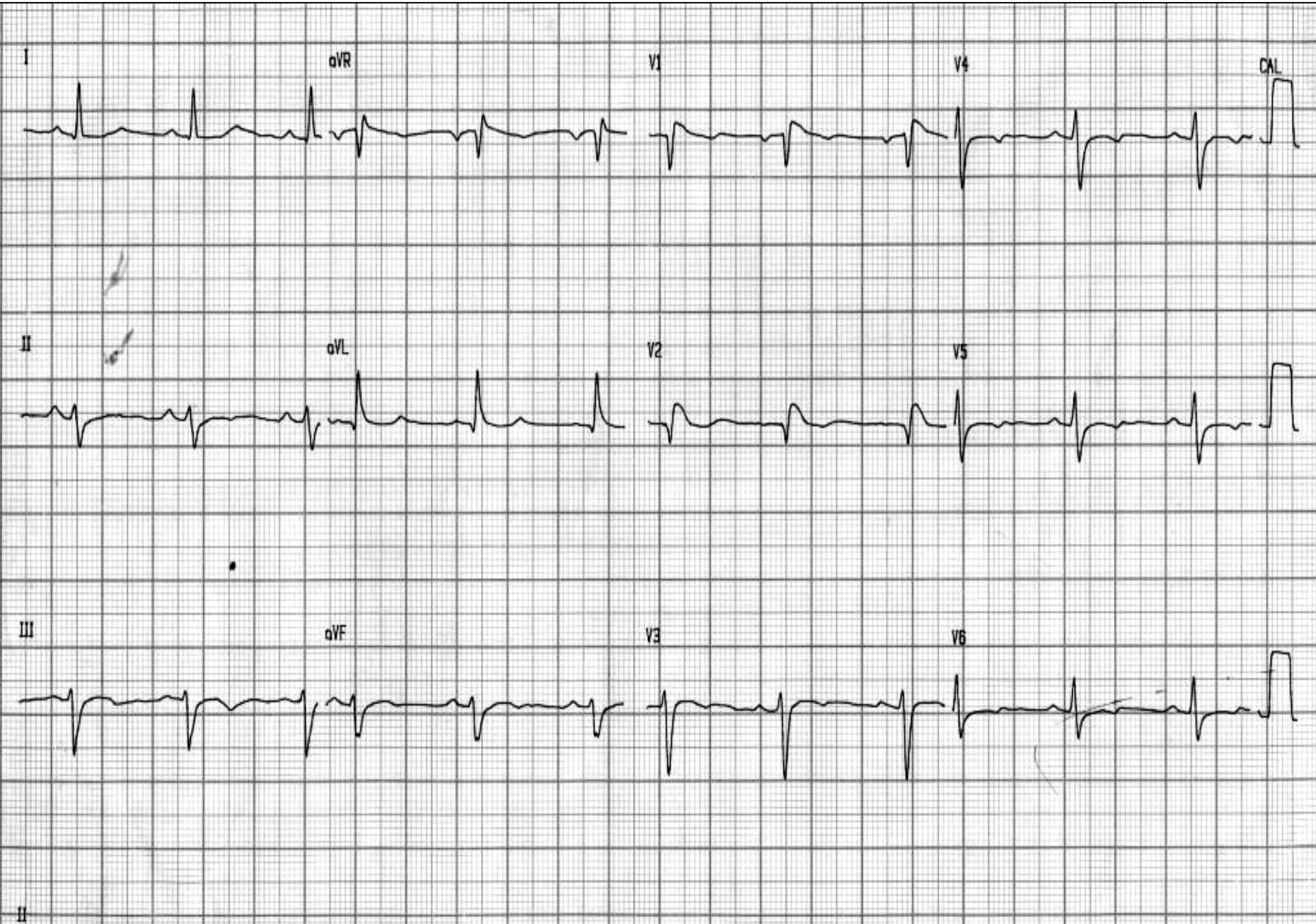
Un abrazo

Raimundo

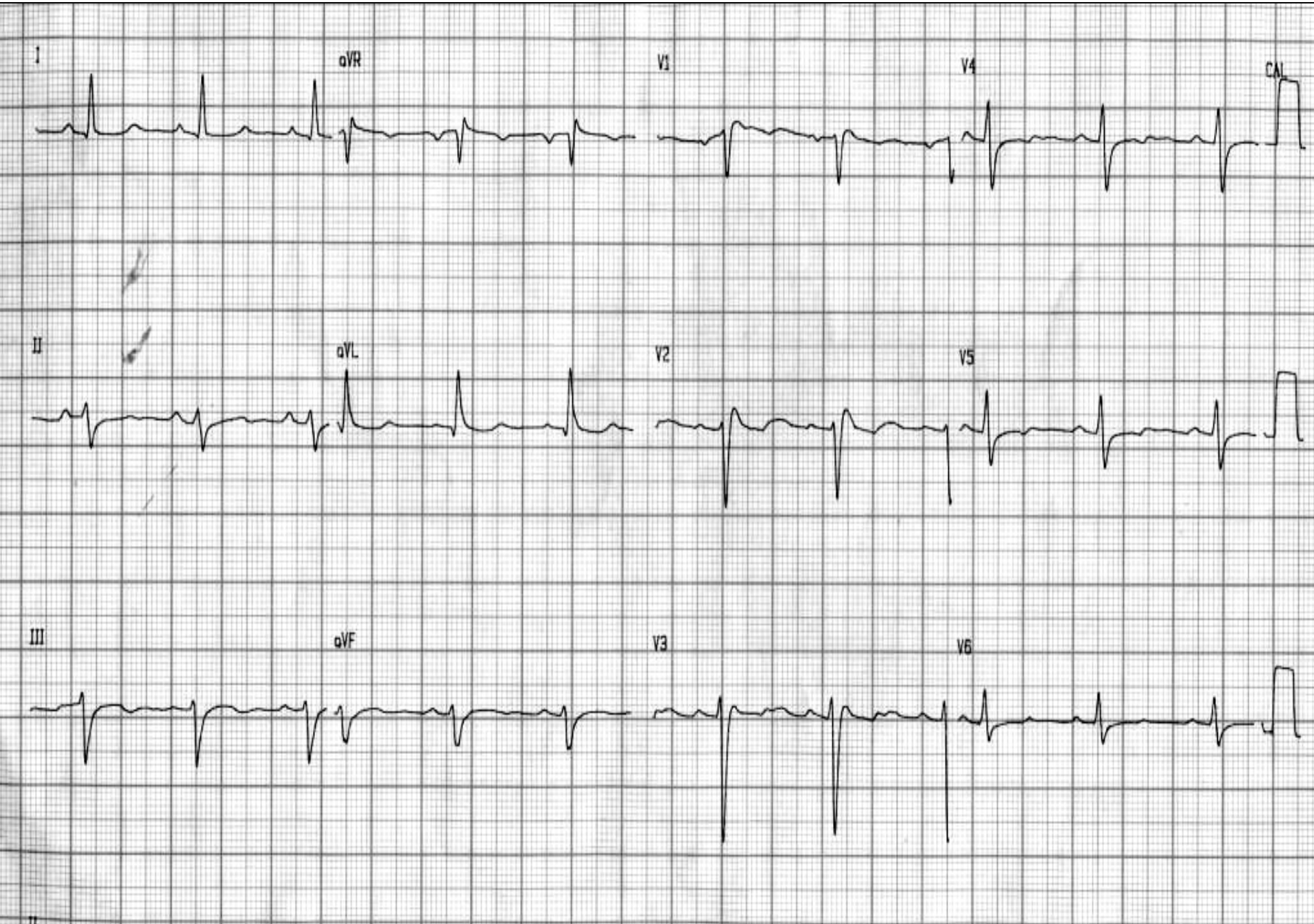
Admission ECG



ECG March /03/2012



ECG March 04/2012 Right precordial leads at higher intercostal space positions: V_{1H}-V_{2H}-V_{3H};



Colleagues opinions

Dear Raimundo
Thanks for this interesting case.
Assuming the absence of CAD, I would suggest a Procainamide (Ajmaline) challenge to completely ruled out a sodium channel dysfunction.
Chest pain in patients with Brugada seems not uncommon, but I am not sure what the reason is.

Adrian Baranchuk MD FACC FRCPC
Queen's University

Querido Raimundo
Gracias por enviar este interesante caso
Asumiendo la ausencia de enfermedad coronária yo sugeriria prueba farmacológica con ajmalina o procainamida para eliminar totalmente la posibilidad de disfunción del canal de sodio.
Dolor en el pecho em pacientes Brugada parece no ser raro, pero yo no estoy seguro cual es el motivo.

Prezado Raimundo
Obrigado por nos enviar este caso iteresante
Tendo em conta a ausencia de doença coronariana eu sugiro realizar a prova farmacológica com ajmalina o procainamida com o intuito de afastar totalmente a posibilidade de disfunção do canal de sódio.
Dor no peito em pacientes portadores da síndrme de Brugada parece nao ser infrequente, porem não estou certo se este é o motivo.

You need to exclude aortic dissection given the pattern of back pain. The 12lead ECG is diagnostic of the Brugada pattern. As she is without sx of Arrhythmias an EP study is of no value [see Viskin and Wilde HRS journal] although one might argue that determination of the VERP <200 ms as shown by Priori (JACC last month) defines arise factor with a hazard ratio of 4.I think we need more experience using this finding.
In addition, she is a female and there is no fractionation of the QRS.
Finally,consider genetic testing mainly for approach to the family evaluation.

Es necesario excluir la disección aórtica dado el patrón del dolor dorsal. El ECG es diagnóstico de patrón Brugada. Como ella está sin señales de arritmias un estudio EF no tiene ningún valor [ver Viskin y Wilde revista HRS], aunque se podría se hiviera necesidad determinar el periodo refractario ventricular efectivo "ventricular effective refractory period" (VERP) <200 ms, como lo muestra por Priori (en el JACC el mes pasado) define el "factor emergido" con un hazard ratio de 4. Personalmente creo que necesitamos más experiencia en el uso este hallazgo. Además la paciente es una mujer y no hay fraccionamiento del complejo QRS.Por último, tenga en cuenta las pruebas genéticas, principalmente para el abordaje y evaluación familiar.

É necessário excluir dissecção da aorta dado o padrão de dor nas costas. O ECG é diagnóstico de padrão de Brugada. Como ela não apresenta arritmias o estudo eletrofisiológico não possui valor [ver Wilde revista Viskin e HRS], embora se possa argumentar que a determinação do periodo refractario ventricular efectivo (VERP) <200 ms, como mostrado por Priori (JACC no mês passado) define o fator emergido com um hazard ratio de 4.
Acho que precisamos de mais experiência no uso deste achado. Além disso, ela é uma mulher e não se observa complexo QRS fraccionado.
Finalmente, considere o teste genético, principalmente para abordagem e avaliação da família..

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Caro Andrés: Em minha opinião, trata-se de espamo de artéria descendente anterior. A cinecoronariografia foi normal, o que afasta aterosclerose coronária apesar de se tratar de mulher diabética e com outros fatores de risco. O tratamento é utilizar bloqueador de cálcio.
Um grande abraço do

Hélio Germiniani
Professor Dr. Helio Geminiani (SP) frankgerminiani@uol.com.br Curitiba Brasil

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Dear Andres: In my opinion, it is anterior descending artery spasm. Coronary angiography was normal, which removes coronary atherosclerosis despite being a diabetic woman and other risk factors. The treatment is to use calcium antagonis.

A warm hug from
Hélio

Estimado Andrés: En mi opinión, es un espasmo de la artéria descendente anterior. La angiografía coronaria fue normal, lo que elimina la aterosclerosis coronaria a pesar de ser una mujer diabética y con otros factores de riesgo.
El tratamiento consiste en utilizar antagonistas del calcio.

Un cálido abrazo de
Hélio

Estimado Raimundo, Tus casos siempre son interesantes. Gracias por tomarte el trabajo de compartirlos con nosotros. Está pendiente descartar un síndrome aórtico agudo, lo cual puede hacerse mediante una dosificiación de D-dímeros normales. Si los D-dímeros son anormales es necesario una angioTAC o similar.

Respecto al ECG:

1. **Tu mencionas que tiene bradicardia en unos ECG que no enviaste. Por que no los enviaste? es un foro de arrítmias hermano y no eviaste la arritmia!!?? Los síntomas se correlacionan con la bradiarrítmia? Si se correlacionan, bingo! Bradicardia sintomática. End of story.**
2. **Tiene un patrón ECG de Brugada asintomático. El dolor torácico no forma parte del síndrome de Brugada.**
3. **El patrón ECG es tipo I, por lo cual no tiene indicado test de provocación farmacológico con ajmalina ni similares.**
4. **EEF? No veo con que objetivo. Por la bradicardia? poco útil. Por el Brugada? no indicado.**

Cordiales saludos

Daniel Banina MVD, Uruguay----------

Dear Raimundo, Your cases are always interesting. Thanks for taking the work to share with us. This pending rule out arctic acute syndrome, which can be done by a determination of normal D-dimers levels. If the D-dimers are abnormal it is necessary CT angiography or similar. Regarding the ECG

You mention having bradycardia in some ECG not sent. Why not sent? arrhythmias is a forum brother and do not sent ? Symptoms correlate with bradyarrhythmia? If correlated, bingo! Symptomatic bradycardia. End of story.

She has a Brugada ECG pattern asymptomatic. Chest pain is not part of Brugada syndrome. The ECG pattern is type 1, which indicated no pharmacological provocation test with ajmaline or similar.

EEF? I do not see what purpose. By the bradycardia? unhelpful. By Brugada? not given.

Aclaración: Querido Banina te escrive Andrés
Raimundo no envió estos trazados donde existe bradicardia sinusal con pausas porque en ese momento el no tenia los trazados en su poder. Estaban en manos del residente y se los pediria el lunes.
Fijate que en la historia dice que los irá a enviar.
La falta del envío no tuvo como objetivo esconder nada.
Los síntomas no ser relacionaron con la arritmia
.El dolor dorsal de carácter opresivo, irradiado al precordio de larga duración (3h) sin factores desencadenantes ocurrió con la FC normal.
Nunca tuvo sincope, o lipotimias.
Su antecedentes familiares en parientes menores de 45 anos son negativos para Muerte Súbita o sincope

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Explanation: Dear Banina here Andrés responding
Raimundo does not send these ECGs with sinus and pauses because at that time he had no them in his possession. They were with his resident and would request on Monday. Note that in the history says: "I will be sent".
The lack of shipping aimed not hide anything.
Symptoms not are related to the arrhythmia
Dorsal pain with oppressive character, radiating to the precordium, and long durations (3 h) without triggers occurred with normal heart rate.
She never had syncope or fainting.
Her family history is totally negative in relatives under 45 years of age related SCD or syncope.

Hola Daniel
Que bueno poder leerte y escucharte. Ojala participaras mas seguido. Voy a estar en tu tierra en octubre y espero poder charlar tendido contigo.
Aquí mis puntos de disidencia contigo (de lo que NO hablo es porque estoy de acuerdo):
1. El dolor toracico no forma parte de la definicion del sindrome, pero es muy frecuentemente relatado. Muchos de los pacientes que he visto fueron descubiertos en la guardia por dolor toracico y patron tipo I.
2. Esta es una observación correcta, pero muy estricta de tu parte. Si tu tienes un patron tipo I de libro, pues estoy de acuerdo que no hace falta el test. Pero en casos como este, yo haria el test para confirmar la disfuncion del canal de sodio.
Entiendo que la angio no mostro patologia aortica, pero concuerdo en tu anejo.
Y en el resto, por supuesto, concuerdo totalmente.
Aprovecho para contarles que el III Consenso en Brugada aparecera a mitad de anio, con algunos cambios en la interpretación del ECG realmente muy interesantes (saldra en J Electrocardiology).
Salud
Adrian Barachuk

Hello Daniel: That's good to read you and hear you. Hopefully you will participate more often. I'll be on your land in October and hope to chat with you lying.Here are my points of dissent with you (of what I speak is NOT because I agree): 1. Chest pain is not part of the definition of the BrS, but is most often reported. Many of the patients I have seen were discovered in the emergence room for chest pain and pattern type 1. 2. This is a correct observation, but very strict on your part. If you have a typical type 1 pattern, I agree with you do not need the test. But in cases like this, I would do the test to confirm the sodium channel dysfunction. I understand that the angiogram showed no aortic disection, but agree on your annex. And the rest, of course, I agree completely.Take this opportunity to tell you the Brugada Consensus III will appear in the middle of this year, with some changes in ECG interpretation really very interesting (coming out in J Electrocardiology)
AB

Dear Adrian: what tests are necessary to confirm a diagnosis of an aortic dissection? Once the possibility of a dissection has been raised, an imaging study of the aorta is needed. A pain that starts at the front of the chest would suggest that the aorta near the heart is involved. In this situation, a standard echocardiogram may be useful. If the pain arises in the back of the chest(as this case) or in the abdomen, a computed tomographic scan (which is most sensitive when radiographic x-ray contrast is given), transesophogeal echocardiogram, or magnetic resonance imaging study is necessary. The particular test would depend on which of these tests is most readily available, and most expertly done and interpreted.

