Young man with dilated and arrhytmogenic right ventricle

Homem jovem com ventrículo direito dilatado e arritmogênico.

Case report of Raimundo Barbosa-Barros M.D. " The Fox"
Fortaleza Ceará –Brazil
Coronary Center Hospital de Messejana Dr. Carlos Alberto Studart Gomes Fortaleza-Ceará-Brazil

Identification

J.P.S.F, male, 26 years old, born in Itatira-CE, Brazil, single, farmer
Main complaint:

Patient, admitted in this service on July 22nd, 2012 with symptoms of palpitations, associated to dizziness and profuse sweating. He denied suffering precordial pain, dyspnea, and other clinical symptoms.

Uncles and cousins with similar symptoms (SIC) however without history of SCD.

Previous pathology history
2007: Syncope and admission ECG: VT with morphology of LBBB.
Previous diagnosis of Ebstein's Anomaly on September 10th, 2008 Pre-op Echo: dilated RV with low location of the septal leaflet of the tricuspid valve. By surgical description: with no anatomical evidence of Ebstein's anomaly (finding: significant tricuspid failure with dilated RV)
Correction in December 2008 →tricuspid bioprosthesis.

Physical examination at admission
Cardiovascular system: regular heart rhythm, S3 (gallop rhythm), normal heart sounds, no murmur;
Respiratory system: vesicular murmur in both hemithoraxes;
Abd: moderate ascites and hepatomegaly (2 cm from right costal margin)
Limbs: palpable peripheral pulses, edema (2+/4+), pitting edema

Identificação Portuguese

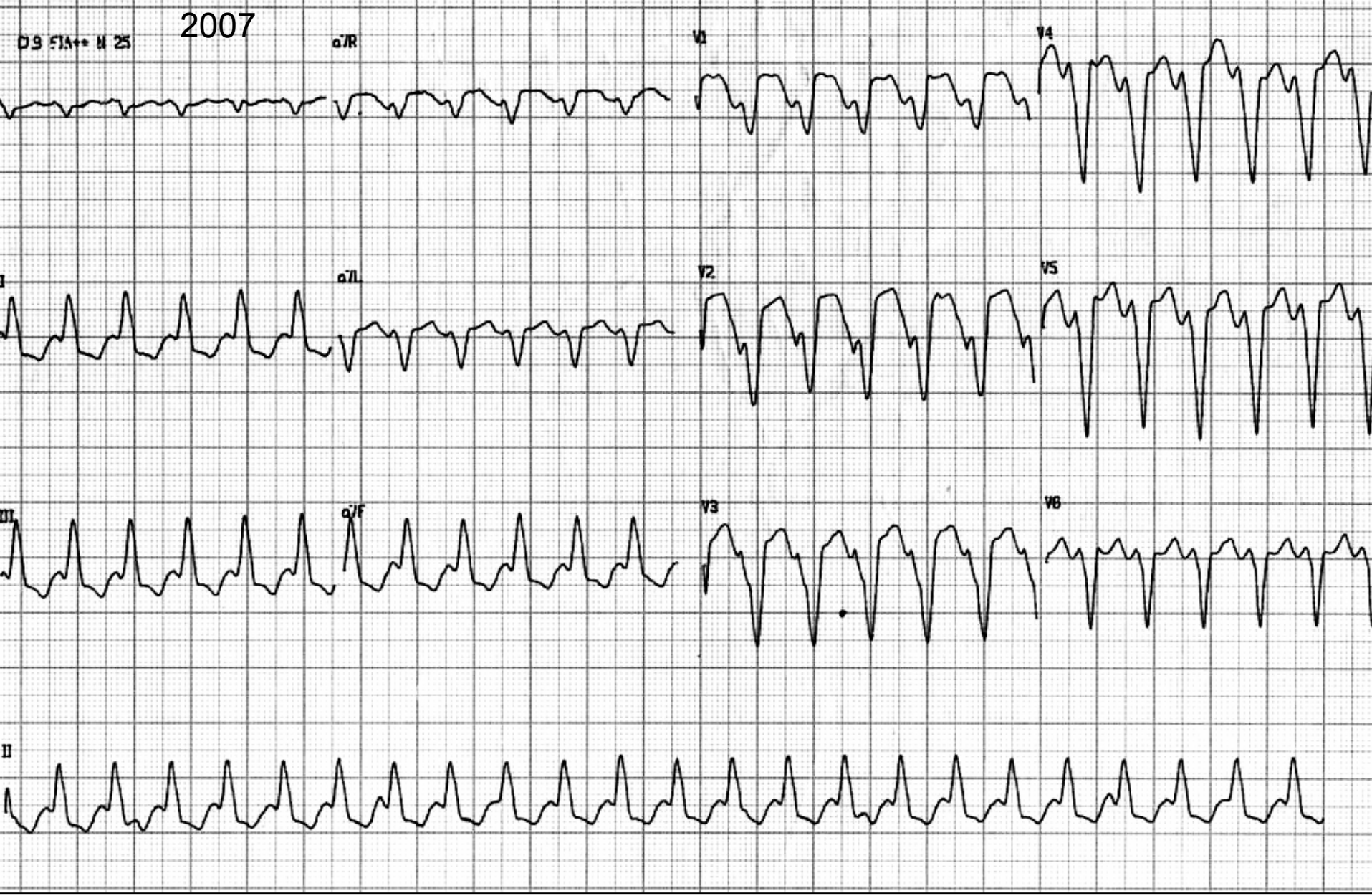
•J.P.S.F, 26 anos, natural e procedente de Itatira-CE, solteiro, agricultor
Queixa principal: ¨coração acelerado¨
Paciente, deu entrada neste serviço no dia 22/07/2012 com quadro de palpitações,associado a vertigem e sudorese profusa.Negava precordialgia, dispnéia e demais queixas clínicas.
Tios e primos com sintomas semelhantes(SIC) porém sem relato de MS
HPP
2007: Síncope e ECG de entrada: TV com morfologia de BRE.
Diagnóstico prévio de Anomalia de Ebstein em 10/09/2008

ECO pré-op: VD dilatado com implantação baixa do folheto septal da VT

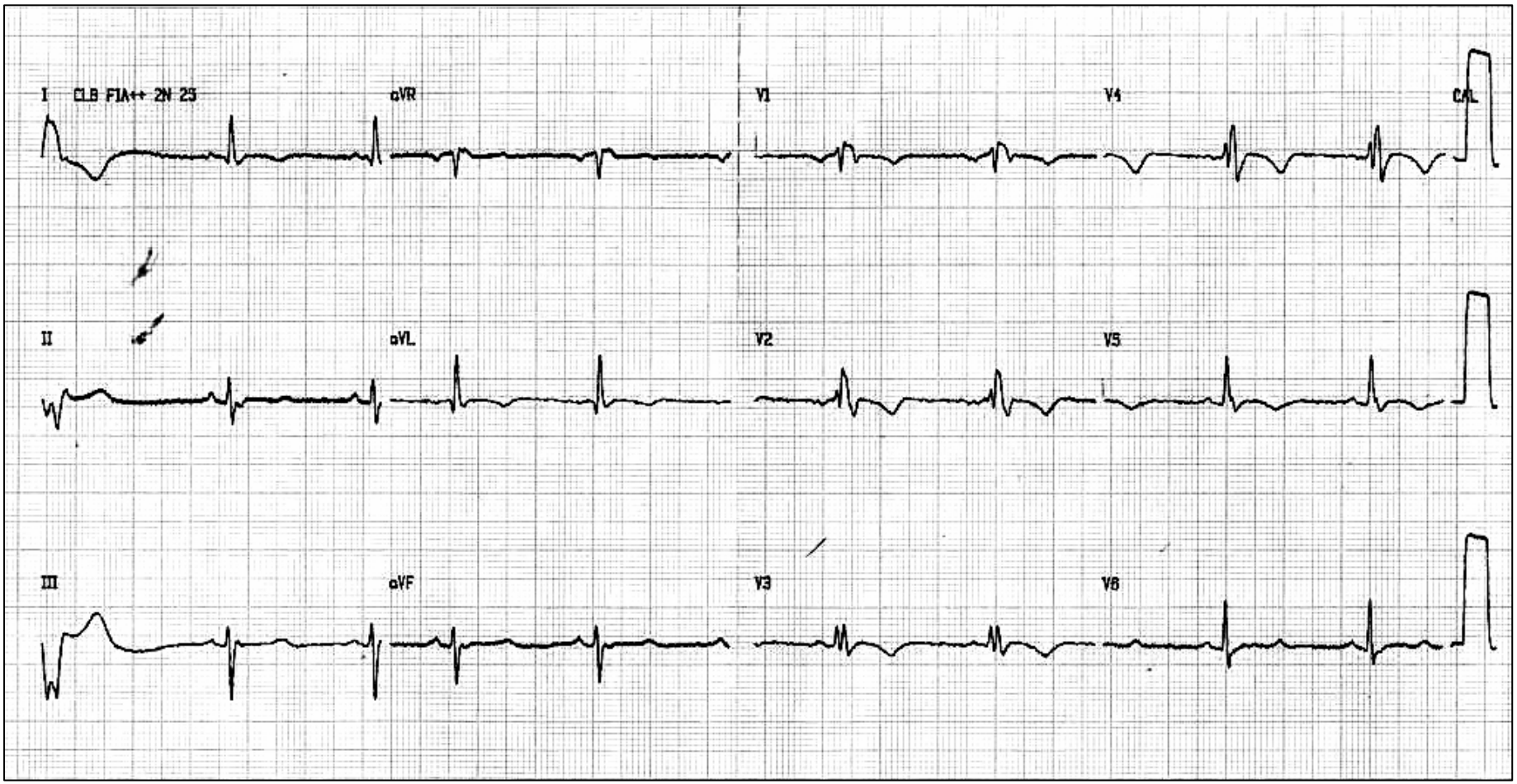
Pela descrição cirúrgica: sem evidência anatômica de Anomalia de Ebstein (achado: insuficiência tricúspide importante com VD dilatado)

Correção em Dezembro/2008 →Bioprótese tricúspide
Exame físico da admissão
ACV:RCR, 3T(Ritmo de galope), BNF, sem sopro;
AR:MV + em AHT;
Abd:Ascite moderada e hepatomegalia(2cm do RCD)
Ext:PPP, edema(2+/4+), cacifo +