Retrograde aortography was the first accurate diagnostic technique of evaluating suspected acute aortic dissection The diagnosis of aortic dissection is based on direct angiographic sings, including visualization of two lunina or an intima flap(considered diagnostic) or on indirect signs (considered suggestive), such as deformity of the aortic lumen, thickening of the aortic walls, branch vessels abnormalities, and aortic regurgitation. Aortography had long been considered the diagnostic gold standard for the evaluation of aortic dissection antemortem, although it true sensitivity could no be defined. However the more recent introduction of alternative diagnostic modalities has shows that aortography is not as sensitive as previously through approximately more than 20% of cases this invasive method is not diagnostic.

Andrés Ricardo Pérez-Riera

Estimado Adrian: ¿qué pruebas son necesarias para confirmar un diagnóstico de la disección aórtica? Una vez que la posibilidad de una disección se ha levantado, un estudio de imagen de la aorta es necesario. Un dolor que comienza en la parte frontal del pecho sugiere que la aorta cerca del corazón está implicada. En esta situación, un ecocardiograma transtorácico puede ser útil. Si el dolor se presenta en la parte posterior del tórax (como en este caso) o del abdomen, la tomografía axial computorizada (la cual es más sensible cuando se da contraste radiográfica de rayos X), ecocardiograma transesofágico, o estudio de resonancia magnética es necesario. El métdo escogido en particular dependerá de cuál de estas pruebas es más fácilmente disponible, y de expertos que tengamos en cada area.

La aortografía retrógrada fue la primera técnica de diagnóstico preciso de la evaluación de sospecha de disección aórtica se basa e en los signos angiográficos directos, incluyendo la visualización de dos lumenes o un colgajo de la íntima (que se considera diagnóstico) o en signos indirectos (que se considera sugestivos), como la deformidad de la luz de la aorta, engrosamiento de las paredes de la aorta, anomalías ramas vasculares e insuficiencia aórtica. Aortografía ha sido considerado durante mucho tiempo el estándar de oro diagnóstico para la evaluación de la disección de la aorta antes de la muerte, a pesar de que la verdadera sensibilidad no se podia definir. Sin embargo, la introducción de las más recientes modalidades de diagnóstico nos mostraron que aortografía no es tan sensible como anteriormente se pensaba, y que aproximadamente en mas del 20% de los casos este método invasivo no es diagnóstico(falso negativo).

Andres.

Querido amigo Andrés informe isto aos integrantes do foro

1. **Não sei o motivo que levou o colega da emergência solicitar o cateterismo. Devo esclarecer que muitas vezes não se deve esperar os marcadores para tomada de decisão principalmente nos pacientes com Sindrome coronariana aguda com supradesnivelamento do segmento ST. Eu imagino que o colega interpretou as alterações do segmento ST como isquémicas.**
2. **A aortografia retrérgrada nào foi realizada**
3. **Apesar da localização da dor (dorso) as outras características da dor não sugeriam síndrome aortica aguda(lembrar que a paciente já tinha apresentado episódios semelhantes prévios)**
4. **Já entrei em contato com a residente para solicitar a dosagem do cálcio sérico**
5. **A discordância entre o cateterismo e oEcocardiograma em relação à avaliação da função ventricular é un fato muito comum**
6. **Também não sei o motivo de porque estava usando cálcio**

Un abrazo

Raimundo

Dear friend Andrés please report the following observations to the members of the forum

1. I do not know the reason that motivated the emergency room colleague to request catheterization. I should clarify that it is often is not necessary to wait biomarkers for decision making, especially in patients with ST-segment elevation acute coronary syndrome. I imagine that my colleague interpreted the ST segment changes as being ischemic.
2. Retrograde aortography was not conducted (back pain) because other features of pain do not suggested acute aortic dissection
3. I contacted with the colleague resident to request ionic seric calcium
4. The disagreement between the catheterization and the Echocardiogram regarding the evaluation of the left ventricular function is a common fact in clinical cardiological practice.
5. I am not aware of why she was using calcium carbonate

A embrace

Raimundo Barbosa Barros M.D,

Final comments

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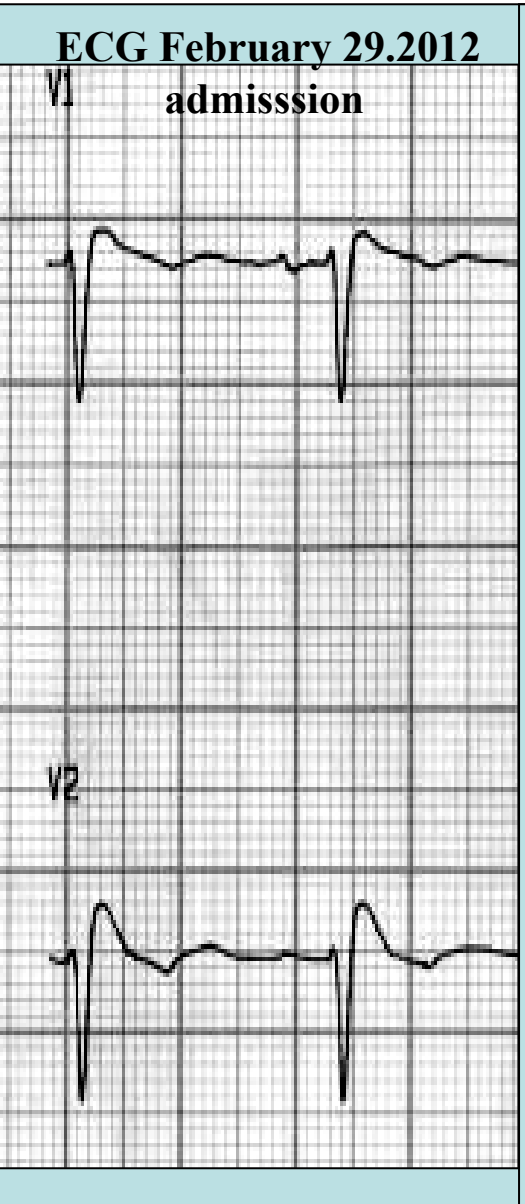
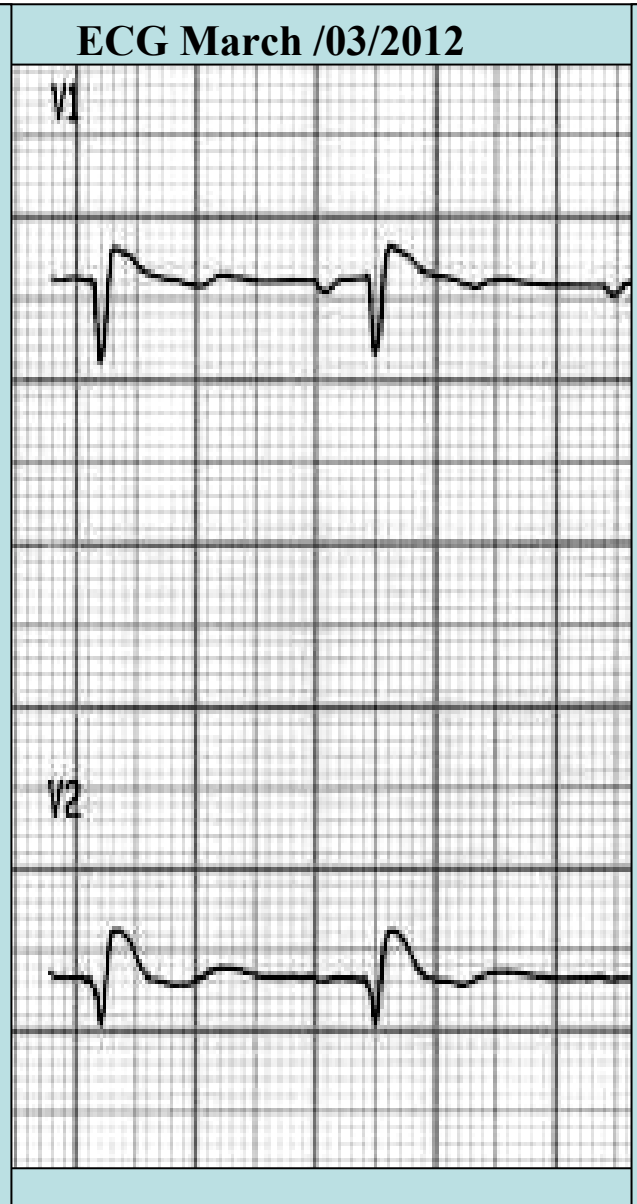
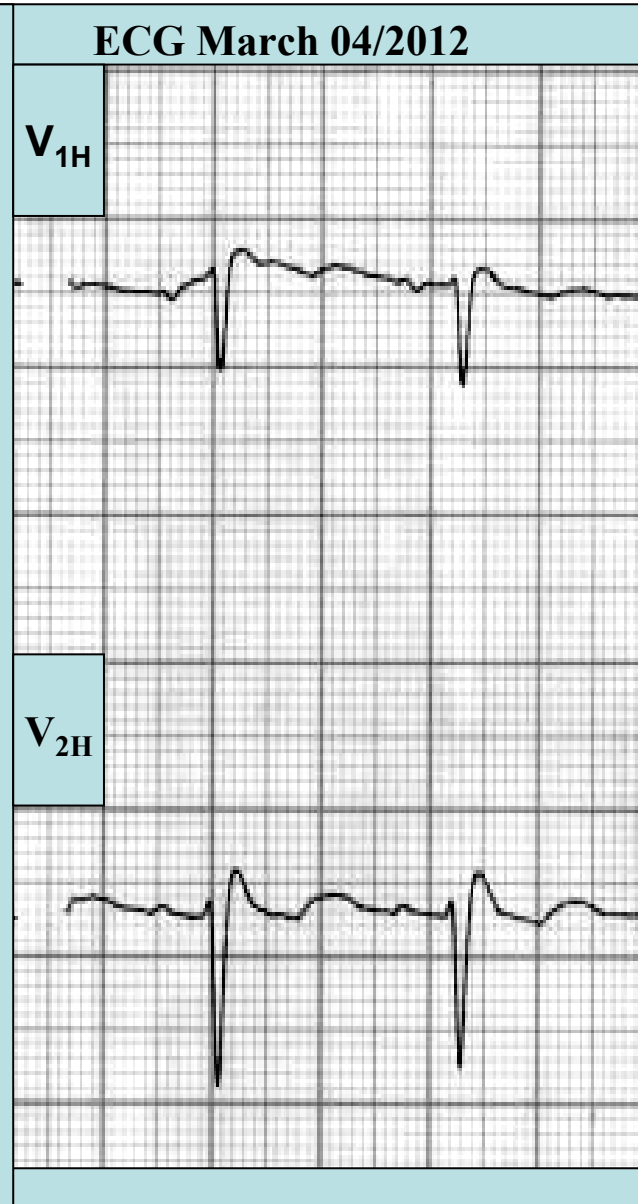
(1) Does this patient have an acute thoracic aortic dissection? suggestive dorsal pain
(2) Is this ECG repolarization pattern really a Brugada type 1 ECG pattern?
(3) How can be determined whether this patient is at risk for sudden cardiac death?
(4) Should this patient receive an implantable cardioverter-defibrillator (ECG)?







(1) Does this patient have an acute thoracic aortic dissection?

About 96% of individuals with acute aortic dissection present with severe pain that had a sudden onset. It may be described as tearing in nature, or stabbing or sharp in character. 17% of individuals will feel the pain migrate as the dissection extends down the aorta. Incidence: 2000 cases per year in the US

The location of pain is associated with the location of the dissection. Anterior chest pain is associated with dissections involving the ascending aorta, while interscapular (back our case) pain is associated with descending aortic dissections.

If the pain is pleuritic in nature, it may suggest acute pericarditis caused by hemorrhage into the pericardial sac. This is a particularly dangerous eventuality, suggesting that acute pericardial tamponade may be imminent. While the pain may be confused with the pain of a MI aortic dissection is usually not associated with the other signs that suggest MI, including heart failure, and ECG changes.

Individuals with aortic dissection who do not present with pain have chronic dissection.

Less common symptoms that may be seen in the setting of aortic dissection include CHF (7%), syncope (9%), cerebrovascular accident (3-6%), ischemic peripheral neuropathy, paraplegia, cardiac arrest, and SD. If the individual had a syncopal episode, about half the time it is due to hemorrhage into the pericardium leading to pericardial tamponade.

Neurologic complications of aortic dissection (i.e., cerebrovascular accident (CVA) and paralysis) are due to involvement of one or more arteries supplying portions of the central nervous system.

If the aortic dissection involves the abdominal aorta, compromise of the branches of the abdominal aorta is possible. In abdominal aortic dissections, compromise of one or both renal arteries occurs in 5–8% of cases, while mesenteric ischemia (ischemia of the large intestines) occurs 3–5% of the time.

What part of the physical exam raises the possibility of an aortic dissection?

During the physical examination, it is important to check the blood pressure in both arms and the pulses in both wrists, both legs and both sides of the neck over the carotid arteries. If an aortic dissection is present, a difference in blood pressure can sometimes be found between the arms and the differences in the pulse can be detected.

High blood pressure could indicate a number of factors:
A predisposing factor to aortic dissection.
Pain from the dissection
A partially or completely blocked artery to one or both kidneys.
An abnormally large difference between the top (systolic) blood pressure and the bottom (diastolic) blood pressure, could be due to a leakage of blood back into the heart (aortic regurgitation).
Very low blood pressure can also occur. Many people with the Marfan syndrome are treated with medications to keep their blood pressure at the very bottom of the normal range. It is important to ask patients with a known diagnosis of the Marfan syndrome their normal blood pressure so that, if the emergency providers detect a blood pressure of, for example, 100/60, they are aware that it is the patient's usual blood pressure and not the result of an acute event. This is essential so that doctors do not try to raise the blood pressure, which would be a potential disaster in the setting of a dissection.

What tests are necessary to confirm a diagnosis of an aortic dissection?

Once the possibility of a dissection has been raised, an imaging study of the aorta is needed. A pain that starts at the front of the chest would suggest that the aorta near the heart is involved. In this situation, a standard echocardiogram may be useful. If the pain arises in the back of the chest or in the abdomen, a computed tomographic scan (which is most sensitive when radiographic x-ray contrast is given), transesophogeal echocardiogram, or magnetic resonance imaging study is necessary.

The particular test would depend on which of these tests is most readily available, and most expertly done and interpreted.

If a patient is having severe anterior chest pain, the emergency room physician may first consider a MI or an inflammation of the lining around the heart. However, if the ECG doesn't show an obvious heart attack, and pericardial inflammation is being considered, a test such as an echocardiogram could document that possibility. In that situation, if the aorta is dissected close to the heart, the dissection may appear on the echocardiogram and the correct diagnosis would be achieved without having had to consider it as a first diagnosis.

What are other possible causes of chest pain?

There are many other causes for the type of chest pain associated with an aortic dissection. These include a MI and inflammation of the lining around the heart (pericarditis). Problems with the esophagus and the spine also could cause pain in the same general area, although they tend to have different character and concomitant symptoms.

Can an aortic dissection be stabilized?

Dissections that begin away from the heart (Type B or distal dissection) often can be stabilized and may not require immediate surgery. However, a dissection that starts near the heart (Type A or proximal)—in the part of the aorta leading up to the neck—does not tend to stabilize. A dissection in this area is exposed to the full force with which the heart pumps blood on each beat, which extends the tear. Proximal dissections require immediate surgical intervention.

Information gathered from the imaging technology can indicate the likelihood of stabilization. In addition, it is important to see if the aorta in any segment is 5-6 cm or more in diameter, which would indicate elective, if not immediate, surgery. An aorta of 5-6 cm means the aortic wall has been thinned and stretched, and is at a great risk for further enlargement and, potentially, rupture.

How can a dissection be stabilized?

Medication

Upon diagnosis of a dissection, it is important to lower the blood pressure to the bottom end of the normal range, or even a little lower, with medication. In addition, either a beta blocker or verapamil is used to slow the pulse and make the heart beat with less force. These medications can be given intravenously in order to be effective in minutes.

In a dissection that starts away from the heart, if the blood pressure stabilizes, the pain stops, and there's no compromise of blood flow to the kidneys and other vital organs, then the approach is usually based on aggressive use of medications to lower blood pressure to as low as 90-100 mm Hg and to slow the pulse, and careful monitoring to ensure that the aorta doesn't enlarge further.

Surgery

Surgery would be considered if the tear in the descending aorta seems to stabilize, but then grows progressively, or if there is a rapid rate of change in an aorta size not yet considered to be at risk for rupture. Regardless of the cause of an aortic aneurysm, surgery should be considered once the aortic diameter reaches twice normal. On average, this corresponds to 5-6 cm for the thoracic aorta. A lower threshold is recommended for people with the Marfan syndrome with severe aortic regurgitation, family history of aortic dissection or the need for other major surgery.

A patient who is extremely anxious may be aided by some sedation, which may help potentiate the effects of medicine and control blood pressure. However, it is important for patients in this situation to be awake and alert enough to be able to describe the pain and symptoms. If someone has a large dissection that begins near the heart, or the tear is very extensive and they continue to have pain even after the blood pressure has been brought down to a low level, proceeding with surgery as soon as the surgical team is assembled is essential. In the brief time before surgery, medication to control pain can be used without loss of needed diagnostic information.

When is surgery necessary?

Symptomatic ascending aortic dissections or aneurysms, whether acute or chronic, require emergency surgical treatment. Acute descending aortic dissections require admission to intensive care for monitoring and blood pressure control. Those with pain that does not resolve with blood pressure control will need urgent surgery. Those with evidence of organ ischemia (kidneys, bowel, spinal cord) will also require urgent surgery. In patients with chronic descending aortic dissections, pain may indicate impending rupture and, therefore, warrant urgent surgery.