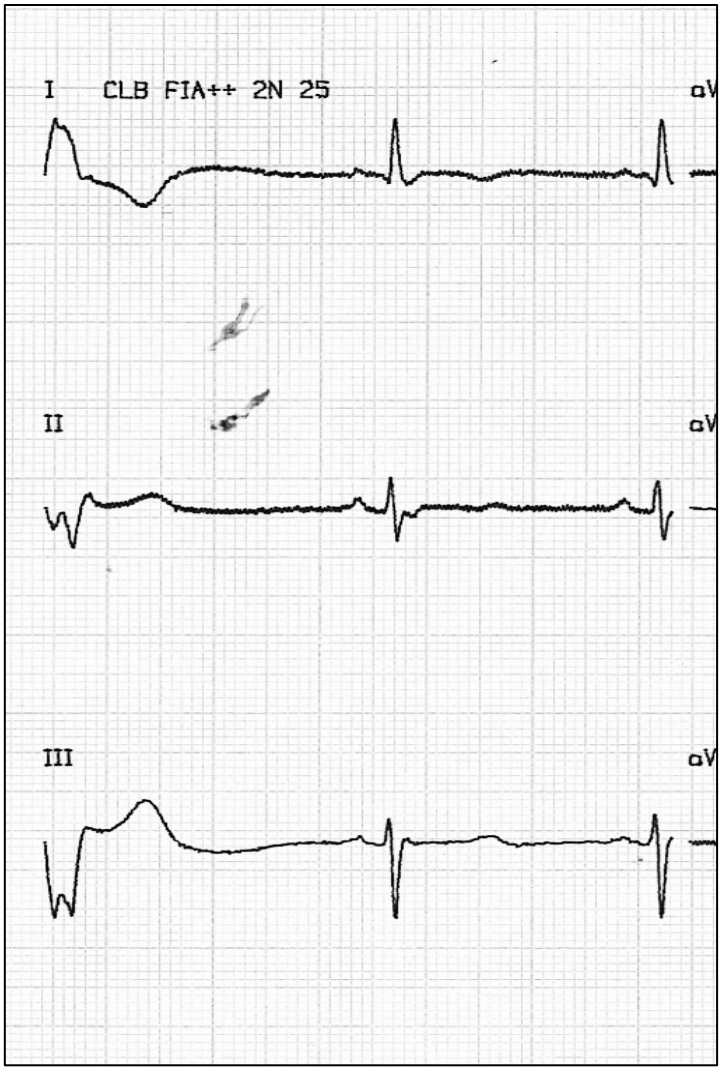
2007



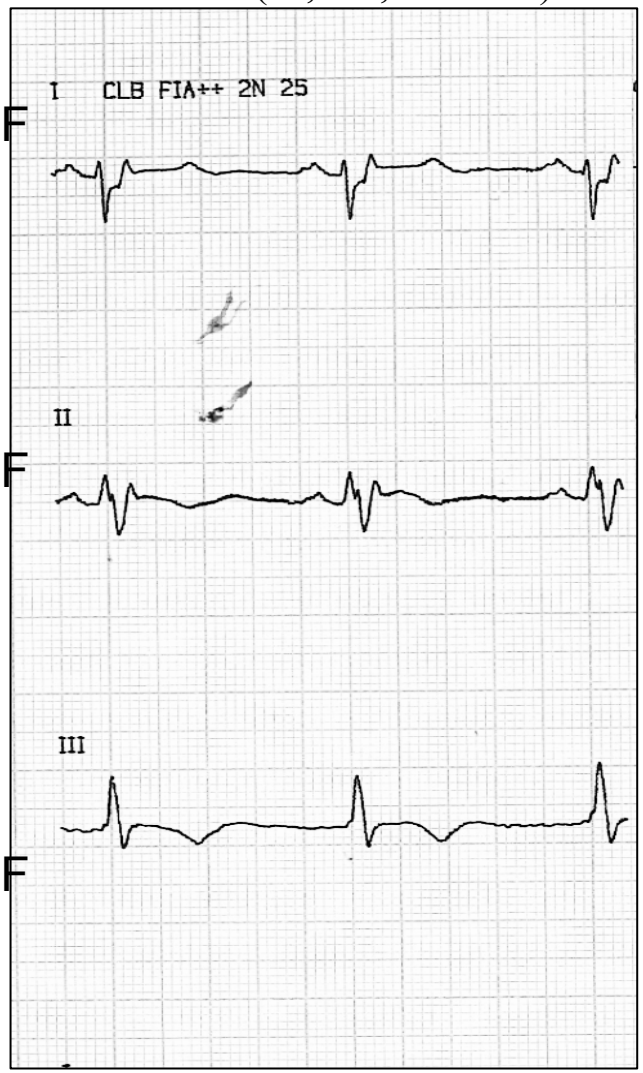
22-08-2012
2N



Conventional bipolar leads



Fontaine bipolar precordial leads
F-ECG (FI, FII, and FIII)



ECO – 10/09/2008

CONCLUSÃO

Os achados são compatíveis com anomalia de Ebstein:

- Grande dilatação das câmaras cardíacas direitas. Ventrículo direito medindo: diâmetro anteroposterior 63mm , via de sáida 48mm. Átrio direito mede 99mm, com área estimada em 54 cm². Volume do AD: 145ml/m²
- Hipocinesia difusa do VD. Contratilidade preservada na via de saída do VD
- Implantação anormal do folheto septal da válvula tricúspide; folheto anterior com alterações morfológicas, longo e com porção aderida à parede livre do VD. Grande falha de coaptação dos folhetos, com baixas pressões em câmaras direitas.PSAP estimada em 17mmHg
- Tronco pulmonar e ramos de diâmetros normais
- Dilatação da veia cava inferior (2. 57cm), com discreta variação respiratória.
- Câmaras esquerdas com diâmetros e contratilidade preservadas
- Pequeno derrame pericárdico

Great dilatation of right chambers. Anteroposterior diameter of RV=63mm, RVOT: 48mm, RA 99mm, RA area 54cm^2, RA volume estimation 145ml/m^2.
Diffuse hypokinesis of RV. RVOT with preserved contractility.
Tricuspid septal leaflet with low implantation and deformed. IVC dilated (2.53cm)
Normal left heart chambers.
Minimal pericardium effusion

July 24th, 2012

TTE →

EF:63% ;

Right cardiac chambers with significant increase and presence of spontaneous contrast;

Preserved LV overall and segmentary contractility;

RV systolic dysfunction;

Tricuspid bioprosthesis with normal aspect, presents area of opening by PHT of 2.1 cm^2 and medium gradient. of 2.1 mmHg;

Pulmonary artery systolic pressure=23 mmHg

July 25th, 2012

Holter→Infrequent premature ventricular contractions

24/07/12

ECO TT→ FE:63% ;

Câmaras cardíacas direitas com aumento importante e presença de contraste espontâneo ;
Contratilidade global e segmentar de VE preservada;
Disfunção sistólica de VD;
Bioprótese tricúspide de aspecto normal, apresenta área de abertura pelo PHT de 2,1cm² e grad. médio de 2,1mmHg;
PSAP=23mmHg

25/07/2012

Holter→Ectopia Ventricular pouco frequente

Evolução

EEF: 10/08/2012

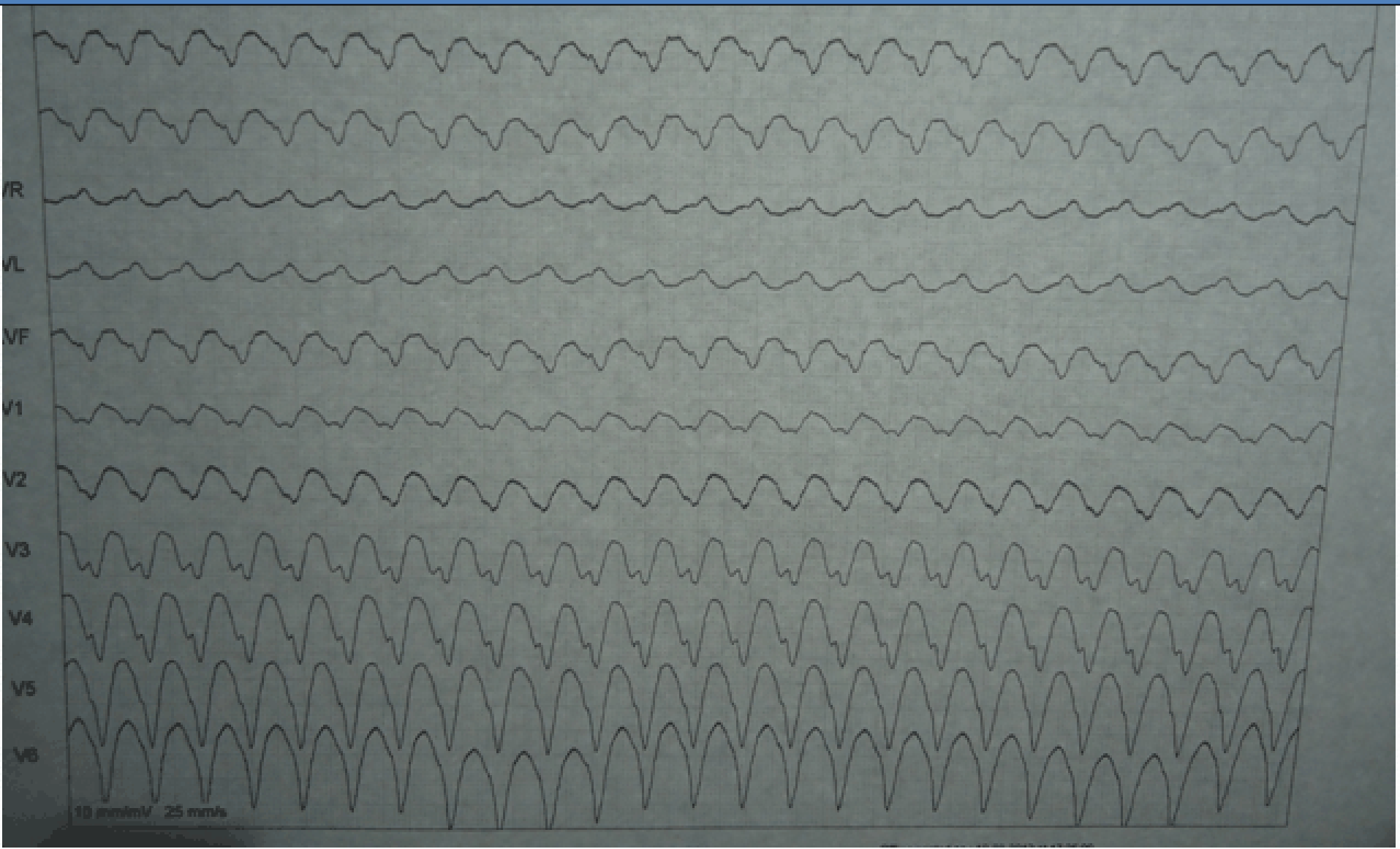
Realizado ablação do istmo cavo-tricúspideo com bloqueio bidirecional;
Protocolo de estimulação ventricular com indução de TVMS→Degeneração para TV polimórfica com instabilidade hemodinâmica →CVE(200J);
Após ablação do Flutter, apresentou bradicardia sinusal(FC= 40bpm), que aos poucos melhorou(FC= 50bpm)

Evolution

EPS: August 10th, 2012

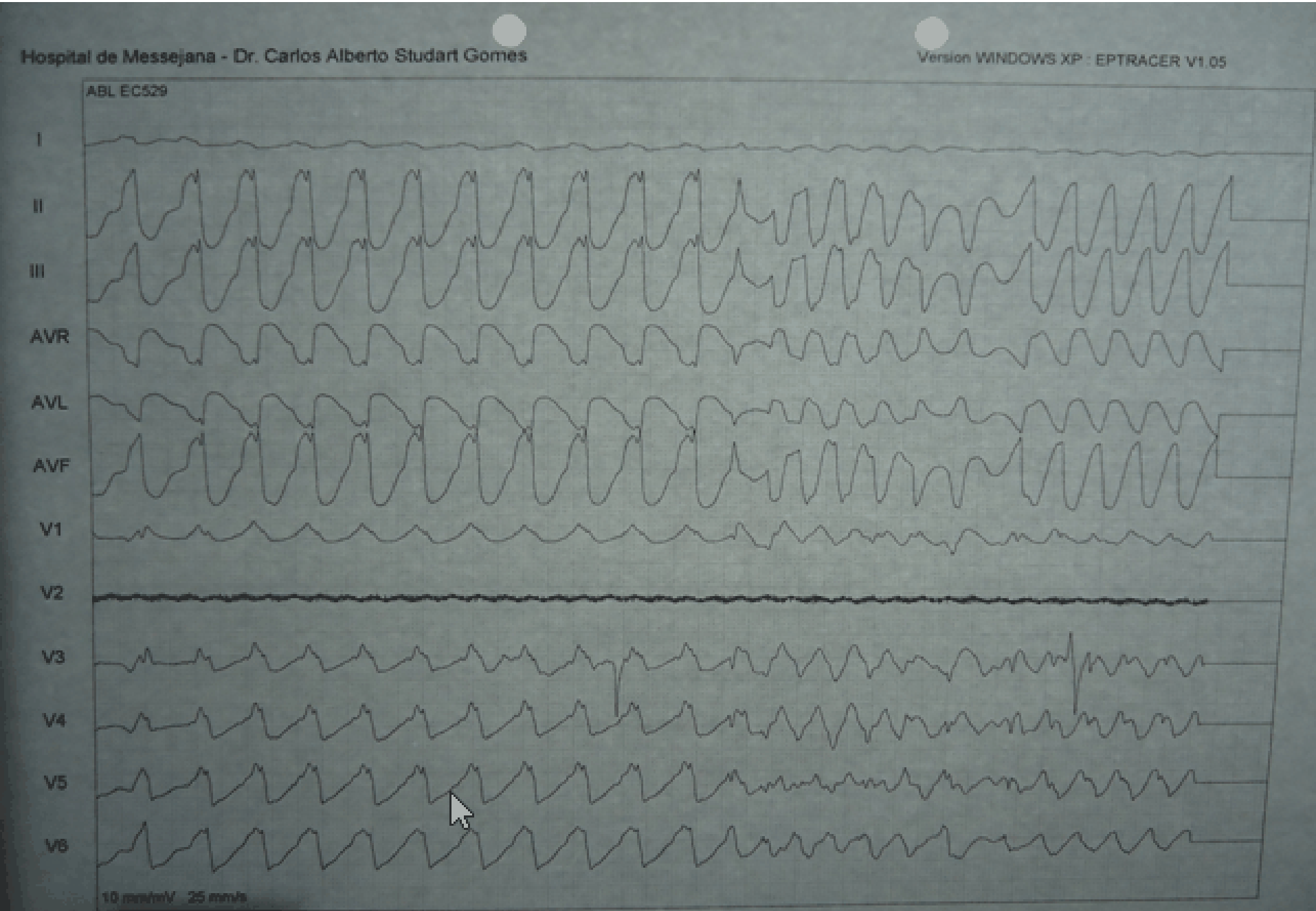
Ablation of cavo-tricuspid isthmus with bidirectional block;
Protocol of ventricular pacing with induction of SMVT→Degeneration into polymorphic VT with hemodynamic instability→ECV (200 J);
After ablation of flutter, he presented sinus bradycardia (HR=40 bpm), that improved soon (HR=50 bpm)

SMVT during EPS

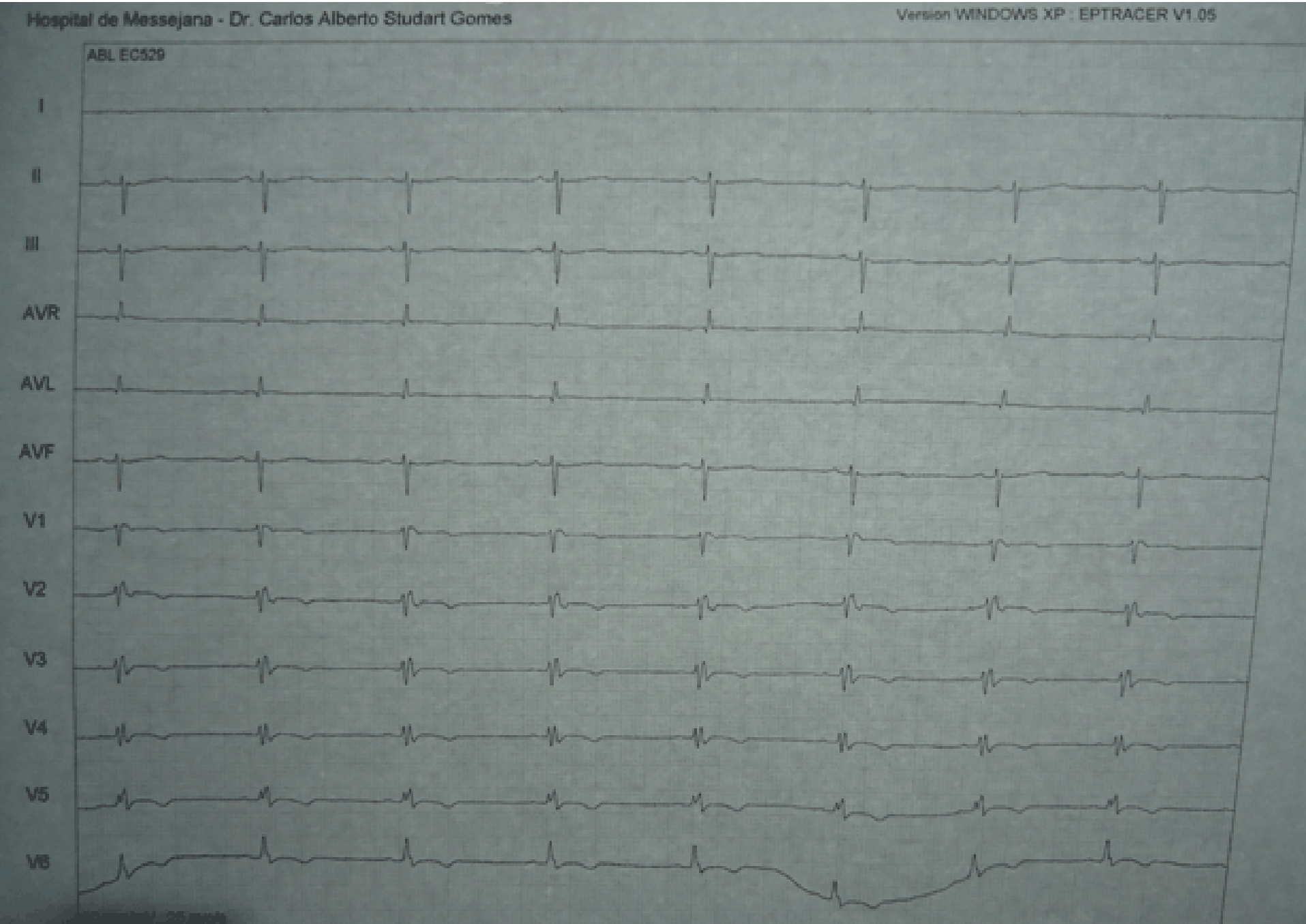


Evoluiu para TVP e FV

It evolve in to PVT and VF



Após CVE **Post ECV**



Colleagues opinions

Dear Andres and Raimundo,

The case as reported and illustrated, suggests the possibility of ARVD.

Echo is compatible (but the history of tricuspid insufficiency is NOT!). Of course the case could have been misinterpreted initially.

The ECG suggests ARVD since it presents:

1. **RBBB + axis at the left**
2. **Low voltages**
3. **Negative T from V1 to V4**
4. **Possible (the quality would not allow to state this, as Ricardo would say) epsilon in V1**
5. **The other element in favor of MSVT comes fro the RVOT, which in the setting of structural heart disease and this ECG, strongly suggests ARVD.**

I'm ready to learn more because I have NEVER seen a case where tricuspid valve had been replaced and the patient would end up having ARVD!!!!

Due to the data provided here it is not clear why the ablation of the CT isthmus was made.

The approach of the ablation of this VT was not by induction but through substrate modification, since usually the patients collapse into VT.

Non-fluoroscopic mapping should have been used.

Josep's group, with Antonio Berruezo heading it, described a beautiful technique for VT ablation in ARVD. Pancho should have the bibliographical reference in his mind, could you tell us Pancho?

Raimundo: we need clarification:

1. **The patient does not have a NMR made?**
2. **Why ablation of the flutter?**

Warm regards and thank for this beautiful case.

AB

Queridos Andrés y Raimundo:
El caso como esta contado e ilustrado sugiere la posibilidad de Displasia Arritmogenica del VD. El Eco es compatible (pero la historia de la Insuf tricuspidea NO!). Claro, que el caso puede haber sido mal interpretado incialmente.
El ECG es sugestivo de ARVD ya que presenta:

1. **BRD + eje a la izquierda**
2. **Bajos voltajes**
3. **T negativas de V_1 a V_4**
4. **Posible (la calidad no permite aseverarlo, como diria Ricardo) epsilon en V_1**
5. **El otro elemento a favor es TVMS proveniente del tracto de salida del VD, que en el contexto de cardiopatia estructural y ese electro, fuertemente sugieren ARVD.**

Estoy listo a aprender mas, porque NUNCA vi un caso donde se hubiera reemplazado la tricuspide y el pte terminara teniendo una ARVD!!!! Por los datos brindados aqui, no queda claro porque se le realizo ablacion del istmo CT. El abordaje de la ablacion de esta TV no era mediante induccion sino mediante modificacion de sustrato, ya que usualmente los pacientes se colapsan en TV. Se tendria que haber usado navegacion No fluroscopica.El grupo de Josep, con Antonio Berruezo a la cabeza, describieron una hermosa técnica para la ablacion de TV en ARVD. Pancho debe tener la cita bien presente, si la podes pasar Pancho. Raimundo: necesitamos aclares:
1. No tiene RNM?
2. Porque ablacion de aleteo?
Un abrazo y gracias por este caso tan lindo
AB
Querido Adrian 1-Estoy aguardando a RNM 2-Un trazado (no anexado) mostró aleteo auricular. Antes del EEI el ECG durante la taquicardia con QRS ancho fue malinterpretado por colegas del servicio de electrofisiologia como si se tratara de un arritmia supraventricular (aleteo auricular con conduccion aberrante).Mi opinion desde el inicio fue favorable para el diagnóstico de TV del VD.
Un abrazo Raimundo

Clinical picture quite compatible with arrhythmogenic right ventricular cardiomyopathy (ARVC).
I gather there was no evidence for Sarcoid or other infiltrative myopathy. We had a patient with a Desmin myopathy who presented with an ARVC type picture.
Note both baseline ECG and clinical VT episode. During the clinical VT episode,note the the late transition in the precordial leads a finding that was recently reported by our group as being an important method of distinguishing ARVC from right ventricular outflow tract tachycardia. RVOT-VT (1). The other arrhythmias induced in the lab are from different foci.
I would treat with course of Sotolol and a Defibrillator. If arrhythmias cannot be controlled consider ablation which should include endo as epicardial examination.