In general, the decision for immediate surgery is based on indicators of especially high risk, such as the presence of a proximal dissection, or continued pain despite blood pressure control.

In this very intriguing case, I think that we should consider the following questions:
which are the elements in favor and which against the presence of Brugada syndrome (BrS).

Elements in favor:

1. The reference in the intergatory about the occurrence of pauses accompanied by sinus bradyarrhythmia. This phenomenon has been observed in carriers of the SCN5A gene mutation, isolated or associated to BrS.
2. Greater duration of QT interval in right precordial leads in comparison to the left ones (see in next slides).
3. The presence of left anterior fascicular block (LAFB): this dromotropic disorder is found in approximately 9% to 10% of the cases in BrS. However, we think that in this case it is not relevant, since LAFB can be found in hypertension and diabetes mellitus, present in this case.

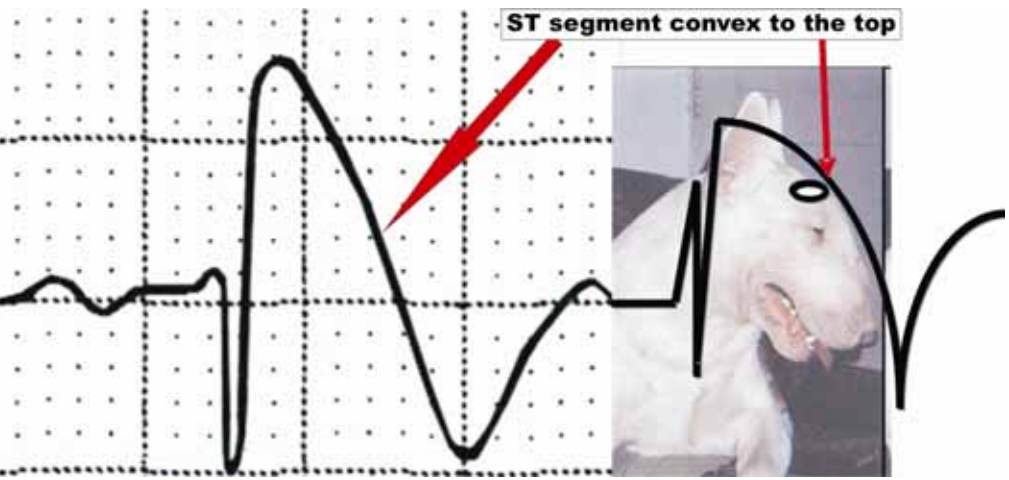
Elements against or indifferent to the diagnosis:

1. Repolarization pattern in some of the right precordial leads corresponding to typical Brugada type-1 pattern? Yes? or no? Answer: ventricular repolarization pattern is not completely characteristic, since ST segment elevation does not show constant superior convexity or it is not descending oblique rectilinear. Unlike patients carriers of Brugada type-1 ECG pattern, in this case it is possible to establish with accuracy the location of the J point.(see nexts slides) Finally, T wave is not completely negative, as it happens in the classical electrocardiographic pattern. In this case, it appears as biphasic (minus-plus); i.e. with its first part slightly negative and the final part mildly positive.
2. Mild involvement both of systolic and diastolic function of the left ventricle, detected by echocardiogram. Nevertheless, this fact is not relevant, since it could be a consequence of the concomitant presence of diabetes mellitus and hypertension.
3. Absolute absence of family history of syncope or SCD in relatives younger than ≤45 years of age in 1st, 2nd, or 3rd degrees.
4. Female gender with spontaneous pattern has a much rarer occurrence, but it is possible.

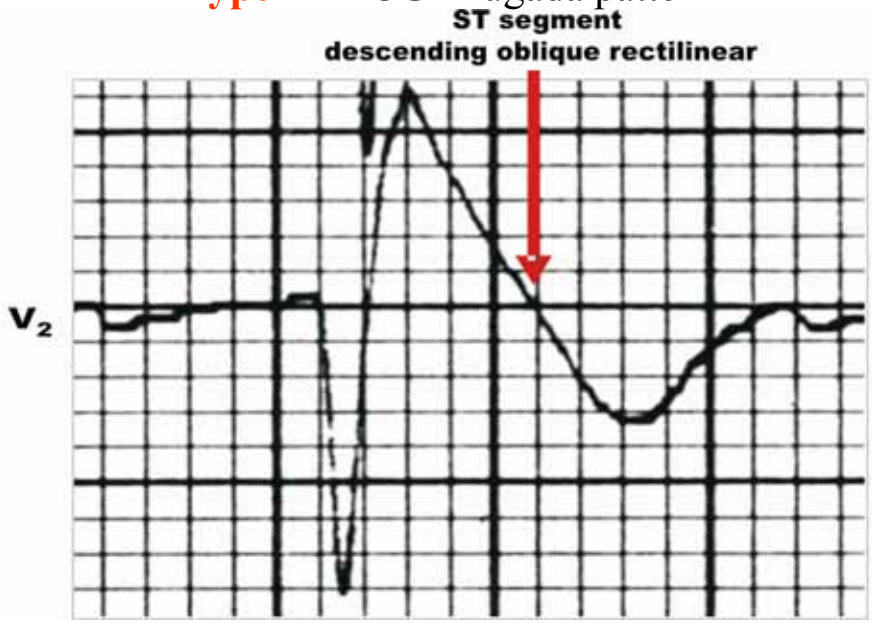
Type 1 ECG Brugada pattern is characterized by J point and ST segment elevation (≥2mm) convex to the top (**Type 1A**) or rectilinear oblique descendent (**Type 1B**) followed by a negative symmetric T wave in the right precordial leads. The ratio ST-segment elevation at J point/ST elevation after 80 ms in V_1-V_2 according to Corrado et al (1), distinguishes ECG Brugada pattern from athletes: in the latter group the ratio is <1, whereas in Brugada pattern is >1. Corrado (1) considered that the index QRS-ST at high take-off/ST at 80 ms is>1 in type 1 Brugada pattern and <1 in athletes. However this not always happens(2) In spite of that this index is still valid. Usually the pattern is seen only in V_1-V_2 but in some cases is recorded only in V_1 and in others is still observed in V_3.

Type 1A ECG Brugada pattern

"Bull terrier pattern"



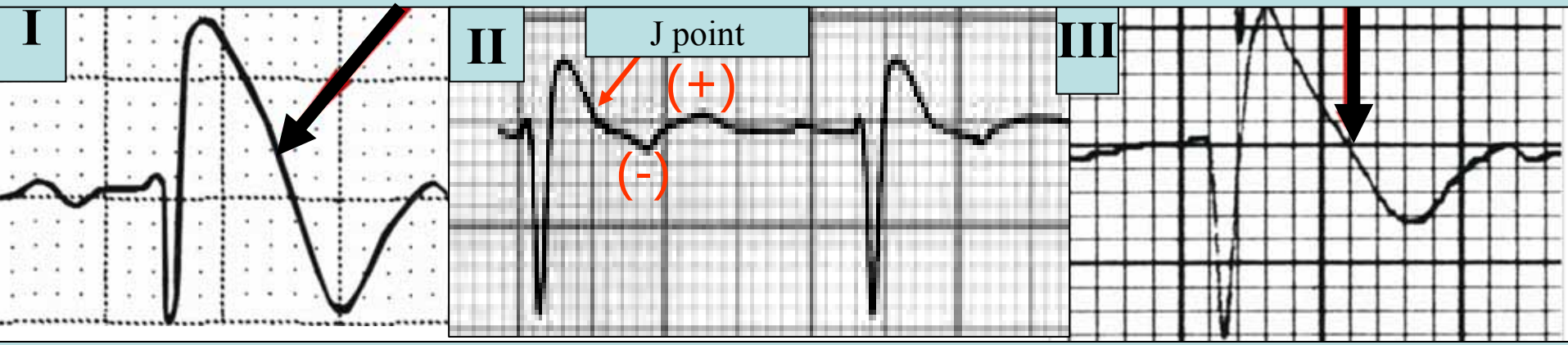
Type 1B ECG Brugada pattern



Differently of present case report, in the types 1 ECG Brugada patterns is impossible to determinate the exact localization of the J point, consequently also is not possible the measurement of the QRS duration.

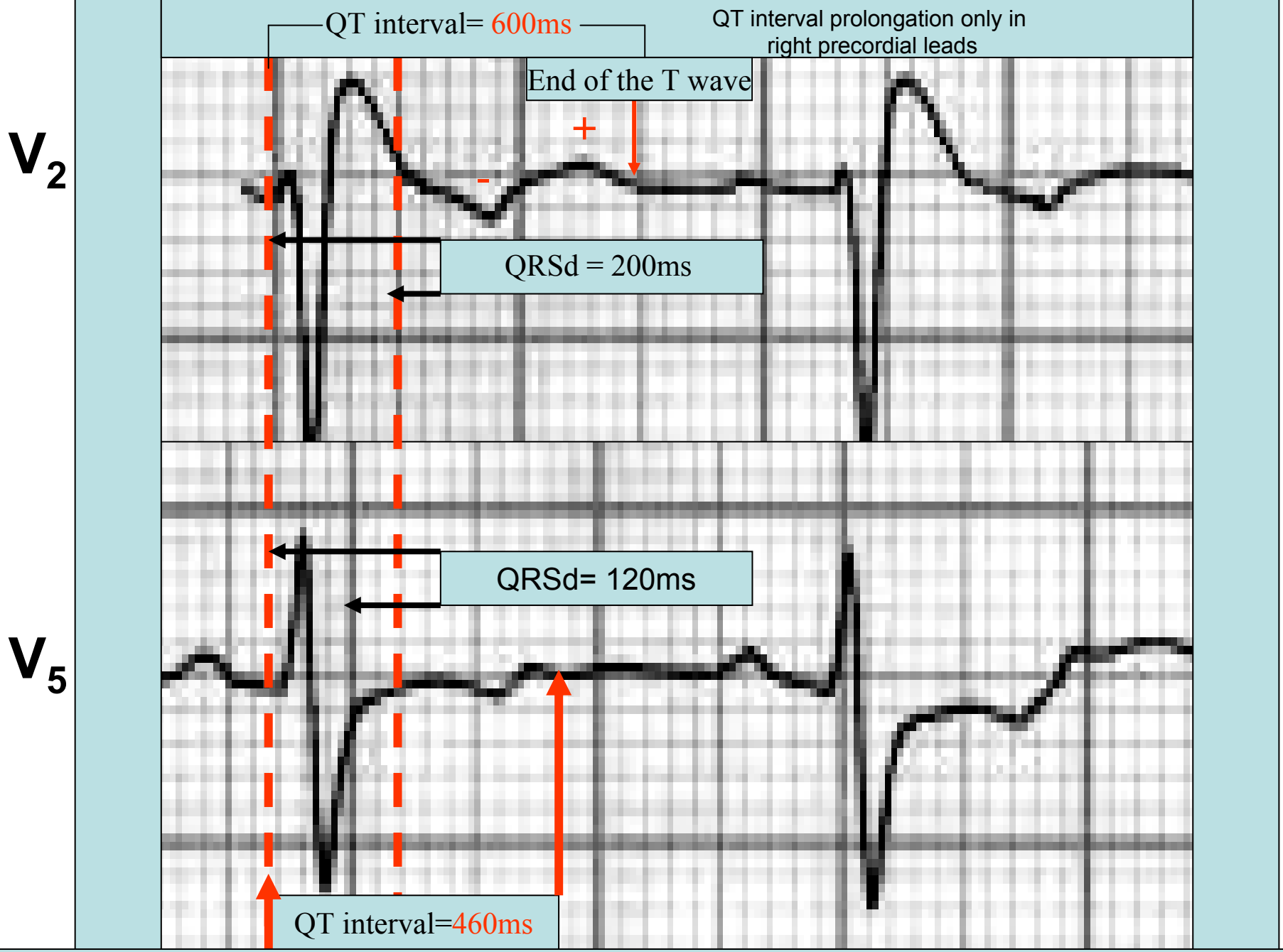
1. Corrado D, Pelliccia A, Heidbuchel H *et al*; Section of Sports Cardiology, European Association of Cardiovascular Prevention and Rehabilitation; Working Group of Myocardial and Pericardial Disease, European Society of Cardiology. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. Eur Heart J 2010;31:243.
2. Postema PG, van Dessel PF, Kors JA *et al*. Local depolarization abnormalities are the dominant pathophysiologic mechanism for type 1 electrocardiogram in brugadasyndrome a study of electrocardiograms, vectorcardiograms, and body surface potential maps during ajmaline provocation. J Am Coll Cardiol 2010;55:789.

TRULY ECG TYPE 1A AND 1B BRUGADA PATTERN(1;2)



In truly ECG type 1 Brugada pattern (panels **I** and **III**) is not possible to determinate the exact location of the J point; consequently also the QRS duration (QRSd). In the present case (central panel **II**) J point location is easy to determinate. Consequently, to know the QRSd. Additionally, in this case the T wave is biphasic with the first negative portion(-) and the late upright (minus-plus - +). Definitively this patient has not clear type 1 ECG Brugada pattern.

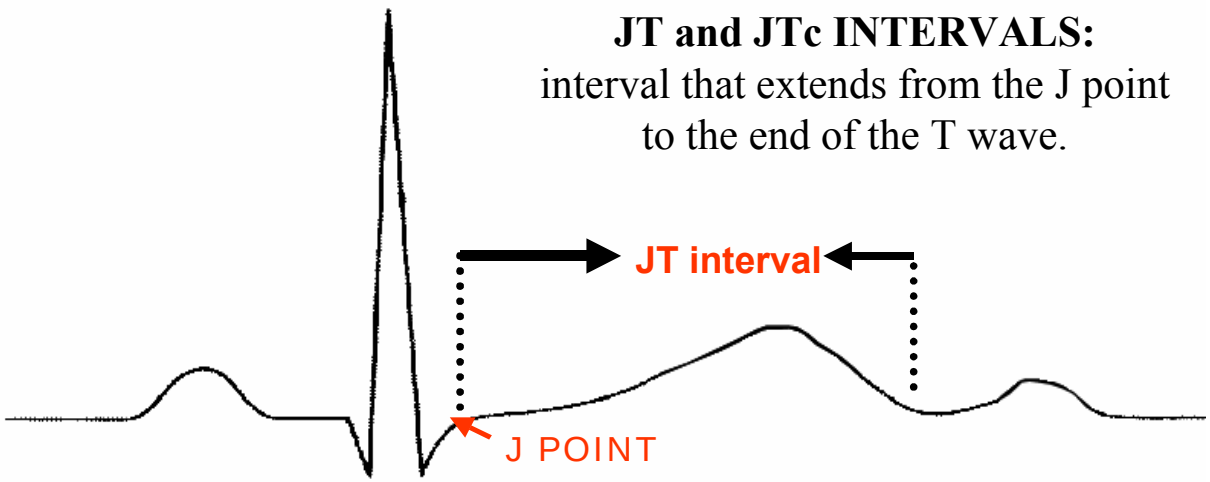
1. Perez Riera A Electrocardiograms Not to Miss In Clinical Approach to Sudden Cardiac Death Syndromes. Editor Ramon Brugada. Associate Editors Josep and Pedro Brugada. Chapter 6 pp 73-90 Springer-Verlag London Limited 2010.
2. Pérez Riera AR, Feminía F, Baranchuck A. Valor del electrocardiograma en el diagnóstico y pronóstico del síndrome de Brugada Rev. Urug.Cardiol. Nº 2 - Setiembre 2011: Vol. 26 122-140.



1. Pitzalis MV, Anaclerio M, Iacoviello M. QT interval prolongation in right precordial leads in Brugada syndrome. J Am Coll Cardiol 2003;42:1632.

Pitzalis et al (J Am Coll Cardiol 2003;42:1632.) showed that BrS may similarirly that ARVC/D present prolongation in QT interval duration from V_1 to V_3 and consequently prolongation of the QT/QTc intervals only in the right precordial leads such as this case.

If the QT interval is prolonged only from V_1 to V_3, being normal from V_4 to V_6, it is clear that this increase may be due to prolongation of ventricular depolarization (QRS complex) and/or by ST/T prolongation (repolarization).



If we admit that in BrS there is some degree of bundle branch block, pseudo RBBB or right end conduction delay(1) clearly the QT interval prolongation is due partly to this. The QTc interval constitutes the classical measurement for ventricular repolarization; however, this parameter includes ventricular depolarization (QRS), and therefore represents the so-called electric systole, which includes depolarization (QRS) and ventricular repolarization (ST/T = JT interval). Thus, when there is a bundle branch block or WPW ventricular preexcitation, the measurement of ventricular repolarization by QTc may be incorrect. In such cases, the measurement of JTc is more accurate than the QTc interval, because it excludes depolarization.