Spanish
Cuadro clínico bastante compatible con Cardiomiopatia/displasia arritmógena del ventrículo derecho (C/DAVD). Deduzco que no había evidencia de sarcoidosis o de otro tipo de miopatía infiltrativa. Tuvimos un paciente con miopatía desmina que se presentó con un cuadro tipo C/DAVD.
Tenga en cuenta tanto el ECG basal como el episodio de TV. Durante este último observe que la zona de transicion está desviada a la izquierda.(la verdad nunca ocurre pues los QRS son rS de V1 aV6), Este es un hallazgo de valor que fue reportado recientemente por nuestro grupo como importante para distinguir la TV de la C/DAVD de la taquicardia monomórfica idiopática del tracto de salida del VD (1). Otro elemento de utilidad es que las arritmias inducidas en el laboratorio son de focos diferentes en el caso de la C/DAVD; Lo trataria con la asociación de Sotolol y el implante de un desfibrilador. Si las arritmias no pudieran ser controladas, deberiamos considerar la ablación con examen tanto endo como epicárdico

Scheinman, Melvin M: Department of Cardiac Electrophysiology, University of California San Francisco, San Francisco, California, USA. scheinman@medicine.ucsf.edu

1. **Hoffmayer KS, Machado ON, Marcus GM, et al. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract tachycardia. J Am Coll Cardiol. 2011 Aug 16;58(8):831-8.**

Dear Professor Melvin: Thank very much for your always cleaver reflections. I have a doubt. You wrote that in this case you treat with sotalol and defibrillator. Recently in a manuscript assigned for you, from a cohort of well-characterized ARVC subjects, neither beta-blockers nor sotalol seemed to be protective. Evidence from a small number of patients suggests that amiodarone has superior efficacy in preventing ventricular arrhythmias (1). Additionally, this patient has a severe right ventricular heart failure with moderate ascites and hepatomegaly. What about anticoagulation?, and the possible indication of carvedilol. In the advanced stages of the disease with low cardiac output syndrome, carvedilol has been shown to improve survival and morbidity in patients with CHF. It has been demonstrated that carvedilol use is associated with dose-dependent reduction in QT dispersion(QTd) independent of the cause of CHF, suggesting that reduction in QTd may be a mechanism by which carvedilol improves outcomes in CHF.

Beta-blocking agents by themselves do not offer a fail-safe protection in adult with ARVC/D (3). They decrease the elevation of the J point and ST segment. Sympathetic over activity is reported to cause SCD. They are of choice in the cases of clearly effort-induced arrhythmias.

Carvedilol is not only useful for controlling arrhythmia but also for improving ventricular function in some patients with ARVC/D. Carvedilol may be a first-line drug for some patients with ARVC/D (4) always in association with espironolactone, furosemide and ACE inhibitor (or angiotensin-converting-enzyme inhibitor.)

1Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, Estes NA 3rd, Marcus F, Scheinman MM; Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol. 2009 Aug 11;54(7):609-15.

2 Pittenger B, Gill EA, Holcslaw TL, Bristow MR.Relation of dose of carvedilol to reduction in QT dispersion in patients with mild to moderate heart failure secondary to ischemic or to idiopathic dilated cardiomyopathy. Am J Cardiol. 2004;94:1459-1462

3 Brugada R, Brugada J, Antzelevitch C, et al, Brugada Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation. 2000; 101:510-515.

4 Hiroi Y, Fujiu K, Komatsu S, et al. Carvedilol therapy improved left ventricular function in a patient with arrhythmogenic right ventricular cardiomyopathy. Jpn Heart J. 2004; 45:169-177.

Thank again for your constant support!

Andrés.

Estimado Profesor Melvin Muchas gracias por sus siempre inteligentes reflexiones. Tengo una duda. Usted escribió que lo trataria con sotalol + CDI.

Recientemente en un manuscrito firmado por usted donde se estudió un cohote con pacientes portadores de CAVD bien caracterizada ni los beta bloquedores ni el sotalol fueron protectivos. Evidencia de un pequeño número de casos sugiere que la amiodarona es superior en eficacia para prevenir las arritmais ventriculares(1) Ademas, este paciente tiene un fallo derecho severo con ascitis y hepoatomegalia de éstasis. Que pensaria de usar anticoagulantes? y que de la posible introducion de carvedilol?

En las formas avanzadas de la enfermedad(como lo es este caso) se ha demostrado que el carvedilol disminuye la dispersion del QT independiente de la causa de la ICC sugiriendo que produce una reducción de la dispersión del intervalo QT como mecanismo suyacente para que el carvedilo mejore al ICC.

Los beta bloqueadores por sí solo no ofrecen una protección en ICC en el adulto con C/DAVD (3).

Estas drogas disminuyen la elevación del punto J y del segmento ST. Y mejoran la hiperactividad simpática, causa de la MCS en estos pacientes. Son de elección en los casos que el esfuerzo-indujo claramente arritmias.

Carvedilol es útil no sólo para controlar la arritmia, sino también para mejorar la función de ventriculo en algunos pacientes con C/DAVD el Carvedilol puede ser un fármaco de primera línea para algunos pacientes con esta enfermedad(4) siempre asociado a espironolactona, inibidores da enzima de conversão da angiotensina ou IECAs e diuréticos de alça.

Andrés.

Your points are well taken. We did find that Amiodarone was the most effective drug but still use Sotalol as a first approach together with restriction of work activities and other drugs for heart failure. We have had only 1 progress to heart transplant, so far.

Sus ponderaciones están bien expresadas. Nosotros encontramos que la amiodarona fue el fármaco más eficaz, pero todavia sigo usando sotalol como primera opción de abordagem, junto con la restricción de las actividades laborales y otros medicamentos para la insuficiencia cardíaca. Hemos tenido sólo un progreso para trasplante de corazón, hasta ahora

Melvin

I should mention one other point. We are beginning a protocol of decongesting the RV in those with markedly abnormal RV with Diuretics and Imdur as was done in an exercise mouse study with ARVC study in JACC

Debo mencionar otro punto. Nosotros estamos comenzando un protocolo de descongestión del ventriculo derecho en aquellos con función marcadamente anormal del VD empleando diuréticos e Imdur. Inspirados en un estudio experimental realizado en ratones con CAVD y ejercicio en estudio publicado em JAAC

Melvin

Andrés comments: What is Imdur? Imdur (isosorbide mononitrate) is in a group of drugs called nitrates. It dilates (widens) blood vessels, making it easier for blood to flow through them and easier for the heart to pump. Imdur is used to prevent angina attacks (chest pain). Imdur will not treat an angina attack that has already begun. The usual adult dose of Imdur is 30-60 mg orally once a day. Drinking alcohol can increase certain side effects of Imdur. A dangerous drug interaction could occur, leading to serious side effects with concomitant use of sildenafil.

Comentarios de Andrés: ¿Qué es Imdur? El Imdur (mononitrato de isosorbida) pertenece al grupo de medicamentos llamados nitratos. Dilata (ensancha) los vasos sanguíneos, haciendo más fácil para que la sangre fluya a través de ellos y más fácil para que el corazón bombee. Imdur se utiliza para prevenir ataques de angina (dolor en el pecho). El Imdur no tratar un ataque de angina que ya ha comenzado. La dosis usual para adultos de Imdur es 30-60 mg por vía oral una vez al día. Beber alcohol puede aumentar ciertos efectos secundarios de Imdur. Una interacción de drogas muy peligrosa puede ocurrir, resultando en efectos secundarios graves con el uso concomitante de sildenafilo.
Source: Drug.com
Andrés.

Estimados Potro y Raimundo. Como bien explico Adrian impresiona una ARVD. Aun si los resultados de la RNM son sugestivos o no, en que cambiara la conducta? presenta TVMS, sincope, y una Insufiencia cardiaca derecha. Si la ARVD lo ha llevado a esta, supongo que chagas ya lo han descartado.
El CDI o la ablacion selectiva del foco arritmogenico (como explciaba Adrian Uds diran bajo cual metodo s el mas adecuado), no cambia que el paciente presenta una micoardiopatia severa del VD con congestion hepatica por falla del VD y ascitis.
Supongo que debe estar anticoagulado. La TRC en este paciente no tiene ninguna indicacion.
Lo que puedan realizar (CDI o ablacion de la TV son temporarios o paliativos), por su miocardiopatia seguira presentando nuevos focos de TV, sea una ARVD u otra miocardiopatia que afecto su VD.
No han contemplado la posibilidad del transplante cardiaco, solo tiene 26 años, esto si cambiaria su expectativa de vida en caso de resultar exitoso, la progresion de su miocariopatia y mas que induce a arritmias severas, tiene mal pronostico en corto y mediano plazo. Y si progresa su hepatopatia sera un mal candidato a transplante cardiaco.
Esta alternativa me impresiona la mas razonable frente al cuadro descripto.
Un saludo
Martin Ibarrola

Dear Potro and Raimundo,
As Adrian explained very well, this seems to be ARVD.
Even if the results of NMR are suggestive or not, how will management change? He present MSVT, syncope and right HF. If ARVD has lead him to this, I guess Chagas disease has been ruled out.
ICD or selective ablation of the arrhythmogenic focus (as Adrian explained, you will probably ask what method is more appropriate) do not change the fact that the patient present severe RV cardiomyopathy with hepatic congestion by RV failure and ascites.
I guess he should be anticoagulated. There is no indication for CRT in this patient.

Whatever can be made (ICD or VT ablation are temporary or palliative) for his cardiomyopathy, he will continue presenting new VT foci, whether this is ARVD or another cardiomyopathy that affected his RV.Have you not considered the possibility of a heart transplant? He is only 26 years old; this would change his expectations of life in case of being successful, the progression of his cardiomyopathy and moreover as it induces severe arrhythmias, so he has a bad prognosis in the short and mid term. And if this liver disease progresses, he will be a bad candidate to heart transplantation.
I think this alternative is the most reasonable one considering the symptoms described.
Regards,
Martin Ibarrola