1. **Peréz-Riera AR, Ferreira Filho C, de Abreu LC, Ferreira C, Yanowitz FG, Femenia F, Brugada P, Baranchuk A; On behalf of the International VCG Investigators Group. Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study.Europace. 2012 Jan 10. [Epub ahead of print]**

In arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) similar to the present case abnormalities in depolarization/conduction in ECG are observed. Prolongation of QRS complex (110 ms) located in right precordial leads (V_1-V_3) in adult patients in absence of CRBBB (prolonged S wave upstroke) from V1 to V3, 55 ms is the most prevalent characteristic of ECG (95% of cases) and are correlated with the severity of the disease and induction of VT in programmed ventricular stimulation. Prolongation in S wave duration in anteroseptal leads of ECG (V_1-V_3) is a significant marker for ARVC/D diagnosis in patients. Automated medition in S wave duration (Marquette Mac12, Mac15 or MacVue) in the surface of ECG leads V_1-V_3, was conducted in 141 healthy children between 5 and 15 years old (9.6 ± 2.7 years old) and they were compared to 27 pediatric patients carriers of ARVC/ D. Available ECGs were assessed in the initial and final phase in patients carriers of ARVC/D, obtained respectively at ages 11.6 ± 3.9 and 14.3 ± 3.4 years old. ARVC/D was diagnosed in children with VT and CLBBB morphology, using diagnostic criteria already published for adult patients, carriers of ARVC/D or who had typical findings in biopsy. The result from the addition of QRS complexes duration from $V_1 + V_2 + V_3$ when divided by the addition of the duration of QRS complexes from V_4 through V_6 ($V_4 + V_5 + V_6$). When this equation results in a value ≥ than 1.2, it constitutes a sign of high sensitivity for ARVC/D diagnosis, since it is present in 98% of patients carriers of this cardiomyopathy.

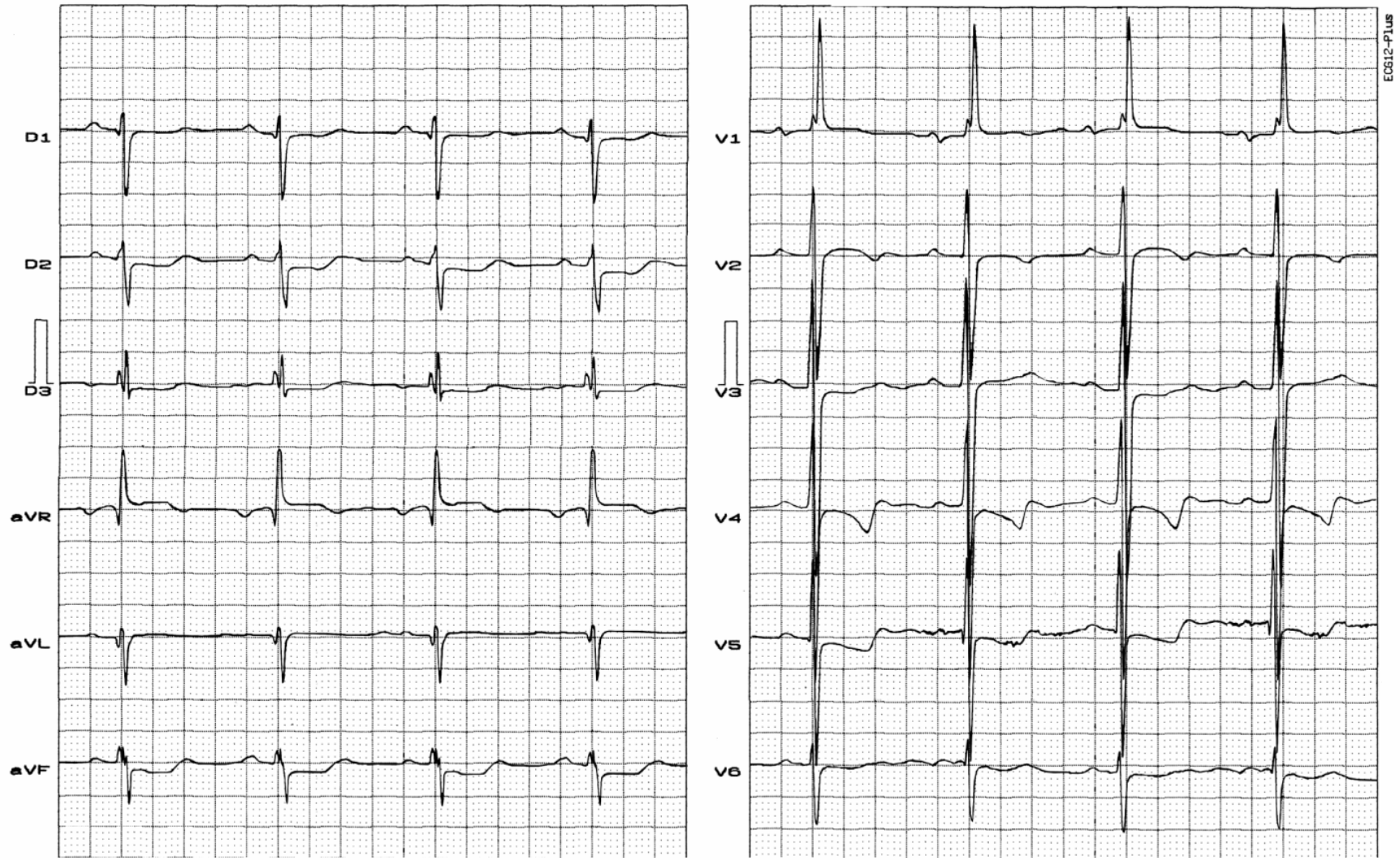
A research showed that the sign is not specific of ARVC/D because it has been observed also in Brugada syndrome. This longer duration of QRS complexes at the right in precordial leads is due to the so-called right parietal block characteristic of ARVC/D. Possibly QRS complexes may be of low voltage, which is observed when the disease is diffuse or there is participation with the conduction system.

The measurement of JTc may be useful to identify LQTS cases with borderline values, where QTc interval could be normal in rest ECG. We find another example in patients carriers of tetralogy of Fallot who underwent surgery, and as a consequence of right free wall ventriculotomy, developed Complete RBBB. In these cases, JTc interval measurement is more sensitive than the QTc interval to detect prolonged repolarization (See example of next 3 slides)

Peter S et al. Ann Noninvasive Electrocardiol 2003;8:238-245

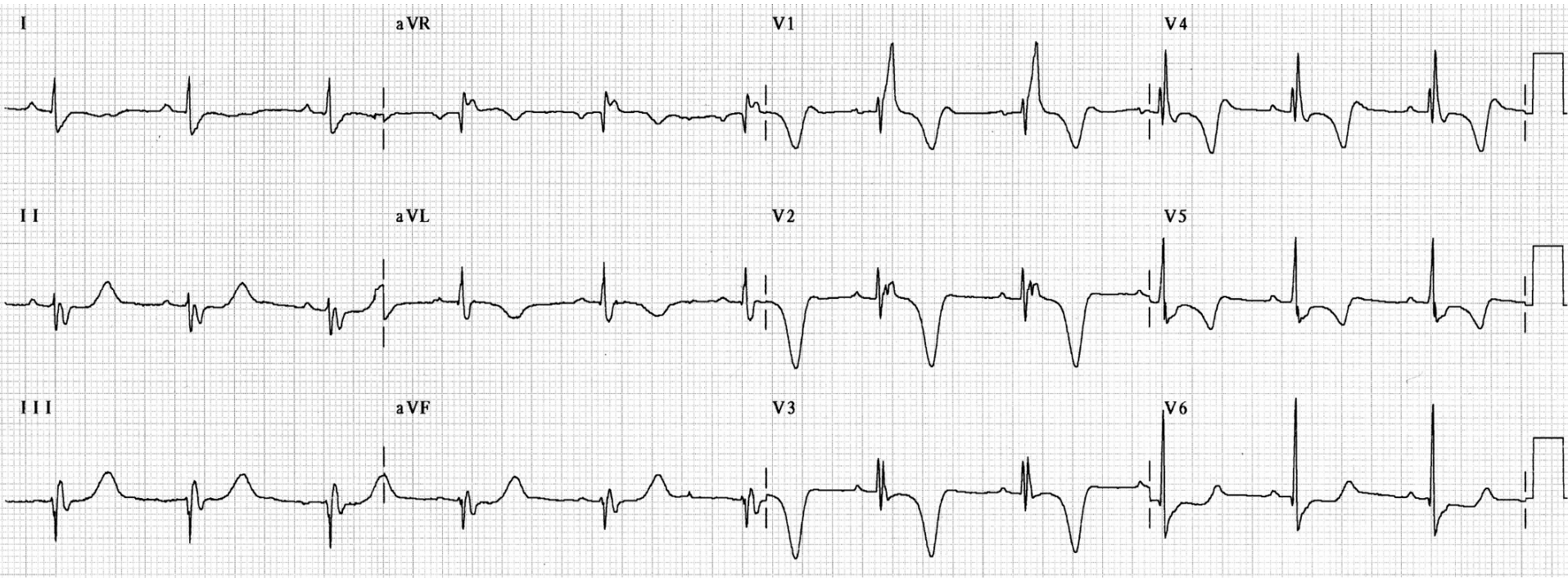
PRE-OPERATIVE ELECTROCARDIOGRAM

Name: RCPL; **Age**: 7 years; **Sex**: female; **Race**: mixed; **Weight**: 23.800Kg; **Height:** 1.21m;
Date: 08/18/03; **Time**: 14:30; Medication used: none stated.



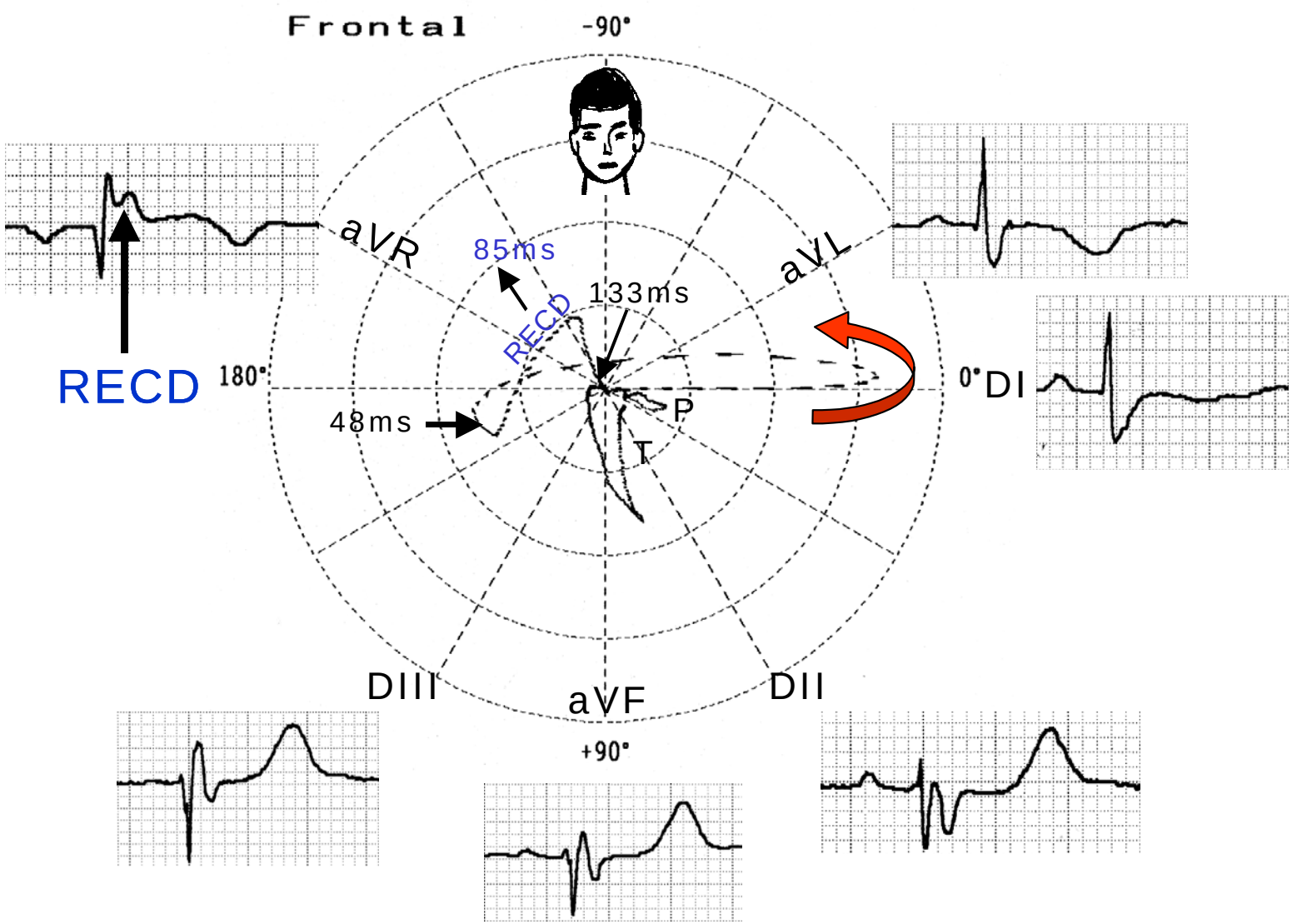
Electrocardiographic diagnosis: In V_1 lead, wide monophasic R wave with notch at the bottom of the ascending ramp and brisk transition from V_1 to V_2: QRS complexes predominantly positive in V_1 to complexes of the rS type in V_2.
Conclusion: Right ventricular systolic overload.

Name: RCPL;**Age**: 7 years; **Sex**: female;**Race**: mixed;**Weight**: 26.000Kg; **Height** : 1.23m;**Date**: 12/12/03;
Medication used: none stated.



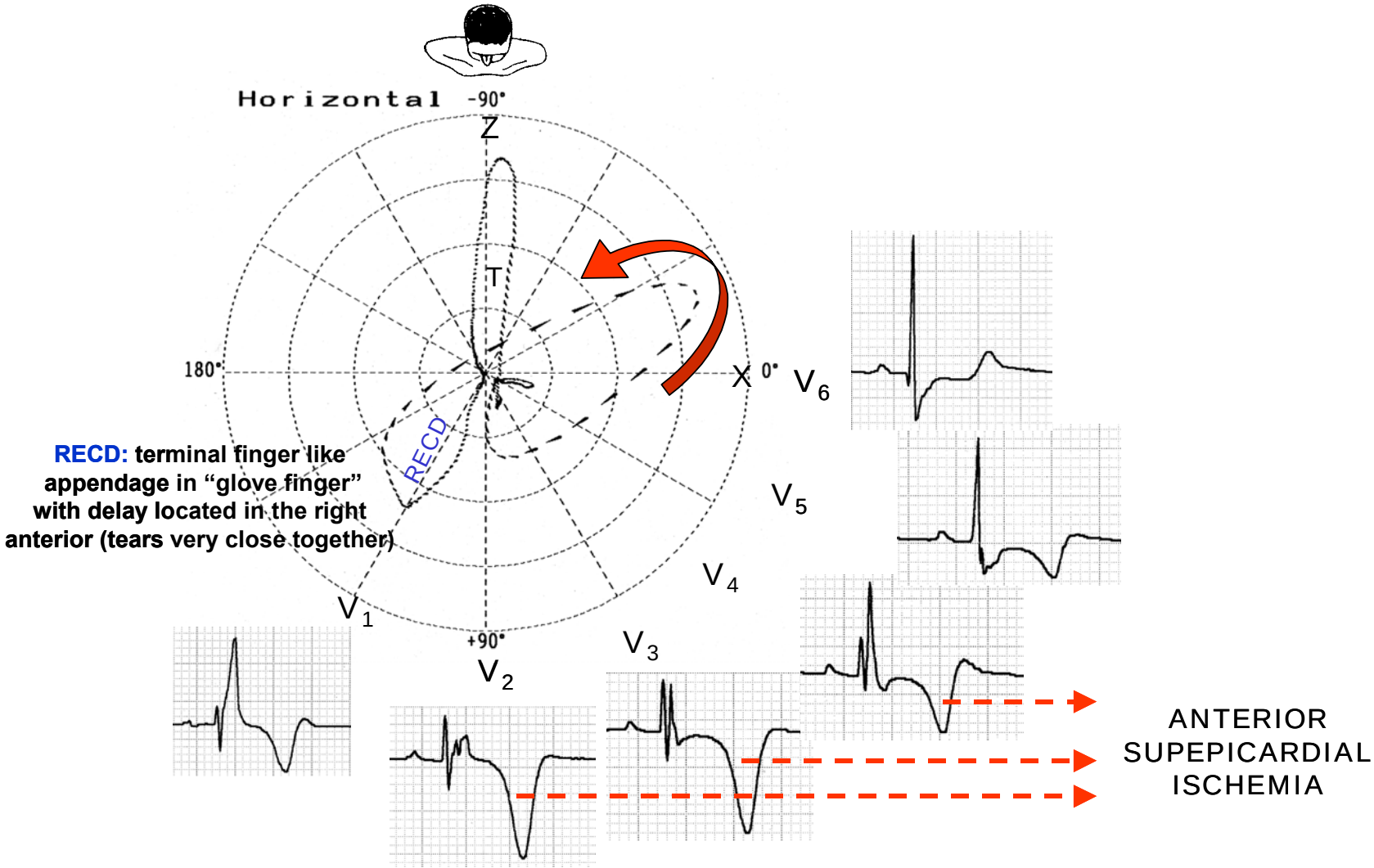
Clinical diagnosis: Late Pos operative total correction of Fallot Pentalogy.
Electrocardiographic diagnosis Rhythm: sinus; **HR:** 65bpm;
P wave: SAP + 26° and to ahead; Duration: 60ms; Voltage: 0.7mV; Aspect: rounded;
PR: 166ms;
QRS: SAQRS: - 225°; Duration of QRS: 133ms (CRBBB).
ST/T: + 109°; **QT:** 487ms. **QTc:** 506ms (prolonged).
Conclusion**:** 1) Complete right bundle branch block: duration of QRS > 120ms (133ms); rsR in V1 and V2, rsR' V3; RSR's'. In aVR lead prominent and broad final R wave and S wave in DI, aVL, V5-V6. 2) Extreme deviation of SAQRS in the right superior quadrant (between + 45° and +- 180° (-225°); 3) Anterior subepicardial Ischemia .T wave with symmetrical branches, profoundly negative and broad base. 4) QTc: prolonged for heart rate: 506ms.