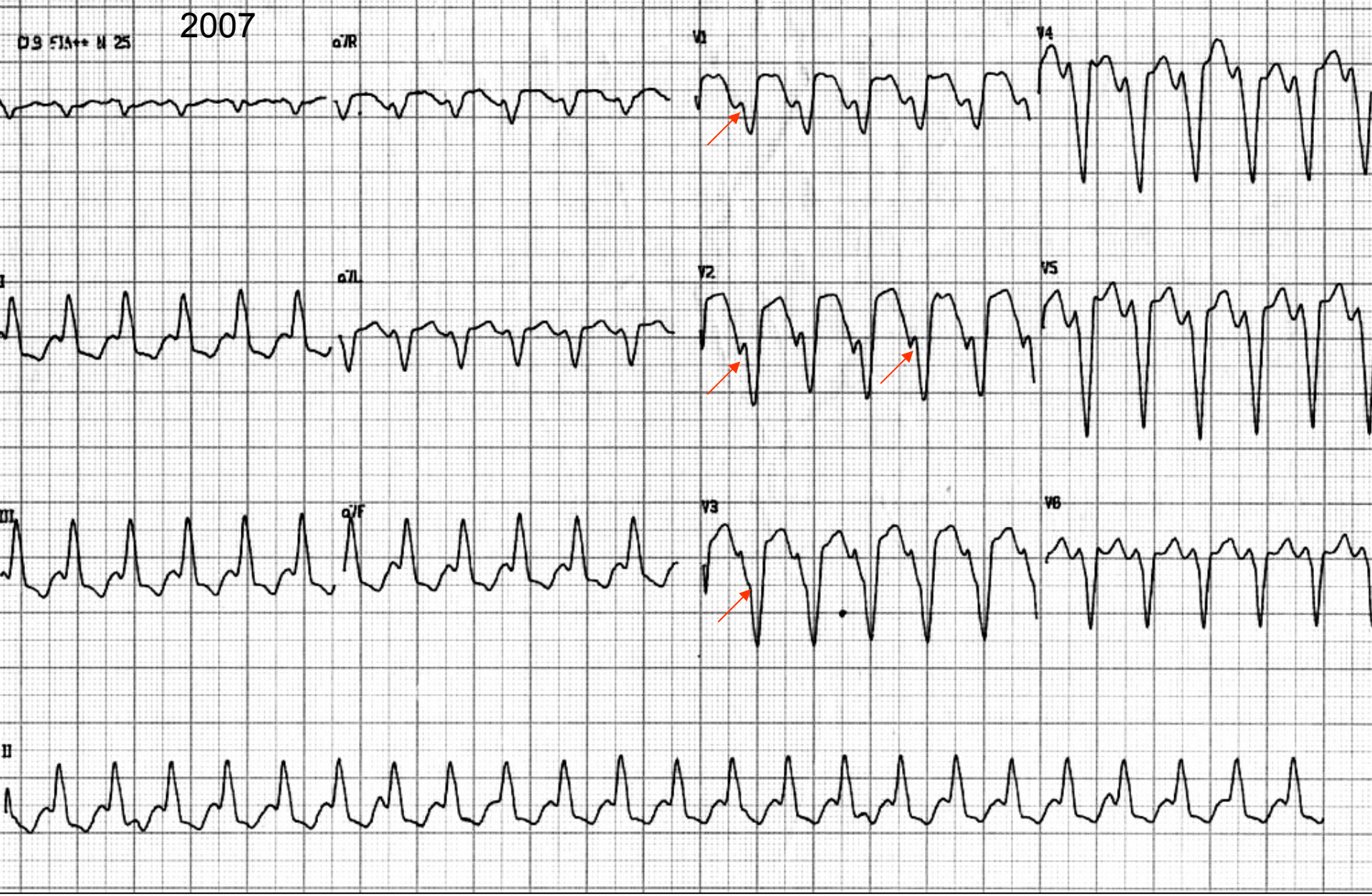
Estimado Potro muy interesante el intercambio con el Dr Melvin. Refiere que en seguimiento de la serie de sus pacientes 1 solo pte presento indicacion de transplante cardiaco. Mi duda obedece a cual fue el tiempo de seguimiento de los pacienets de su serie y cual fue la espectativa de vida y mortalidad en el seguimiento? si tuvieron MS por arritmia y no progresion de su fallo cardiaco o la mortalidad fue del 0% en el seguimiento?.Seguramente la RNM corrobore el diagnostico de ARVD, como podriamos diferenciarlo de un sindrome de Uhl a esta entidad que presenta el paciente fuera de la RNM?
Perdon si tengo mas cuestionamientos que aportes, le envio un saludo.
Martin Ibarrola

Dear Martin: Uhl anomaly, Uhl disease or Uhl syndrome although it is a very rare congenital heart disease of the RV, in principle, different from the ARVC/D it has no arrhytmogenic substrate because has not myocardial ventricular wall. However, several cases have been described with arrhythmias. The RV wall resemble a papyrus by aplasia or hypoplasia of the myocardium. Consequently, the pericardium and endocardium are join. The right ventricle wall resembles a parchment or scroll.
The ARVC is genetically determined with 12 known genetic types.
Uhl's anomaly SAECG has not epsilon waves
The entity was first described in the mid of the last century (1952) by Stephen Henry Magraw Uhl (1). Since then, a few cases have been reported.
In just only 10 pubmed citations exist.Following Professor Fontaine two phenotype forms are recognized
Pediatric form: Affect newborns (differential diagnosis should rule out Ebstein anomaly) wit CHF.
Adult form: features by arrhythmias, CHF, or both frequently confused with ARVC/D
Histology: pathognomonic and unmistakable. Myocardium is totally absent on most of the RV free wall (myocardium is preserved at the base), consisting, in the most severely affected areas, lf epicardium and endocardium searated only by a thin layer of adiposities occupied by coronary vessels, which may exhibit abnormal proliferation of the media . In these areas the wall, is, properly speaking transparent.
Andrés Perez-Riera,

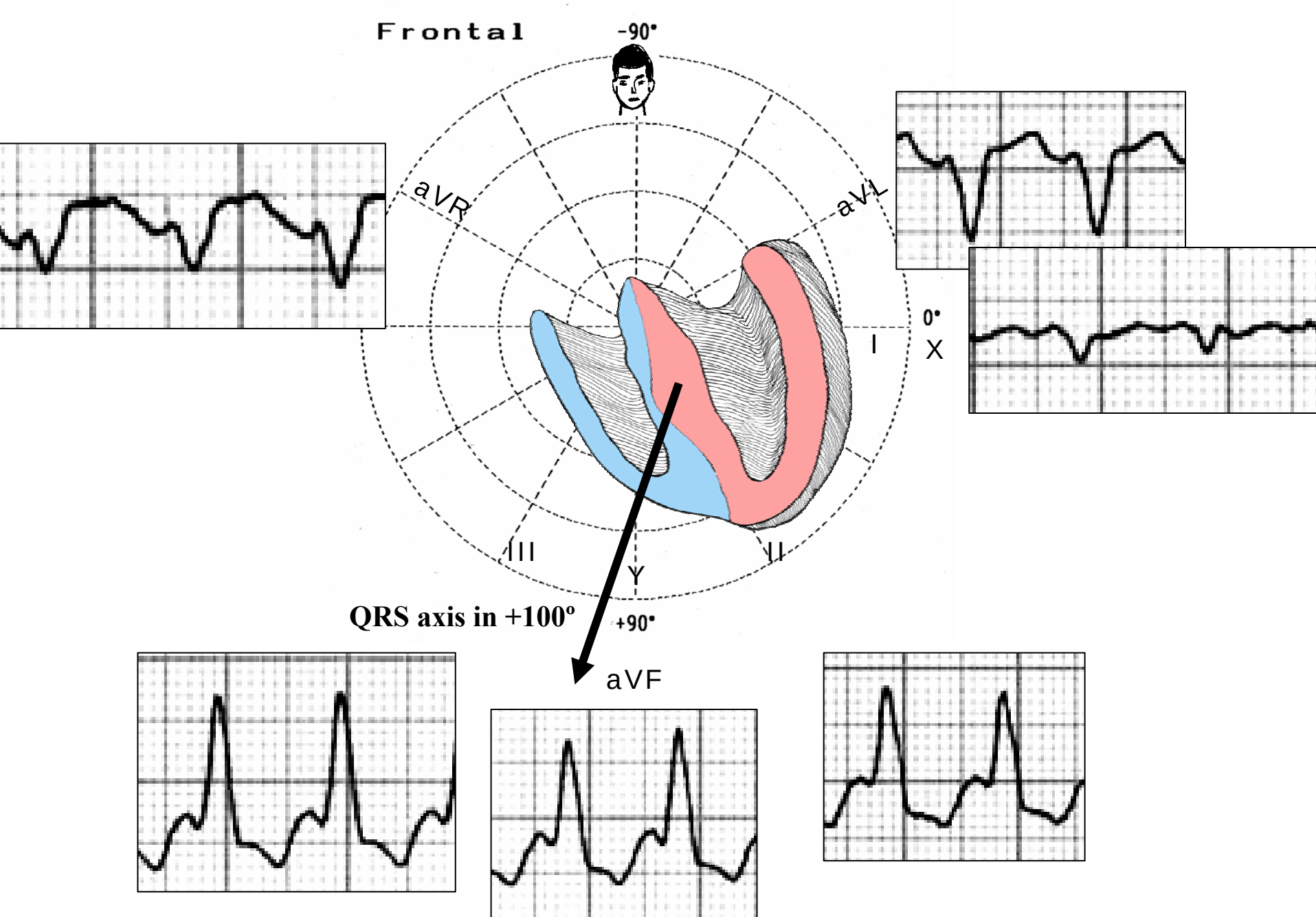
Spanish Estimado Martin: la anomalia, enfermedad o sindrome de Uhl si bien es una enfermedad congénita muy rara del VD, en principio, diferentemente de la ARVC no tiene un substrato arritmógeno les falta la camada media miocárdica de la pared del VD. No obstante se han descripto casos con arritmias.La pared del VD es un verdadero papiro por aplasia o hipoplasia del miocardio. Consecuentemente el pericardio se adiere al endocardio. El VD recuerda a un pergamino. La ARVC es geneticamente determinada con 12 tipos conocidos.
La anomalia de Uhl no tiene positividad del SAECG ni ondas epsilon Fue descripta por vez primera a mediados del siglo pasado (1952) por Henry Stephen Magraw Uhl (1). Desde entonces, unos pocos casos se han comunicado. En el pubmed existen apenas 10 citas.
Andrés.

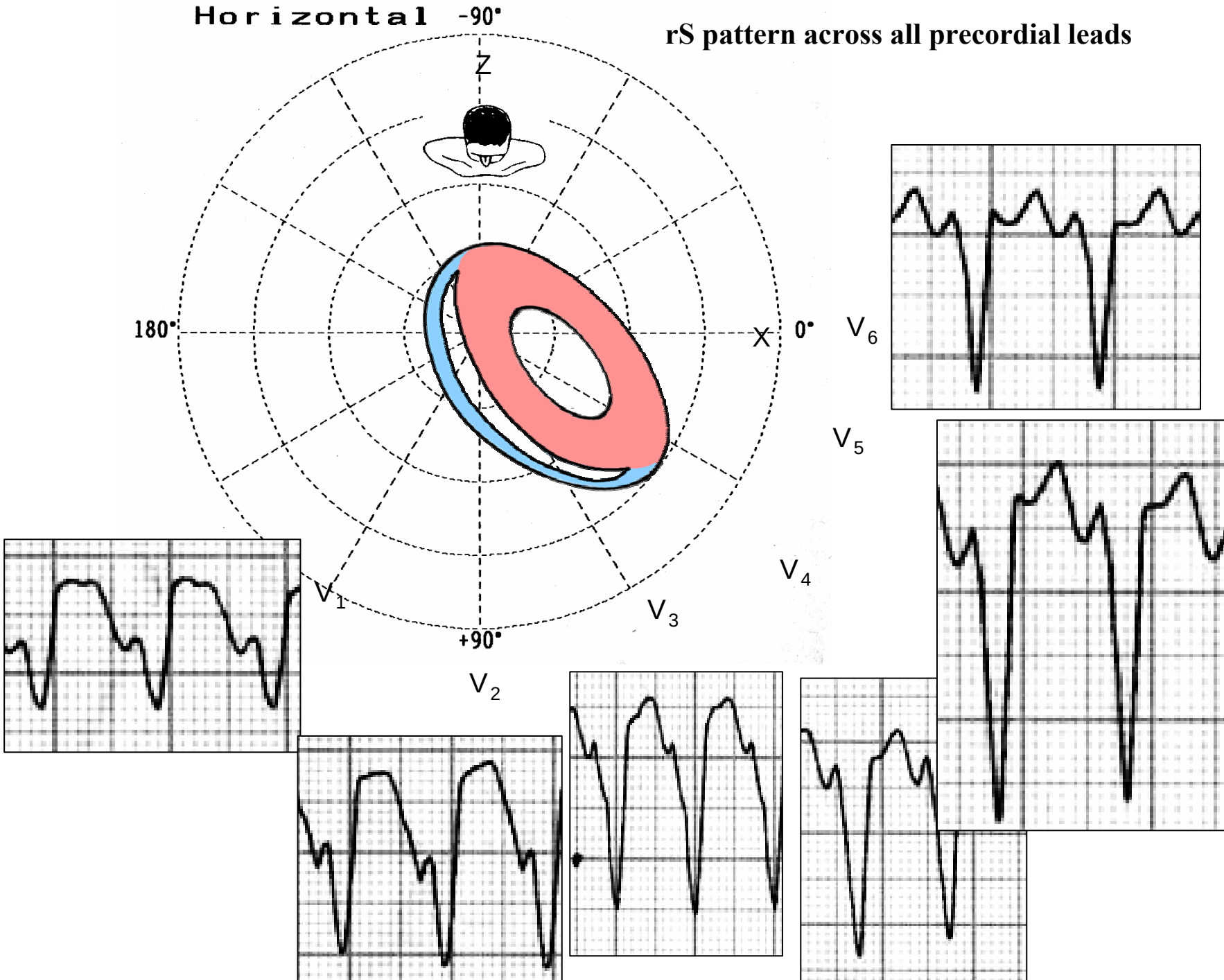
Final comments

By Andrés Ricardo Pérez-Riera M.D.Ph.D.
In charge of ECG/VCG sector – Cardiology Discipline –ABC Faculty- ABC Foundation – Santo André – Sao Paulo - Brazil



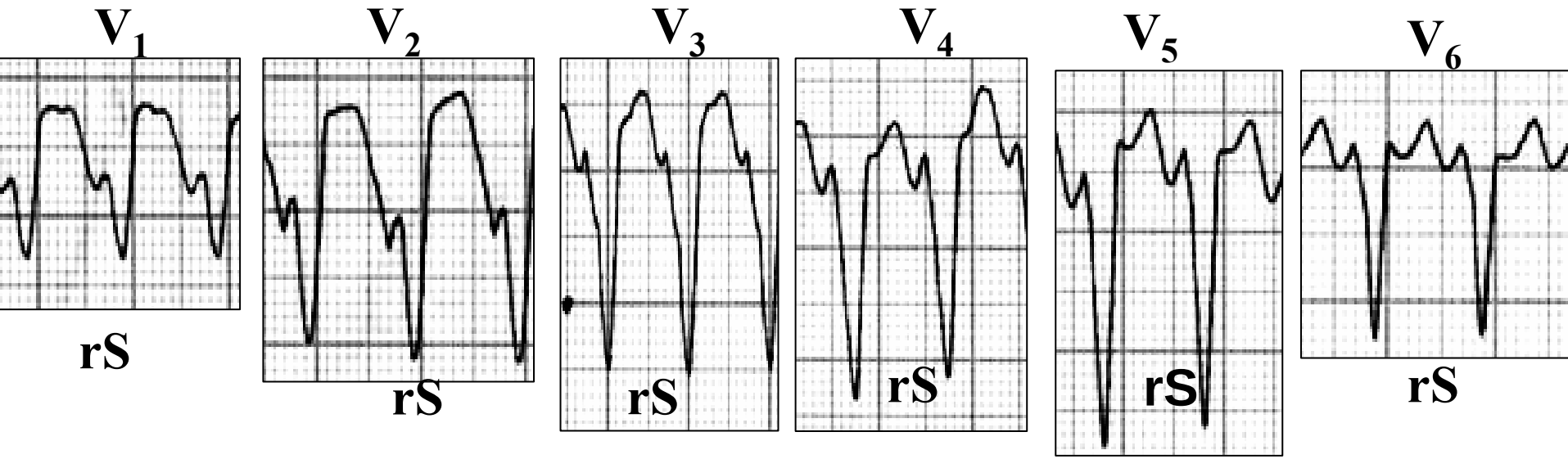
Sustained broad monomorphic VT(QRSD= 165ms) with LBBB pattern and inferior axis. HR near 150bpm, slurred S downstroke from V_1 to V_3 (red arrows) is e signs of VT.


Frontal
-90°
aVR
aVL
0°
I
X
III
II
Y
+90°
aVF
QRS axis in +100°



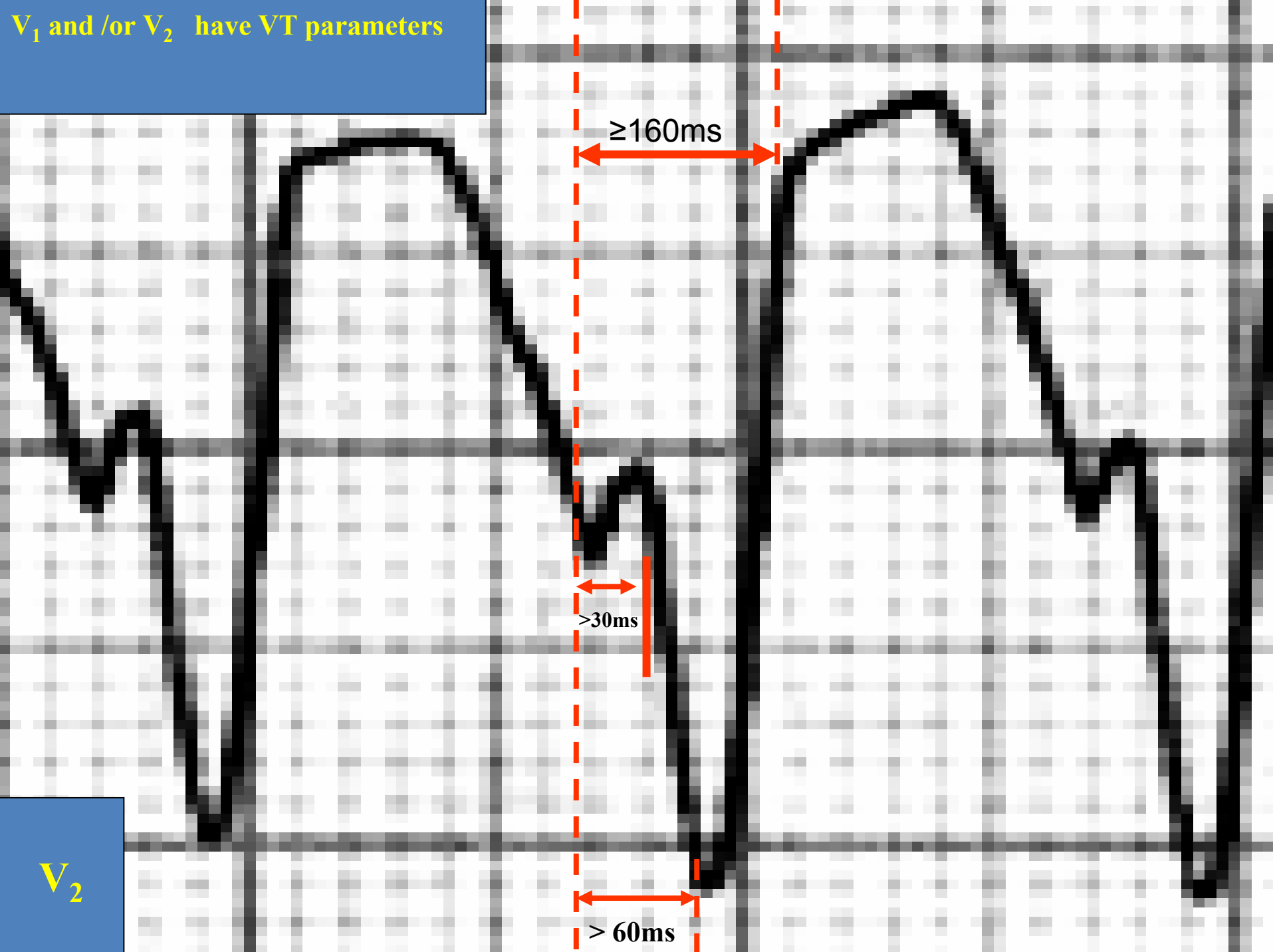
rS pattern across all precordial leads

rS pattern across all precordial leads

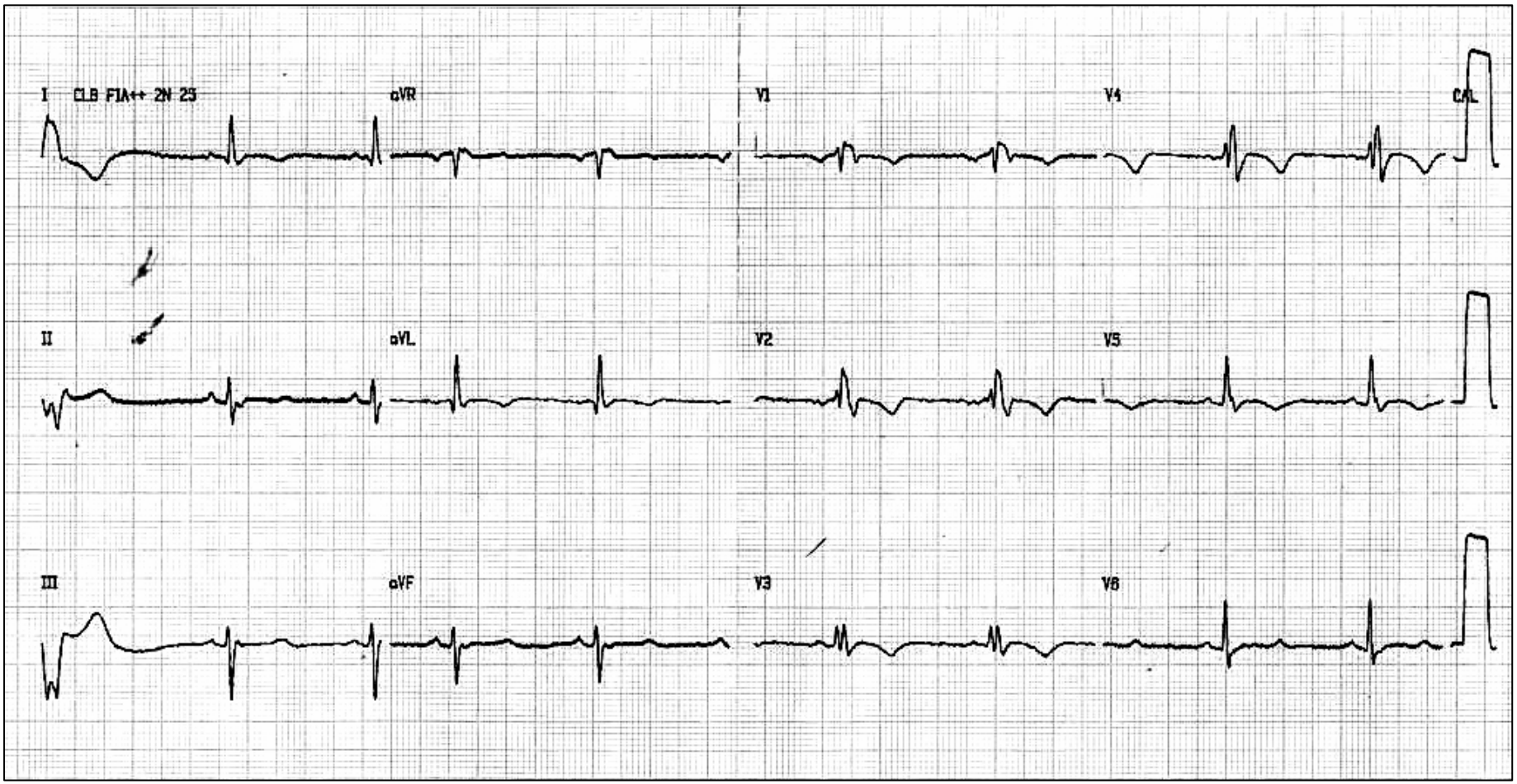


Is this a concordant pattern? Is this QRS pattern a sign of ventricular tachycardia?