LATE POS-OPERATIVE ECG/VCG CORRELATION
(FOURT MONTHS AFTER SURGEY)



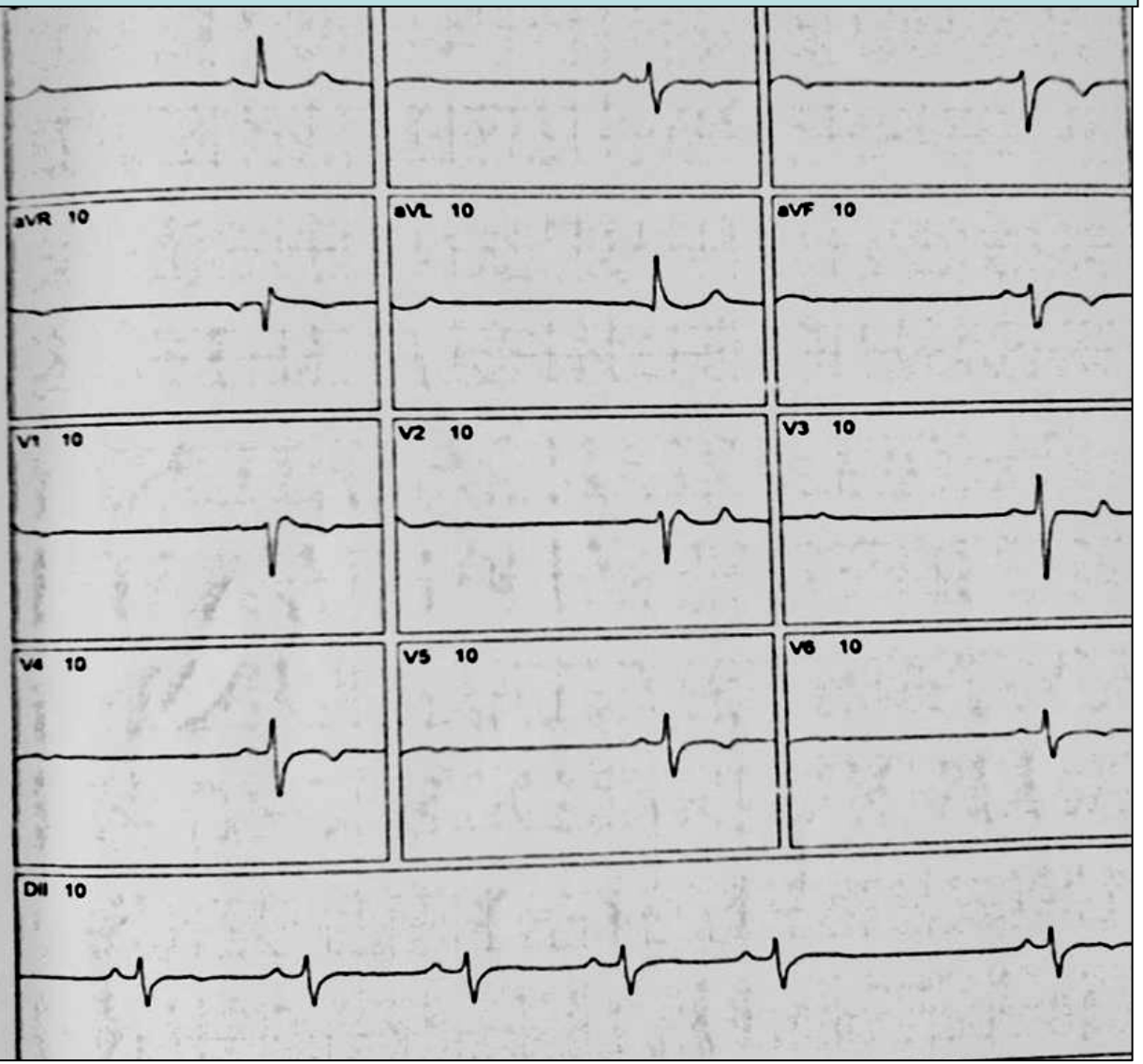
Diagnosis: CRBBB QRSD: 133 ms (>120ms). **RECD (85ms)** located on RVOT area.

LATE POS-OPERATIVE ECG/VCG CORRELATION FOURT MONTHS AFTER SURGERY



Diagnosis: CRBBB Grishman Type or Kennedy Type 1 (afferent limb behind **X** line).
Anterior subepicardial ischemia: T wave with symmetrical branches, profoundly negative and with broad base.

ECG PRESENT CASE



Singnificative sinus bradycardia with sinus arrhyhmia

The prevalence of Brugada-type 1 ECG pattern in Sick Sinus Syndrome (SSS) or SND patients seems to be higher compared with the general population. In addition, SSS patients with the Brugada-type 1 ECG pattern might be a high risk for spontaneous VF.(1;2)

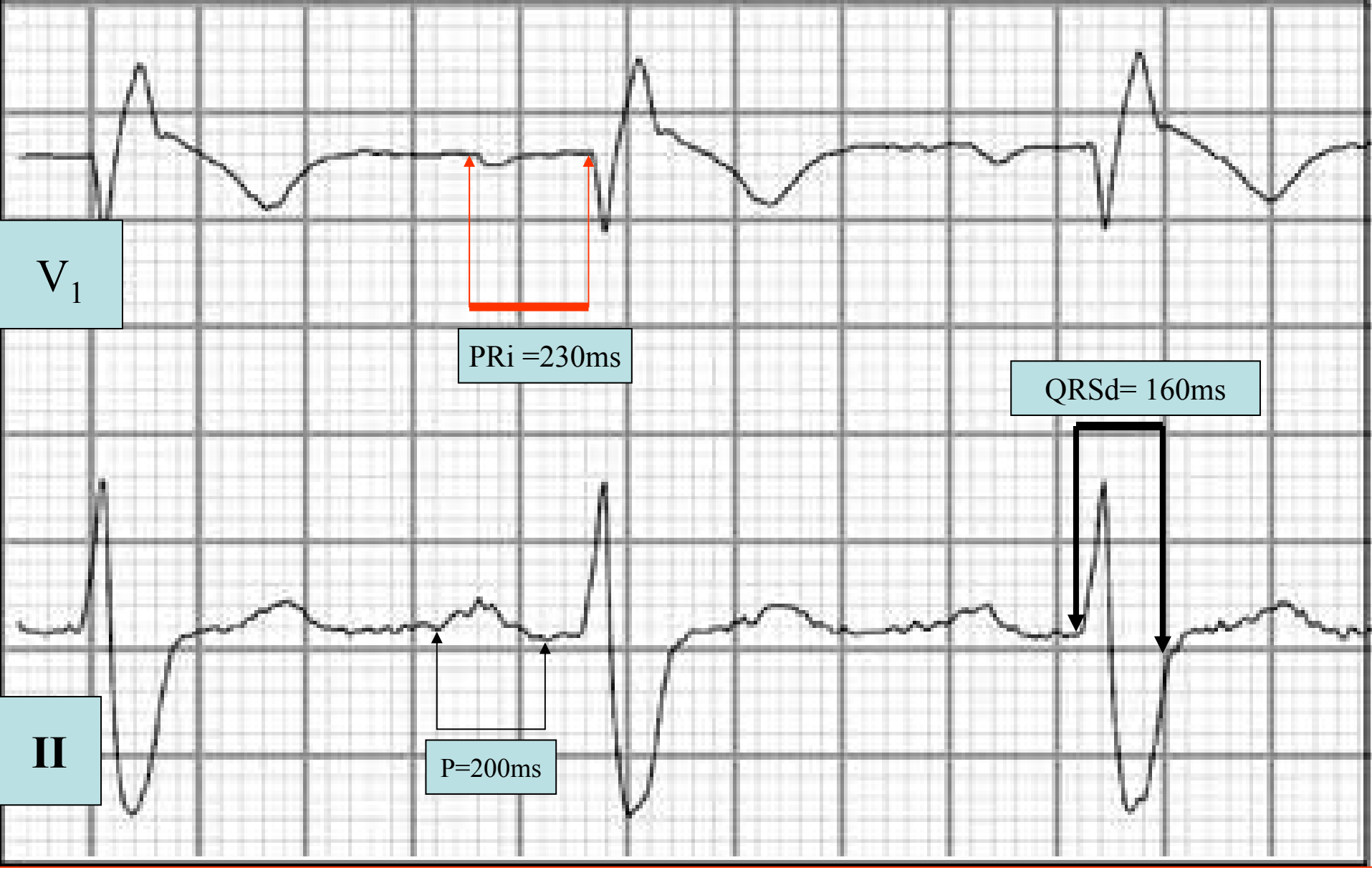
1. Hayashi H, Sumiyoshi M, Yasuda M, et al. Prevalence of the Brugada-type electrocardiogram and incidence of Brugada syndrome in patients with sick sinus syndrome. Circ J. 2010 Feb;74:271-277.
2. Kyndt F, Schott JJ, Probst V, et. al. new SCN5A mutation associates Brugada syndrome and sinus node dysfunction. Circulation 2000; 102:281.

Is this case a sinus node dysfunction associated with Brugada syndrome? Cardiac sodium channel overlap syndromes, overlapping phenotypes or overlapping syndrome?

Cardiac sodium channel are protein complexes expressed in the sarcolemma of cardiomyocytes to carry a large inward depolarizing current (INa) during phase 0 and phase 2 of the cardiac action potential. The importance of I_{Na} for normal cardiac electrical activity is reflected by the high incidence of arrhythmias in cardiac sodium channelopathies, i.e., arrhythmogenic diseases in patients with mutations in SCN5A, the gene responsible for the pore-forming ion-conducting α-subunit, or in genes that encode the ancillary β-subunits or regulatory proteins of the cardiac sodium channel. Variations in the gene encoding for the major sodium channel (Na(v)1.5) in the heart, SCN5A, has been shown to cause a number of arrhythmia syndromes (with or without structural changes in the myocardium), including: (1)

1. The variant 3 of long-QT syndrome: It is now recognized that mutations that increase INa delay cardiac repolarization, prolong action potential duration, and cause long QT syndrome variant 3 with prolongation of ST segment and late onset T wave.
2. Brugada syndrome/Sudden Unexpected Nocturnal Death Syndrome (SUNDS)(2;3)
3. Sudden Infant Death Syndrome (SIDS) or sudden unexpected infant death(4)
4. Progressive cardiac conduction disease/defect (Lenègre disease) or isolated cardiac conduction disease(5) erroneously called Lev-Lenègre syndrome (6)
5. Sinus Node Dysfunction (SND)/Sick Sinus Syndrome (SSS)

1. Wilde AA, Brugada R. Phenotypical manifestations of mutations in the genes encoding subunits of the cardiac sodium channel.Circ Res. 2011 Apr 1;108:884-897.
2. Skinner JR, Chung SK, Montgomery D, McCulley CH, Crawford J, French J, et al. Near-miss SIDS due to Brugada syndrome. Arch Dis Child. 2005 May; 90: 528-529.
3. Vatta M, Dumaine R, Varghese G, et al. Genetic and biophysical basis of suddenunexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet 2002;11:337-345.
4. Tan BH, Pundi KN, Van Norstrand DW, Valdivia CR, Tester DJ, Medeiros-Domingo A,et al. Sudden infant death syndrome-associated mutations in the sodium channel beta subunits. Heart Rhythm. 2010 Jun; 7: 771-778
5. Tan HL, Bink-Boelkens MT, Bezzina CR, et al. A sodium-channel mutation causes Isolated cardiac conduction disease. Nature 2001; 409:1043-1047
6. Napolitano C, Rivolta I, Priori SG. Cardiac sodium channel diseases. Clin Chem Lab Med. 2003 Apr;41:439-444.



Prolonged conduction parameters (P wave, PR and QRS intervals) Left atrial enlargement (LAE), first degree AV block, RBBB, LAFB in an individual with progressive cardiac conduction defect/disease (Lenègre disease). Trifascicular block.

6. Atrial fibrillation(1) Mutations in genes encoding cardiac ion channels (KCNQ1, KCNE1-5, KCNJ2, KCNA5, and SCN5A. Also, mutations in sodium channel β-subunit SCN3B are associated with early-onset lone atrial fibrillation(2). Anothers mutations related with AF are gap junctions (GJA5), and signaling molecules (atrial natriuretic peptide, nucleoporins [NUP155]). These have been reported in isolated cases and small kindreds. The advent of the human genome and HapMap projects and high-throughput genotyping has fundamentally accelerated our ability to discover the genetic contribution to common variation in human disease. In 2007, a genome-wide association study identified 2 genetic variants that associated with AF. More recently, 2 additional AF loci on chromosomes 16q22 and 1q21 have been identified. It is quite likely, however, that the effects of alleles in many genes contribute to common complex diseases such as AF. The overall AF risk associated with common variants identified by the genome-wide association study approach is small (odds ratios, 1.1-2.5) and explains less than 10% of the heritability in lone AF. This raises the possibility that rare independent variants with large effects strong effects may account for a large fraction of the risk for lone AF.
7. Atrial standstill
8. Idiopathic ventricular fibrillation (IVF)(3)
9. SCN5A mutations associate with arrhythmic dilated cardiomyopathy(4)

1. **Chen L, Zhang W, Fang C, et al. Polymorphism H558R in the human cardiac sodium channel SCN5A gene is associated with atrial fibrillation. J Int Med Res. 2011;39:1908-1916.**
2. **Olesen MS, Jespersen T, Nielsen JB, et al. Mutations in sodium channel β-subunit SCN3B are associated with early-onset lone** atrial fibrillation**. Cardiovasc Res. 2011 Mar 1;89:786-793.**
3. **Valdivia CR, Ackerman MJ, Tester DJ, et al. A novel SCN5A arrhythmia mutation, M1766L, with expression defect rescued by mexiletine. Cardiovasc Res. 2002 Aug 1;55:279-289.**
4. **McNair WP, Sinagra G, Taylor MR, et al.** SCN5A **mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol. 2011 May 24;57:2160-2168.**

10. Cardiac sodium channel overlap syndromes, overlapping phenotypes or overlapping syndromes Various SCN5A mutations are now known to present with mixed phenotypes, a presentation that has become known as "overlap syndrome of cardiac sodium channelopathy." In many cases, multiple biophysical defects of single SCN5A mutations are suspected to underlie the overlapping clinical manifestations.
    - 10-I) Long-QT syndrome variant 3 and Brugada syndromes(1;2;3)
    - 10-II) Brugada syndrome and progressive cardiac conduction defect(4) see next slide ECG
    - 10-III) Left ventricular non compaction and Brugada syndrome.(5)
    - 10-IV) Phenotypic Combination of Idiopathic VF and Brugada Syndrome.(6)
    - 10-V) Familial atrial standstill in association with dilated cardiomyopathy(7)

1. Bezzina C, Veldkamp MW, van Den Berg MP, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999 Dec 3-17;85:1206-1213.
2. Cerrone M, Crotti L, Faggiano G,et. al. Long QT syndrome and Brugada syndrome: 2 aspects of the same disease? Ital Heart J 2001; 2(3 Suppl):253-257.
3. Rivolta I, Abriel H, Tateyama M, Liu H, Memmi M, Vardas P,. et al. Inherited Brugada and long QT-3 syndrome mutations of a single residue of the cardiac sodium channel confer distinct channel and clinical phenotypes. J Biol Chem 2001; 276: 30623-30630.
4. Shirai N, Makita N, Sasaki K, et al. A mutant cardiac sodium channel with multiple biophysical defects associated with overlapping clinical features of Brugada syndrome and cardiac conduction disease. Cardiovasc Res. 2002 Feb 1;53:348-354.
5. Kaźmierczak J, Zielonka J, Peregud-Pogorzelska M, Kiedrowicz R, Wielusiński M. Ventricular and supraventricular arrhythmias and heart failure in a patient with left ventricular noncompaction and Brugada syndrome. Cardiol J. 2011;18:310-313.
6. Martinek M, Purerfellner H. A Phenotypic Combination of Idiopathic VF and Brugada Syndrome. Pacing Clin Electrophysiol. 2010 Sep;33(9):e84-7.
7. Fazelifar AF, Arya A, Haghjoo M, Sadr-Ameli MA. Familial atrial standstill in association with dilated cardiomyopathy. Pacing Clin Electrophysiol. 2005 Sep;28:1005-1008.