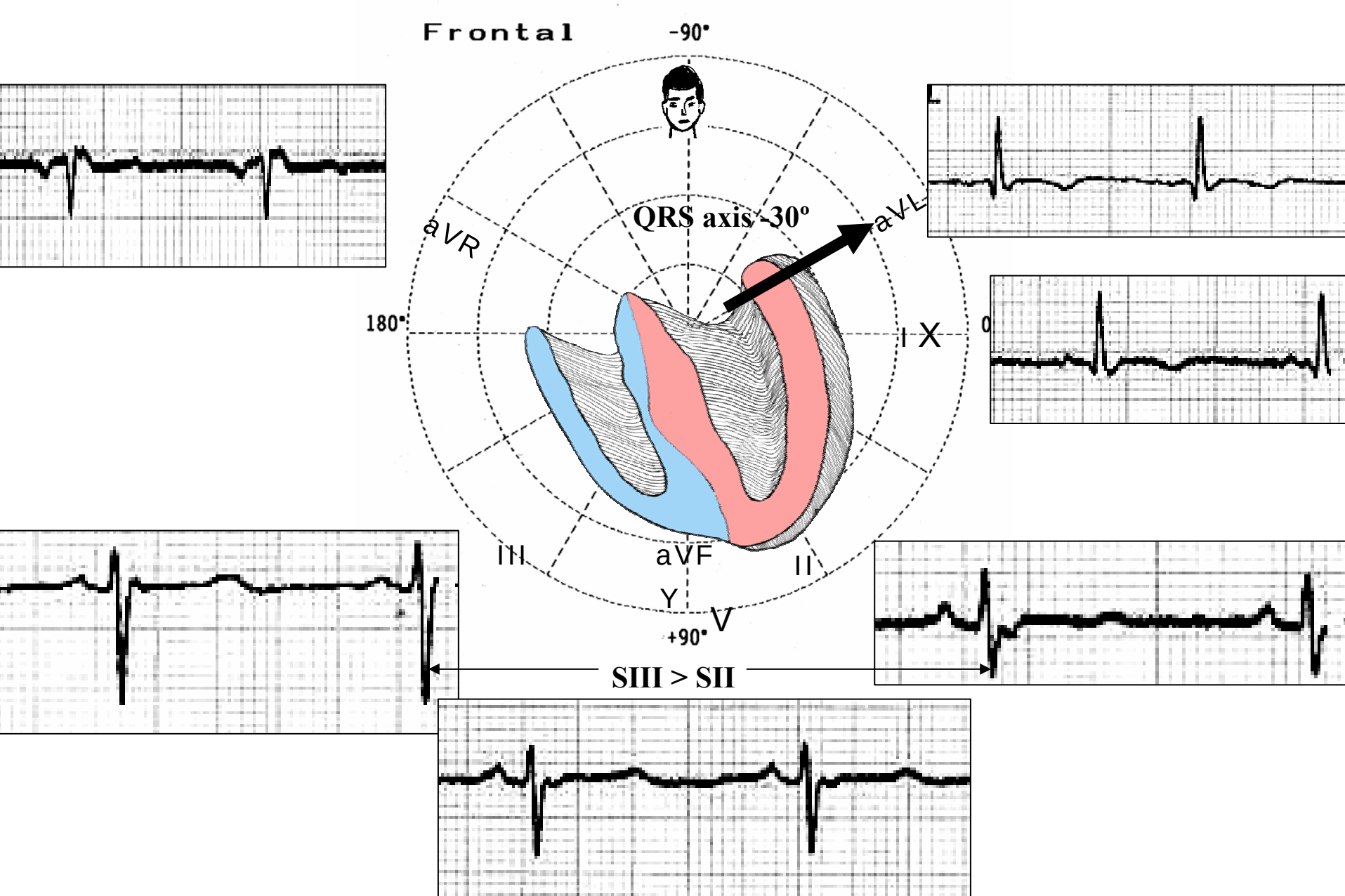
Answer: No, because the term precordial concordance (CONCORDANT PATTERN) consist of QRS complexes entirely negative or entirely positive during wide QRS tachycardia. In this case we have rS pattern, consequently we have not QRS complexes entirely negative.
Precordial concordance is a strong indicator for VT.
Negative precordial concordance is not possible in preexcited SVT because there is no accessory pathway location in which anterograde conduction would produce completely negative QRS complexes in all precordial leads, but it is sometimes seen with LBBB.