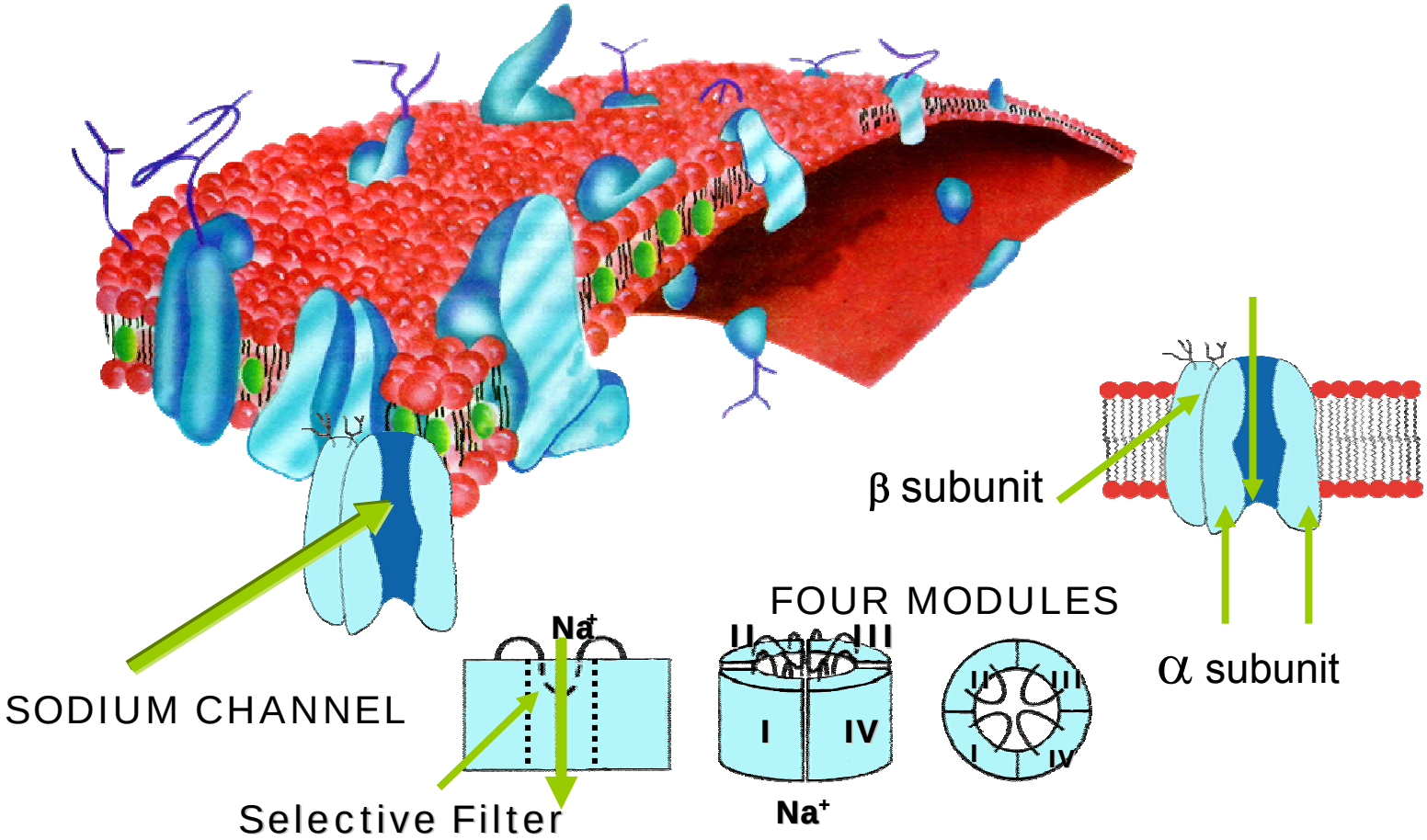
10-VI) SCN5A mutation associates Brugada syndrome and sinus node dysfunction SND.(1;2)

10-VII) Overlap syndrome with a homozygous SCN5A mutation, recessive inheritance that does not seem to follow simple Mendelian rules characterized by early cardiac arrhythmia encompassing sinus node dysfunction (SND), conduction disease, and severe ventricular arrhythmias.(3)

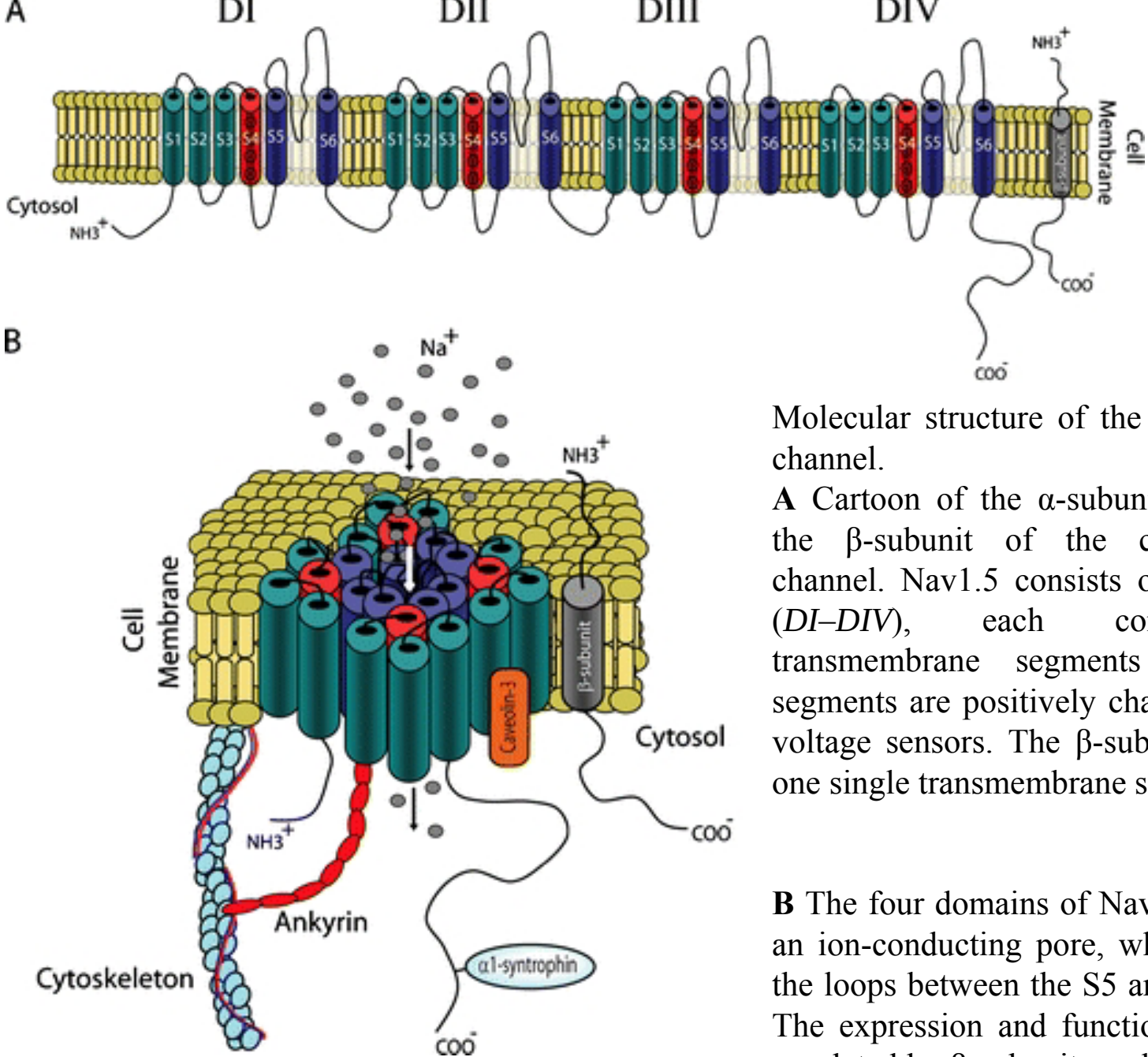
10-VIII) Coexisting early repolarization pattern and Brugada syndrome.(4)

10-IX) Multiple arrhythmic syndromes in a newborn(5)

1. Kyndt F, Schott JJ, Pronst V, et. al. new SCN5A mutation associates Brugada syndrome and sinus node dysfunction. Circulation 2000; 102:281.
2. Hayashi H, Sumiyoshi M, Yasuda M, et al. Prevalence of the Brugada-type electrocardiogram and incidence of Brugada syndrome in patients with sick sinus syndrome. Circ J. 2010 Feb;74:271-277.
3. Neu A, Eiselt M, Paul M et al. A homozygous SCN5A mutation in a severe, recessive type of cardiac conduction disease. Hum Mutat. 2010 Aug;31:E1609-1621
4. McIntyre WF, Pérez-Riera AR, Femenía F, Baranchuk A. Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities.J Electrocardiol. 2011 Dec 16. [Epub ahead of print]
5. Calloe K, Schmitt N, Grubb S, Pfeiffer R, David JP, Kanter R, Cordeiro JM, Antzelevitch C. Multiple arrhythmic syndromes in a newborn, owing to a novel mutation in SCN5A. Can J Physiol Pharmacol. 2011 Oct;89:723-736.



Main α subunit: made up by four modules or domains (I, II, III, and IV), arranged in a circle surrounding a central pore, determining conductance, impedance, and translocation properties of the Na+ cation. Each of these domains contain 6 membrane regions called S1 through S6. Region S4 acts as a voltage sensor. The region between S5 and S6 in the IV domain may block the pore of the channel making up a loop called P loop, which is the most external one. This is the narrowest region of the pore, and it is responsible for its ion selectivity. The internal portion of the pore is made up by a combination of the S5 and S6 regions of the 4 domains. The region between domains III and IV connects the channel after prolonged activation and inactivation periods. The main α subunit is affected by class I antiarrhythmic agents.

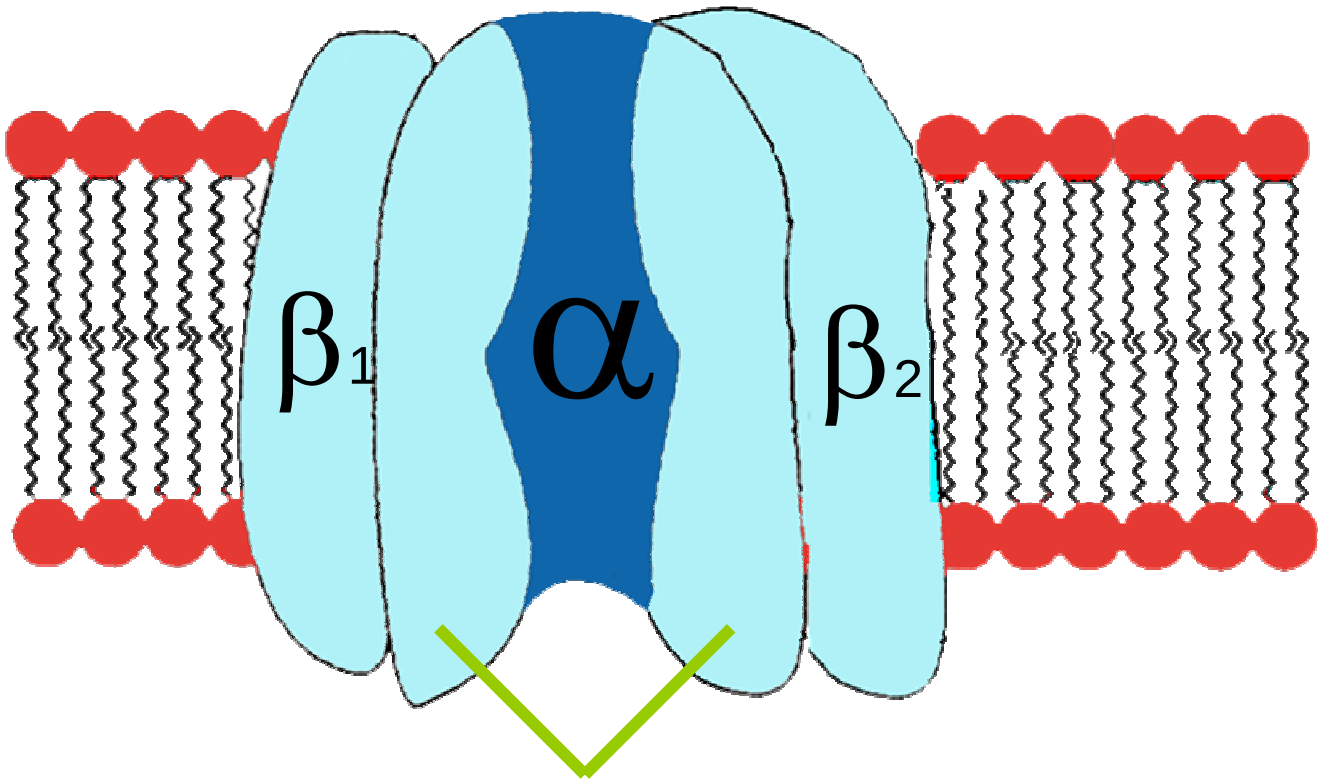


Molecular structure of the cardiac sodium channel.

A Cartoon of the α-subunit (Nav1.5) and the β-subunit of the cardiac sodium channel. Nav1.5 consists of four domains (*DI–DIV*), each containing six transmembrane segments (S1–S6); S4 segments are positively charged and act as voltage sensors. The β-subunit consists of one single transmembrane segment.

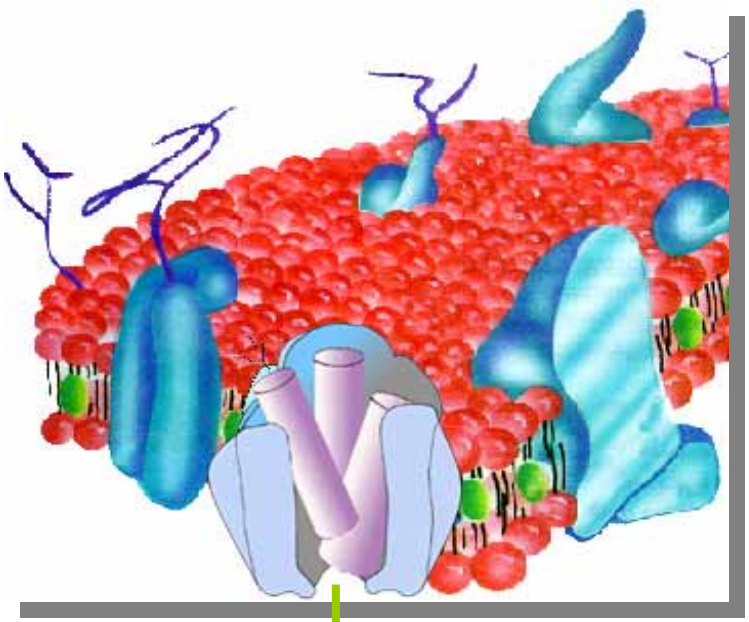
B The four domains of Nav1.5 fold around an ion-conducting pore, which is lined by the loops between the S5 and S6 segments. The expression and function of Nav1.5 is regulated by β-subunits and several directly or indirectly interacting regulatory proteins

Sodium channel subunits



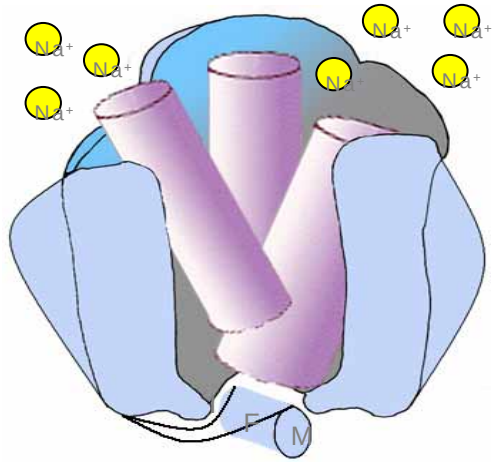
MAIN α SUBUNIT

The Na+ channel is a protein structure, made up by four modules that surround a central pore. It has a main unit, called α subunit and another two ancilliary surrounding ones, β1 and β2. The Na+ channel determines the conduction velocity of the stimulus by the amplitude of its phase 0.

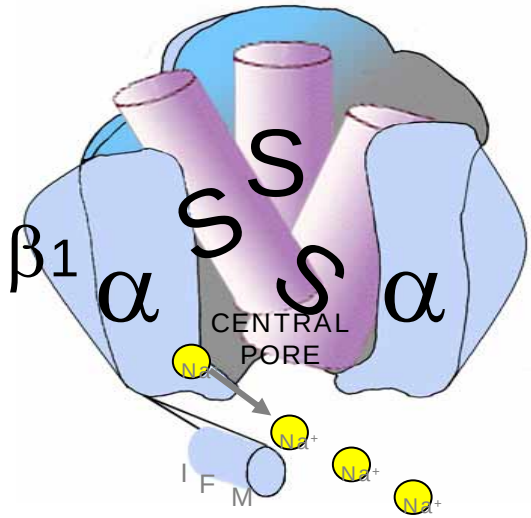


SODIUM CHANNEL STATES

CLOSED

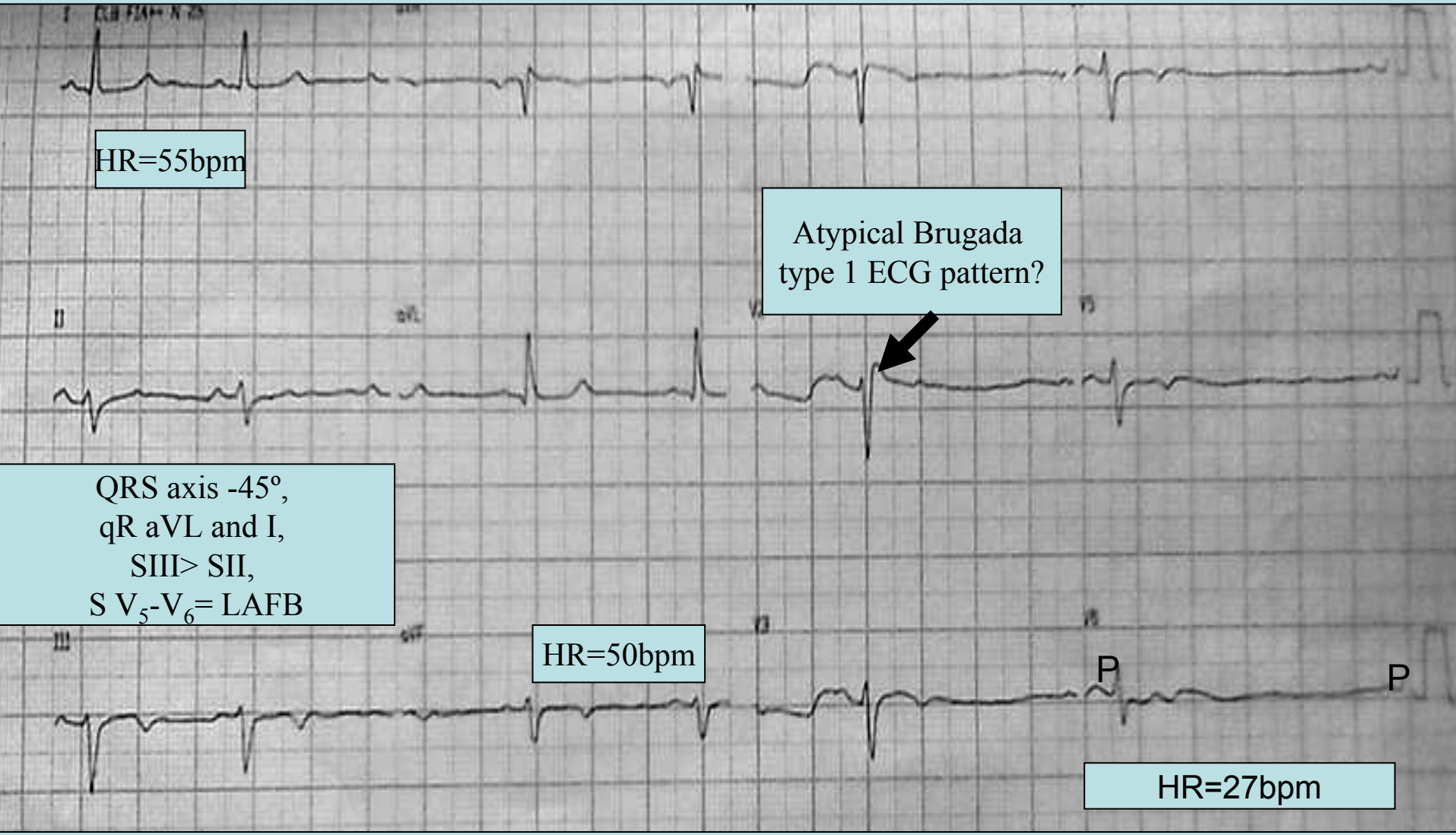


OPEN

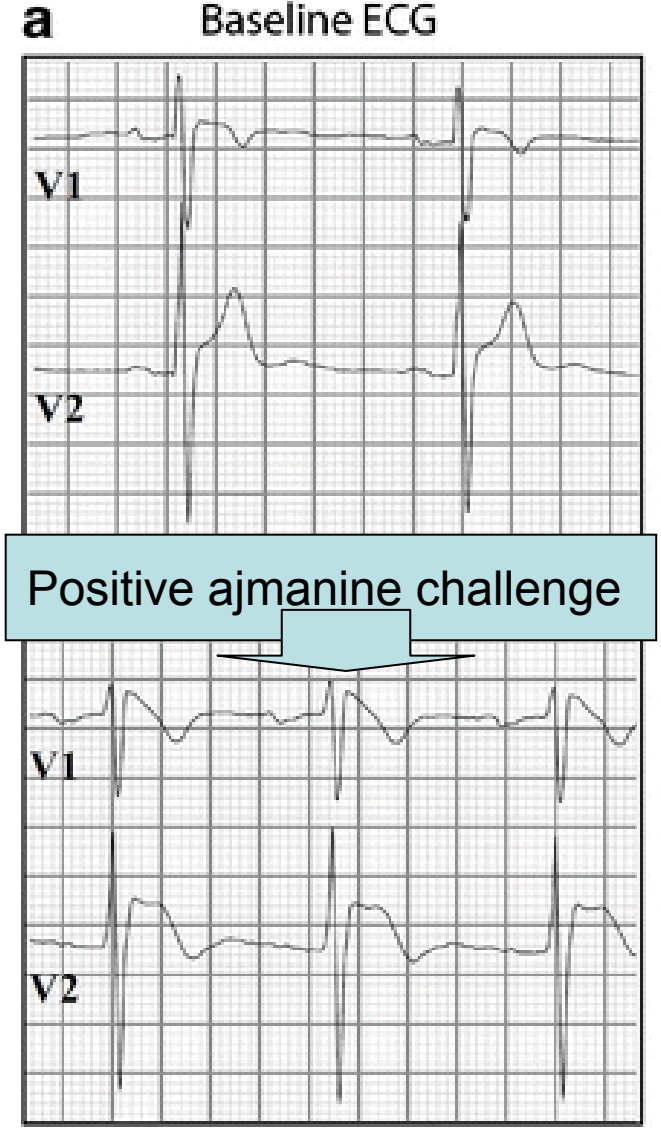


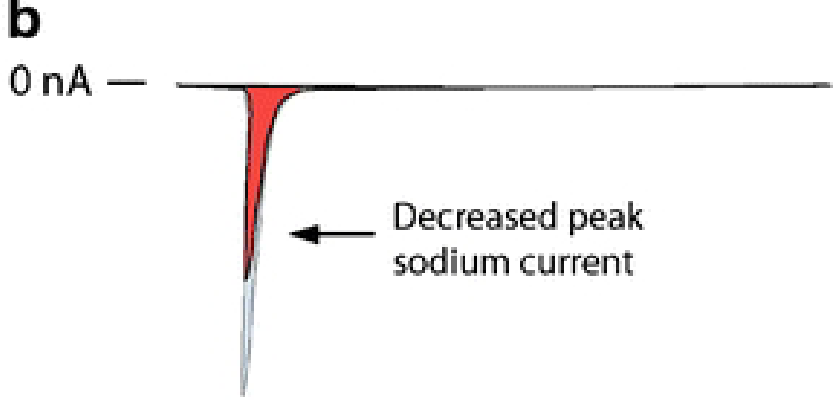
The Na+ channel has three functional states, with two of them being the main ones: open (it allows for Na+ passage) and closed (it prevents Na+ passage), besides a state called inactive. **1) Open state:** it allows for Na+ passage. **2) Closed or resting state:** during this resting functional state, the channel prevents the passage of Na+, because a critical residue (Phe1489F) closes the intracellular mouth of the pore of the channel. This state corresponds to the transmembrane diastolic potential in rest, which in the rapid fiber is found in a value close to -90 mV. In this state, the so-called “gate m” is closed, and the “gate h” is open. The Na+ channel is excitable even being closed. Na+ does not come inside rapidly until the TP is reached; i.e. from the resting potential up to the TP, the cation inflow is slow (base of phase 0).

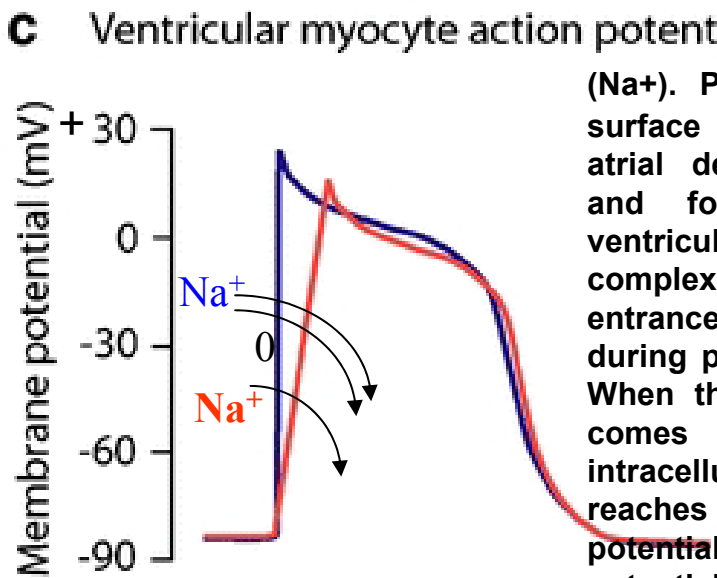
ECG PRESENT CASE



Sick sinus syndrome (SSS), or sinus node dysfunction associated with BrS?







(Na+). Phase is concomitant in surface ECG for the atria, to atrial depolarization (P wave) and for the ventricles to ventricular depolarization (QRS complex). Figure C shows entrance of the cation Na+ during phase 0 in a rapid fiber. When the channel opens, Na+ comes suddenly into the intracellular milieu, when it reaches the so-called threshold potential (TP), reversing the potential of the cell. Thus, phase 0 amplitude extends from ≈ -90 mV to +30 mV (120 mV).

Brugada syndrome

a Type 1 ECG Brugada pattern in V_1 and V_2 after intravenous administration of sodium channel blocking drug ajmaline in an individual with BrS.

b BrS-linked *SCN5A* mutations often lead to peak sodium current reduction.

c Reduced peak sodium current decreases the upstroke velocity of action potential phase 0, which slows cardiac electrical conduction (red color)

In rapid fibers, trans-membrane diastolic resting potential is between ≈ -90 and -80 mV and activation or threshold potential (TP) between -70 mV and -55 mV. Phase 0 in rapid fibers is very wide and fast, since it extends ≈ from -90 mV to +30 mV (median amplitude of 120 mV) and with activation and inactivation time <1 ms. The greater the amplitude of phase 0, the greater the conduction velocity or fiber dromotropism (directly proportional). The portion of phase 0 that extends from the resting potential up to the threshold potential (TP) is called the "base" of phase 0, and it occurs slowly; the portion that extends from the TP up to potential 0, occurs at a greater velocity of inward Na+, being known as Vmax. Finally, the portion of phase 0 that extends from potential 0 up to the reversion apex (≈ +30 mV) is called "overshoot" or Livaud's crista. The response of the rapid fiber is of the all-or-nothing type, which means that when the stimulus reaches the TP, a sudden opening of the Na+ channel occurs, with rapid cation inflow, "summoned" from inside the cells by a double electrical and osmotic gradient:Electrical: because being positive (cation), it seeks the opposite (negative) intracellular milieu. Osmotic: because there is a greater concentration of Na+ in the extracellular milieu (142 mEq/L) than in the intracellular one (10 mEq/L): extracellular/intracellular ratio = 14:1 (1). Rapid phase 0 can be blocked by class I antiarrhythmic agents (IA, IB, and IC) and by a toxin called Tetrodotoxin or TTX (anhydrotetrodotoxin 4-epitetrodotoxin, tetrodonic acid), found in several species of fish such as pufferfish, porcupine fish, ocean sunfish, and triggerfish. This toxin blocks the rapid Na+ channels of contractile cells of cardiomyocytes (ordinary working muscle cells), by inhibiting contraction. Thus, people poisoned with TTX may die by cardiac muscle paralysis without affecting slow fiber AP. This mechanism was discovered by the Japanese researcher Toshio Narahashi, working at the Duke University in the early 60s. Currently, TTX is produced by certain bacteria, such as the pseudomonas tetraodonis and others. Class I antiarrhythmic agents block Na+ channels of rapid channels (2). Class I antiarrhythmic agents have been divided in three categories, depending on the affinity of the drug with the Na+ channel by Vaughan-Williams, later modified by Harrison (3;4).

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3. Vaughan-Williams E A, A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol. 1984 Apr; 24: 129-147.
4. Harrison DC. Antiarrhythmic drug classification: new science and practical applications.Am J Cardiol. 1985 Jul 1; 56:185-187.

Class IA: they have intermediary binding and release kinetics with the Na+ channel. They moderately reduce Vmax and extend AP. The main representatives are: quinidine, procainamide, disopyramide, and ajmaline. Additionally, they have a significant anticholinergic effect. Class IA drugs that block both the rapid Na+ channel and the *I*to channel, such as quinidine and disopyramide, may normalize J point and ST segment elevation in right precordial leads in Brugada syndrome. On the contrary, those drugs of the same class IA, such as ajmaline and procainamide, that act exclusively on the rapid Na+ channel without affecting the *I*to channel, increase J point and ST segment elevation and may trigger fatal tachyarrhythmias in Brugada syndrome (**1**). On the other hand, quinidine is very efficient to prevent induction of ventricular fibrillation, sustained during the electrophysiologic study in patients with idiopathic VF and BrS. This efficacy is maintained in the long term; consequently, the therapy with quinidine guided by the EPS represents a valuable alternative to cardioverter defibrillator in this population (**2**).

Class IB: they have rapid binding and release kinetics with the Na+ channel, so they do not affect QRS duration and JT interval (from the J point up to the end of T wave). They mildly reduce Vmax. They do not modify or shorten AP. The representatives are: mexiletine, tocainide, lidocaine; widely used for the acute management of ventricular tachyarrhythmias (**3**).

Class IC: they have slow binding kinetics with the Na+ channel. They significantly reduce Vmax, and consequently, conduction velocity: more intense negative dromotropic effect and no effect or decrease in AP duration (in the latter aspect, completely different from class IA). As a consequence of this slow kinetics, QRS complex and JT interval duration increase. They may extend refractoriness minimally. The representatives are propafenone, flecainide, encainide, moricizine, and lorcainide. Propafenone is the only one in this group with additional β2 blocking effect, which offsets tachycardia by IC effect.

1. Mandelburger D, Teubl A, Röggla G. Ajmaline challenge in Brugada syndrome. Resuscitation. 2007 Aug; 74(2): 393-394.
2. Belhassen B, Glick A, Viskin S. Excellent long-term reproducibility of the electrophysiologic efficacy of quinidine in patients with idiopathic ventricular fibrillation and Brugada syndrome. Pacing Clin Electrophysiol. 2009 Mar; 32: 294-301.
3. Chaudhry GM, Haffajee CI.Antiarrhythmic agents and proarrhythmia.Crit Care Med. 2000 Oct; 28(10 Suppl):N158-164.

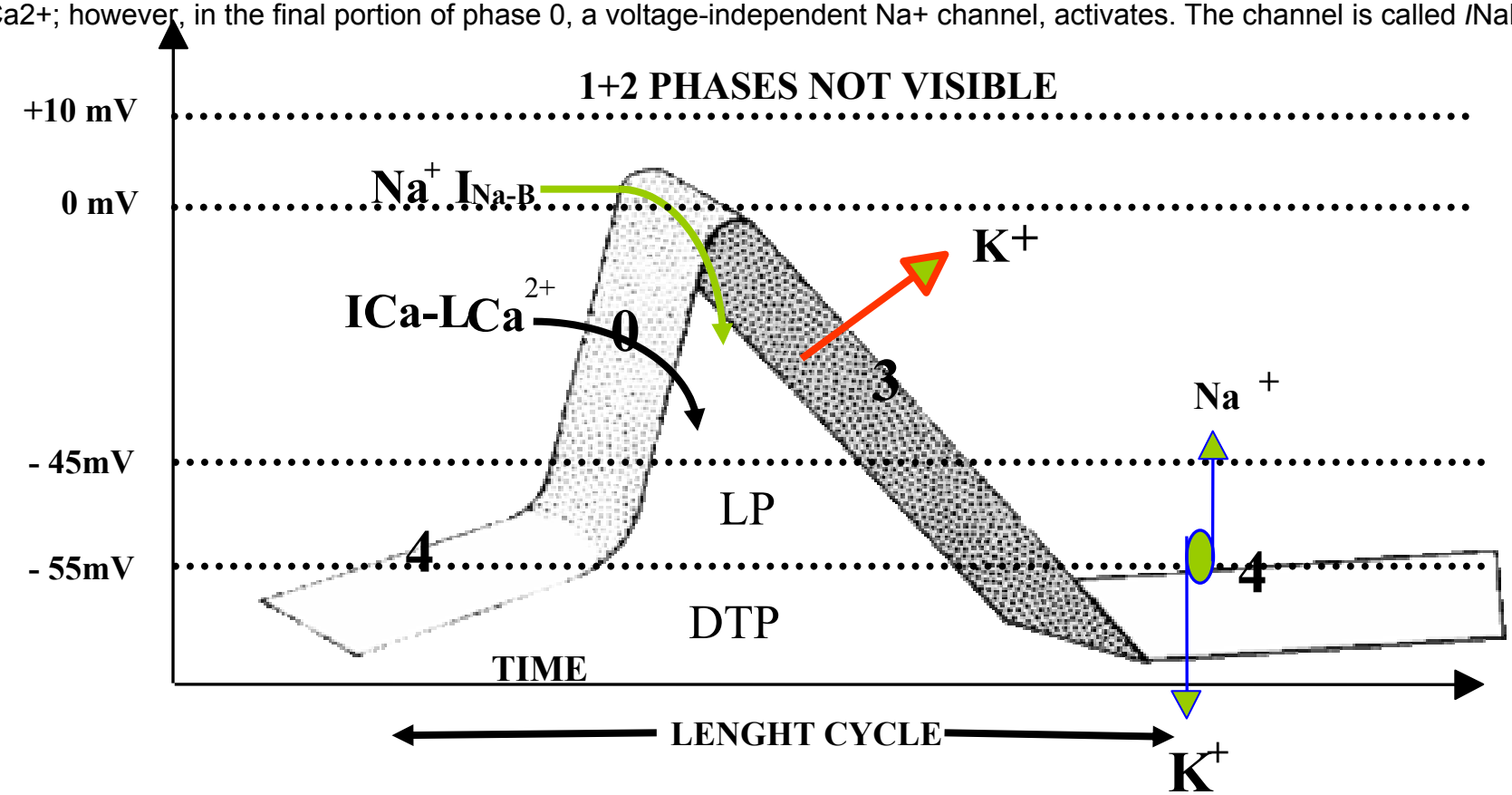
Sick Sinus Syndrome

Sick sinus syndrome (SSS) comprises a variety of conditions involving sinus node dysfunction (SND) and commonly affects elderly persons. While the syndrome can have many causes, it usually is idiopathic or by genetic mutation. Patients may experience syncope, pre-syncope, palpitations, or dizziness; however, they often are asymptomatic or have subtle or nonspecific symptoms. SSS has multiple manifestations on ECG, including 1)Sinus bradycardia; 2) Sinus arrest; 3) Exit block; 4) Sinoatrial block; 5) Alternating patterns of bradycardia and tachycardia (bradycardia-tachycardia syndrome). Diagnosis of SSS can be difficult because of its nonspecific symptoms and elusive findings on ECG or Holter monitor. SSS is a generalized abnormality of cardiac impulse formation that may be caused by an intrinsic disease of the SA node that makes it unable to perform its pacemaking function, or by extrinsic causes.(1) SSS is not a disease with a single etiology and pathogenesis but, rather, a collection of conditions in which the ECG indicates SND (2) SSS is characterized by SND with an atrial rate inappropriate for physiologic requirements. Although the condition is most common in the elderly, it can occur in persons of all ages, including neonates.(3) The mean age of patients with this condition is 68 years, and both sexes are affected approximately equally.(4) SSS occurs in one of every 600 cardiac patients older than 65 years and may account for 50% or more of permanent pacemaker placements in the United States.(5)

1. Mangrum JM, DiMarco JP. The evaluation and management of bradycardia. *N Engl J Med*. 2000;342:703–9.
2. Bigger JT Jr, Reiffel JA. Sick sinus syndrome. *Annu Rev Med*. 1979;30:91–118.
3. Wahls SA. Sick sinus syndrome. *Am Fam Physician*. 1985;31:117–124.
4. Lamas GA, Lee K, Sweeney M, Leon A, Yee R, Ellenbogen K, et al. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. *Am Heart J*. 2000;140:541–551.
5. Rodriguez RD, Schocken DD. Update on sick sinus syndrome, a cardiac disorder of aging. *Geriatrics*. 1990;45:26–30.

ACTION POTENTIAL IN SA NODE P CELLS SLOW CELLS

Slow cells are located within the limits of the SA Node, AV node, and in the mitrotricuspid rings. They are characterized by presenting a not so negative resting potential (≈ -55 mV), a not so wide, slow Ca $^{2+}$-dependent phase 0, and with additional final entrance of Na+ through a channel independent from voltage, called *I*Na+B, and absence of identifiable phases 2 and 3. In SA node cells, phase 0 depends on slow inward Ca2+; however, in the final portion of phase 0, a voltage-independent Na+ channel, activates. The channel is called *I*NaB.



Cells located in the SA node: with three varieties:

Pacemaker, P, or nodal cells: in turn, with two varieties:

Spider-shaped cells

Spindle-shaped cells.

Transitional or T cells

Atrial myocardial cells. SA node and AV node cells are slow and His-Purkinje system cells are fast.

P cells of the SA node (**1**), 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 (**2;3**). 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 (**4;5**). 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 I***f*** channel activity (**6**). 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+, *I*Na+ (Na(v)1.5), the *If* pacemaker channel (HCN4) or the Na+/Ca2+ exchanger (NCX1) and others. Mutations in CAV3 may originate variant 9 of congenital Long QT Syndrome (LQT9) and other inherited arrhythmias. In acquired diseases that lead to congestive heart failure, CAV3 may be affected, originating arrhythmias (**7**).

1. Lakatta EG, DiFrancesco D. What keeps us ticking: a funny current, a calcium clock, or both? J Mol Cell Cardiol. 2009 Aug; 47: 157-170.
2. Baruscotti, M., Bucchi, A., DiFrancesco, D. (2005). Physiology and pharmacology of the cardiac pacemaker ("funny") current. Pharmacology & Therapeutics, 107, 59-79.
3. Barbuti A, Baruscotti M, DiFrancesco D. The pacemaker current: from basics to the clinics. J Cardiovasc Electrophysiol. 2007 Mar; 18: 342-347.
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7. Balijepalli RC, Kamp TJ. Caveolae, ion channels and cardiac arrhythmias. Prog Biophys Mol Biol. 2008 Oct-Nov; 98:149-160.

The fast Ca2+ T type current or T-type Ca2+ channel, transient *I*Ca-T 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 Ca2+ 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 Ca2+ channel is blocked in a selective way by the Ca2+ 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 Ca2+ cation entrance. Mibefradil decreases HR, not affecting contractility (**1**). The great efficacy of bepridil to end with atrial fibrillation or flutter, is due in part to the block of this rapid type Ca2+ channel (**2**). 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).

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2. 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.

Etiology

Most cases of SSS are idiopathic, and the cause can be multifactorial .Degenerative fibrosis of nodal tissue is the most common cause of intrinsic changes in the SA node that lead to SSS. Certain conditions can cause these intrinsic changes. There also are extrinsic causes of SND and conditions that can cause this problem in children .

CAD may coexist with SSS in a significant number of patients, although it is not considered a major cause of the syndrome. It is unclear whether inflammation, sinus node ischemia, or local autonomic neural effects lead to the development of SSS in patients with MI. SND usually is temporary when it follows an AMI. Uncommonly, chronic ischemia may cause fibrosis and lead to symptoms of SSS for months to years after MI

Clinical ManifestationsPatients with SSS often are asymptomatic or have symptoms that are mild and nonspecificSymptoms are related to the decreased cardiac output that occurs with the bradyarrhythmias or tachyarrhythmias. Most of the symptoms are caused by decreased cerebral perfusion, and 50%of patients have syncope or pre-syncope. S ymptoms, which may have been present for months or years, can include Stokes-Adams attacks fainting due to asystole or VF , dizziness or light-headedness, palpitations chest pain or angina shortness of breath, fatigue , headache, nausea, fainting Symptoms caused by the worsening of conditions such as CHF, angina pectoris, and cerebral vascular accident. Peripheral thromboembolism and stroke, which can occur in the presence of bradycardia-tachycardia syndrome, may be related to dysrhythmia-induced emboli.A slow heart rate in the presence of fever, LV failure, or pulmonary edema may be suggestive of SSS.

Associated tachycardia may cause flushing of the face, pounding of the heart, and retrosternal pressure. Other symptoms include irritability, nocturnal wakefulness, memory loss, errors in judgment, lethargy, lightheadedness, and fatigue

More subtle symptoms include mild digestive disturbances, periodic oliguria or edema, and mild intermittent dyspnea.

ECG Manifestations

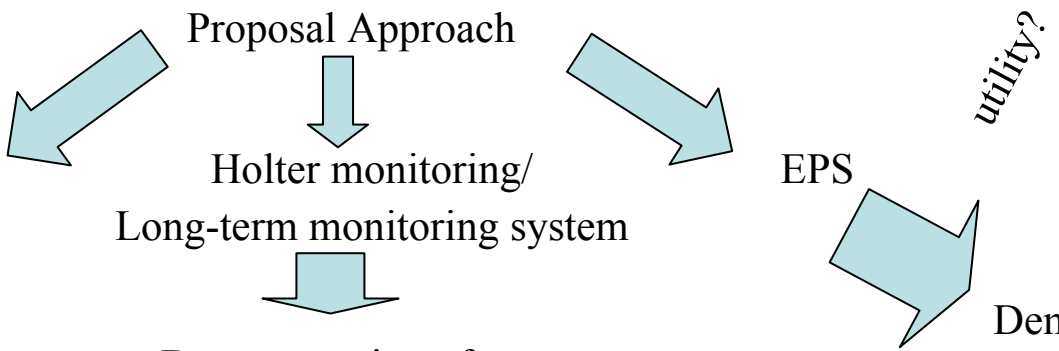
SSS can produce a variety of ECG manifestations consisting of atrial bradyarrhythmias, atrial tachyarrhythmias, and alternating bradyarrhythmias and tachyarrhythmias Supraventricular bradyarrhythmias may include

1. Sinus bradycardia: it is inappropriate and not caused by medications.
2. Sinus arrest with or without junctional escape,
3. Sinoatrial exit block, The sino-atrial exit block that occurs in patients with SSS may demonstrate a Mobitz type I block (Wenckebach block) and a Mobitz type II block.
4. Ectopic atrial bradycardia
5. AF with slow ventricular response. AF is the most common tachydysrhythmia in these patients.
6. The ECG may reveal a long pause following cardioversion of atrial tachyarrhythmias, and a greater-than three-second pause following carotid massage.
7. 60% of patients have tachyarrhythmias.
8. Supraventricular tachyarrhythmias that occur in patients with SSS include
9. Paroxysmal supraventricular tachycardia,
10. Atrial flutter
11. Atrial tachycardia.
12. Rarely, a ventricular escape tachy-arrhythmia may be seen on ECG.
13. SA node re-entrant rhythm is another ECG manifestation.
14. Bradycardia-tachycardia syndrome may be seen on ECG or cardiac rhythm strip this syndrome is more common in older patients with advanced SSS.

Diagnosis hypothesis and proposal approach

Sinus node dysfunction concomitant with Brugada syndrome.?:

Cardiac sodium channel overlap syndrome, overlapping phenotype or overlapping syndrome?



Eventual unquestionable Brugada type 1 ECG detection

Isoproterenol infusion during the EPS to look for infrahisian AV block or organic SSS after injection of ajmaline or to know if SSS or suprahisian AV block are reversible after atropine and are vagal-related(3). Implantable cardioverter defibrillator, including upgrade from Permanent pacing is indicated for symptomatic bradyarrhythmias. .

1. **Sumiyoshi M, Nakazato Y, Tokano T, et al. Sinus node dysfunction concomitant with Brugada syndrome. Circ J. 2005 Aug; 69:946-950.**
2. **Morita H, Fukushima-Kusano K, Nagase S, et al.Sinus node function in patients with Brugada-type ECG. Circ J. 2004 May;68:473-476.**
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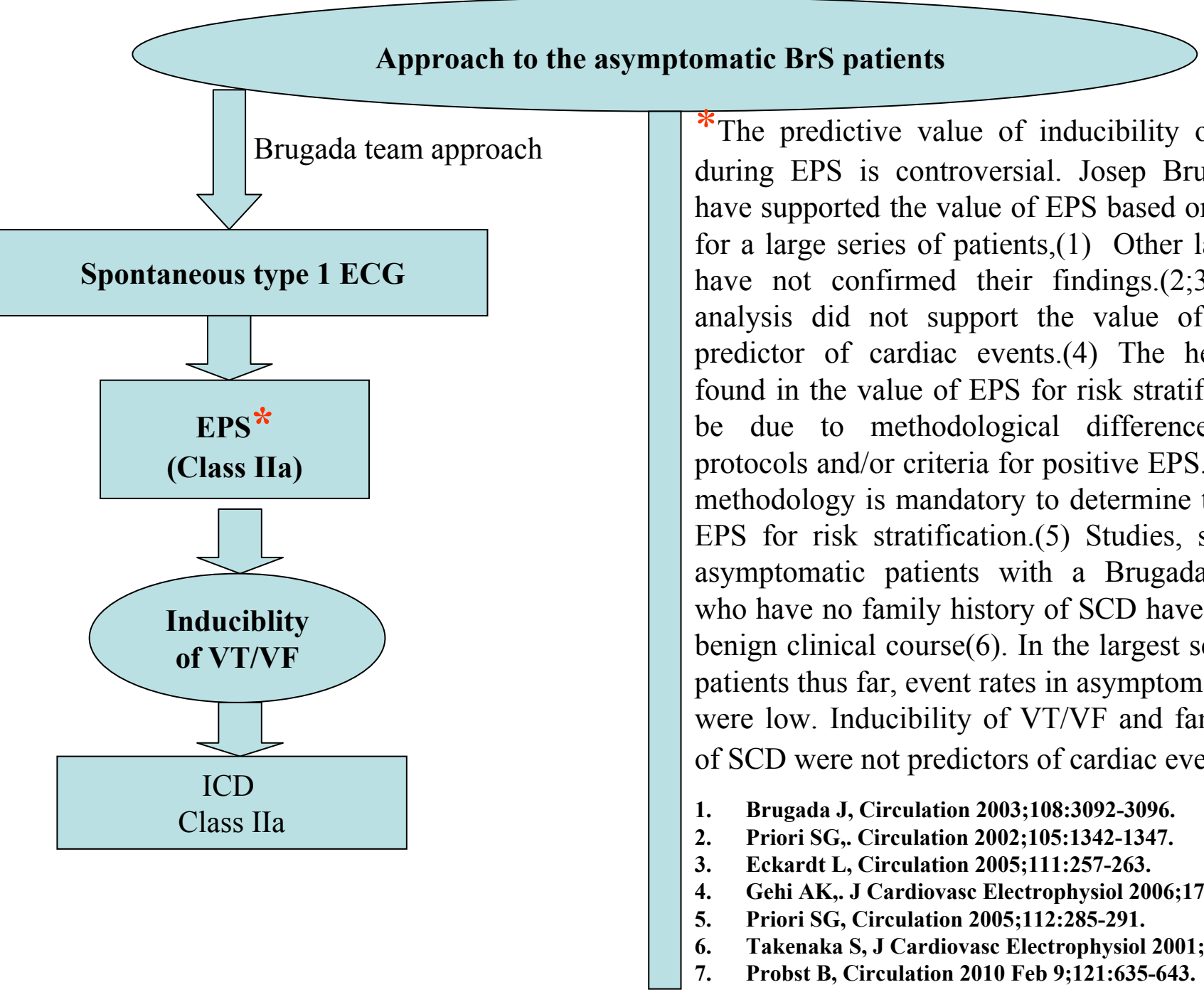

*The predictive value of inducibility of S-VT/VF during EPS is controversial. Josep Brugada et al. have supported the value of EPS based on the results for a large series of patients,(1) Other large studies have not confirmed their findings.(2;3) A meta-analysis did not support the value of EPS as a predictor of cardiac events.(4) The heterogeneity found in the value of EPS for risk stratification may be due to methodological differences in EPS protocols and/or criteria for positive EPS. A standard methodology is mandatory to determine the value of EPS for risk stratification.(5) Studies, suggest that asymptomatic patients with a Brugada-type ECG who have no family history of SCD have a relatively benign clinical course(6). In the largest series of BrS patients thus far, event rates in asymptomatic patients were low. Inducibility of VT/VF and family history of SCD were not predictors of cardiac events.(7)

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3. **Eckardt L, Circulation 2005;111:257-263.**
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INDICATIONS FOR PERMANENT PACEMAKER IMPLANTATION IN SICK SINUS SYNDROME
Class I*1. SSS with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. In some patients, bradycardia is iatrogenic and will occur as a consequence of essential long-term drug therapy of a type and dosage for which there are no acceptable alternatives.
2. Symptomatic chronotropic incompetence Class IIa1.
SSS occurring spontaneously or as a result of necessary drug therapy, with heart rate less than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. Class IIb1.
In minimally symptomatic patients, chronic heart rate less than 30 bpm while awake Class III1.
SSS in asymptomatic patients, including those in whom substantial sinus bradycardia (heart rate less than 40 bpm) is a consequence of long-term drug treatment.
SSS in patients with symptoms suggestive of bradycardia that are clearly documented as not associated with a slow heart rate.
SSS with symptomatic bradycardia caused by nonessential drug therapy

SSS = sick sinus syndrome; bpm = beats per minute.
**—Class I represents conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective. Class II represents conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa represents conditions in which the weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb represents conditions in which the usefulness/efficacy is less well established by evidence/opinion. Class III represents conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.*

1. *Information from Gregoratos G, Cheitlin MD, Conill A, Epstein AE, Fellows C, Ferguson TB Jr, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). J Am Coll Cardiol 1998;31:1178,1182.*

Treatment

Pacemaker therapy is warranted in many patients with SSS. lists practice guidelines from the American College of Cardiology/American Heart Association task force on permanent pacemaker placement in patients with this condition.(1) It is essential to document symptoms concurrent with the dysrhythmia when evaluating whether pacemaker placement will be beneficial.

The treatment of choice for symptomatic bradyarrhythmias in patients with SSS is the placement of a pacemaker.(3;4) Artificial pacemakers are well tolerated in elderly patients.(2) In all patients with this syndrome, except those with chronic AF, atrial-based pacemakers are recommended(1;5)

The mainstay of treatment is atrial or dual-chamber pacemaker placement, which generally provides effective relief of symptoms and lowers the incidence of AF, thromboembolic events, HF, and mortality, compared with ventricular pacemakers.

1. **Gregoratos G, Cheitlin MD, Conill A, Epstein AE, Fellows C, Ferguson TB Jr, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation).** ***J Am Coll Cardiol.*** **1998;31:1175–209.**
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