V_1 and /or V_2 have VT parameters
≥160ms
>30ms
> 60ms
V_2

22-08-2012
2N



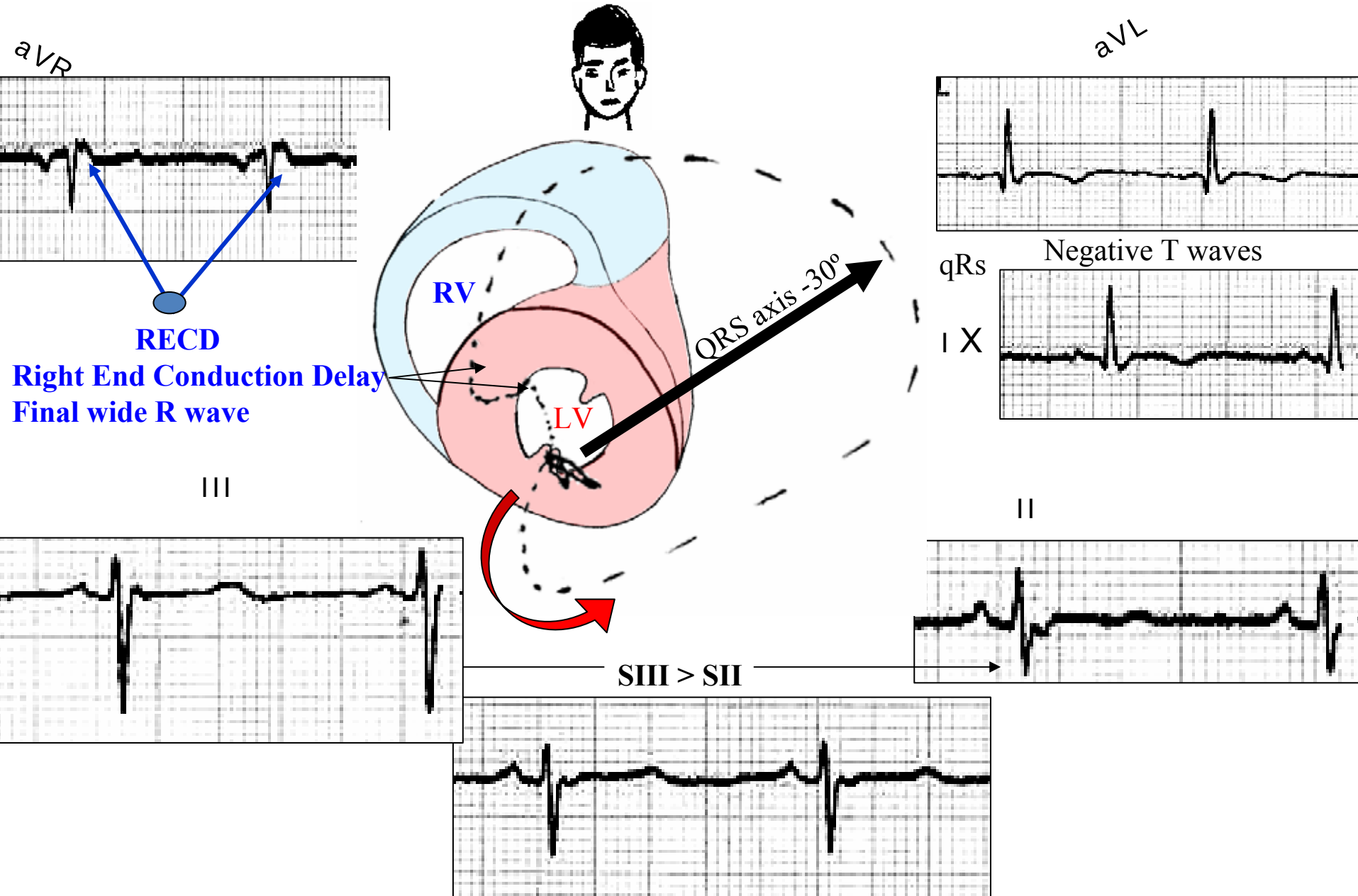
2N

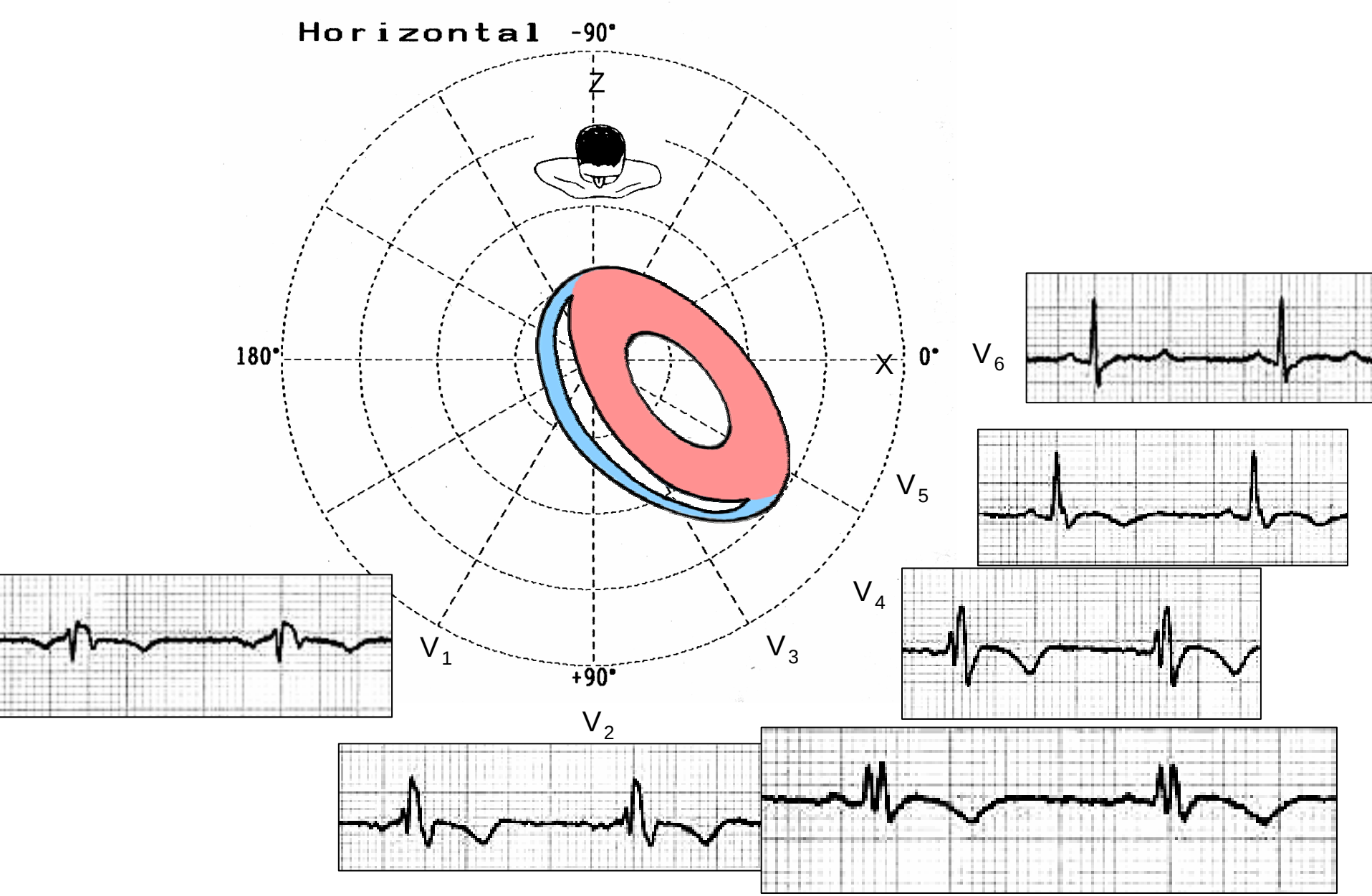


Hypothetical QRS loop depolarization in frontal Plane

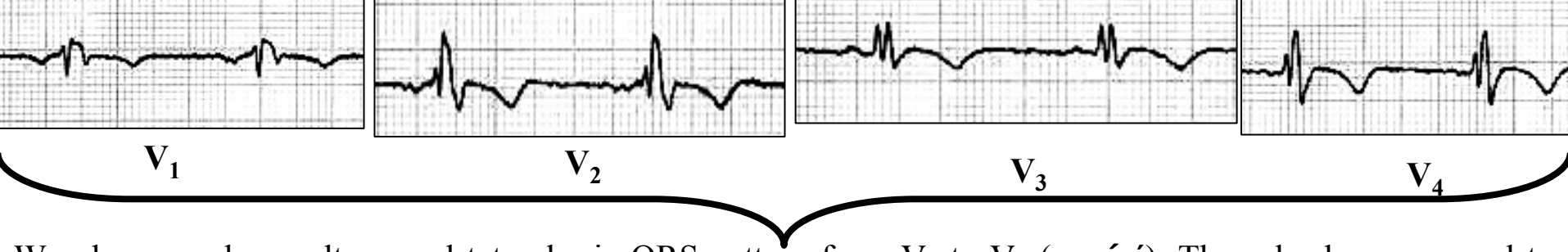
2N

Minimal degree of Left Anterior Fascicular Block + RECD near RVOT





Tetraphasic QRS pattern from V_1 to V_4 rsr´s´.



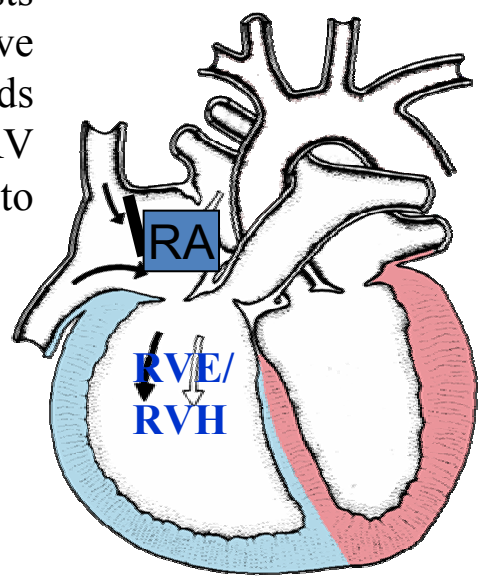
We observe a low voltage and tetraphasic QRS pattern from V_1 to V_4 (**rsr´s´**). These leads correspond to right ventricle free wall.

The five Right ventricle regions predominantly hypertrophied and correlations with modified leads are:

1) Trabecular region of Right Ventricle: V_2
2) Inferior right paraseptal region: V_3 and V_4
3) **Right ventricule free wall: from V_1 to V_4**
4) Right ventricular outflow tract, basal or infundibular region: aVR, V_{1H}, V_{2H} and V_{3H}
5) Right ventricular inflow tract: aVR. V_{4R}, and V_{5R}.

Tetraphasic pattern form V_1 to V_4 is indicative of diastolic, volumetric or eccentric Right Ventricular Enlargement/Right Ventricular Hypertrophy (**RVE/RVH**) affecting diffusely all free RV wall.

In the present case there are negative T waves from V_1 to V_5. Nava et al suggests that the extension of T loop negativity in horizontal plane loop of VCG and T wave on precordial leads of ECG are probably caused by dislocation of the LV backwards secondary to RV dilatation, asynchronous RV repolarization or intra parietal RV conduction defects. In 24 cases T wave was negative only on V1 in 37%; from V1to V2 in 25%; from V_1 to V_3 in 8%; form V_1 to V_4 in 4% and form V_1 to V_5 in 8%



1. **Nava A, Canciani B, Buja G, et al. Electrovectorcardiographic Study of Negative T Waves on Percordial Leads in Arrhtyhmogenic Right Ventricular Dysplasia: Relationship With Right Ventricular Volumes J of Electrocardiol 1998: 21: 239-245**.

Factors affecting the changes in Right Ventricular Enlargement(RVE)/Right VentricularHypertrophy(RVH)

1) Modifications in the positional orientation of the heart that the enlargement Imposes (rotations).

2) Modality and severity of hemodynamic enlargement/hypertrophy.

A) Systolic or pressure enlargement/hypertrophy:

Adaptation

Strain pattern

B) Diastolic, volumetric or eccentric enlargement/hypertrophy.

3) Region of the right ventricle predominantly enlarged:

- 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, V_{1H}, V_{2H} and V_{3H}
- Right Ventricular Inflow Tract (RVIT): V_{4R}, V_{5R} and aVF.

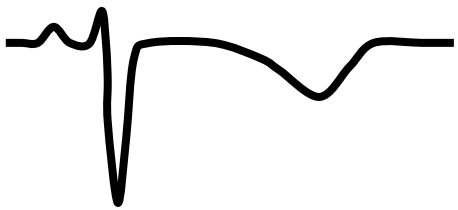
Factors conditioning ECG and VCG modifications in RVE.

Polarity of T wave from V_1 to V_3 in ARVC/D

V_1

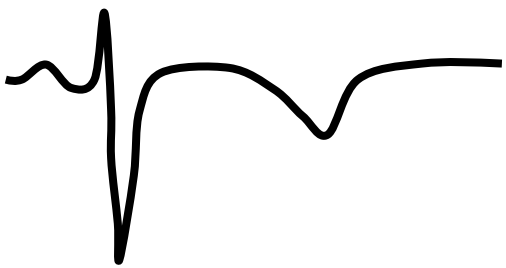
In absence of CRBBB in patients >12 years old, negative T wave from V_1 to V_3 is a sign with great value for diagnosis.

V_2



In normal, young patients, there is usually positive T polarity in V_1; however, it may flatten and nearly always has a positive polarity in V_2.

V_3

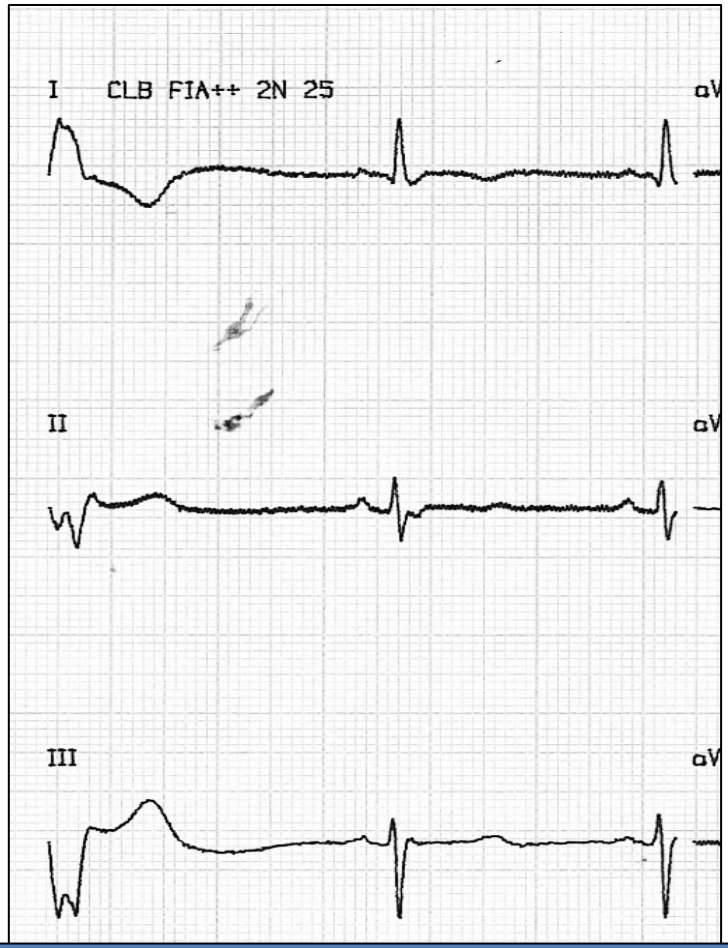


In symptomatic patients carriers of ARVC/D, the ECG generally shows T wave inversion in V_1 and V_2, which may reach up to V6[1].

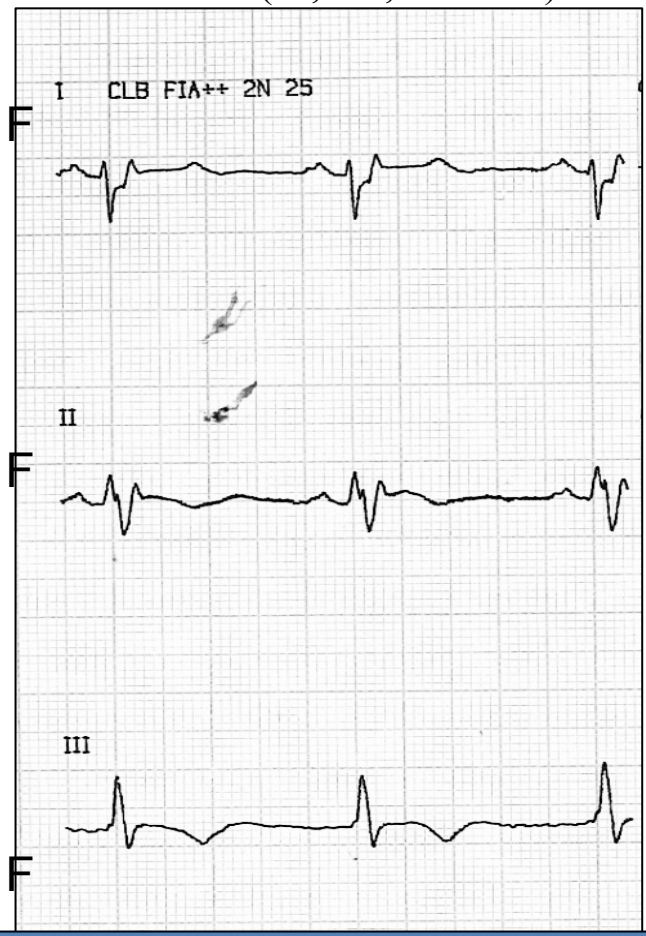
T wave from V1 to V3 in ARVC/D.

1. **Fontaine G, Tsezana R, Lazarus A, Lascault G, Tonet J, Frank R. Repolarization and intraventricular conduction disorders in arrhythmogenic right ventricular dysplasiaAnn Cardiol Angeiol (Paris).1994 Jan;43:5-10.**

Conventional bipolar leads



Fontaine bipolar precordial leads
F-ECG (FI, FII, and FIII)



The Fontaine bipolar precordial leads are placed at the manubrium of sternum, xiphoid, and V4 positions using the right arm connection, left arm connection, and left foot connection, respectively

The Fontaine bipolar precordial leads

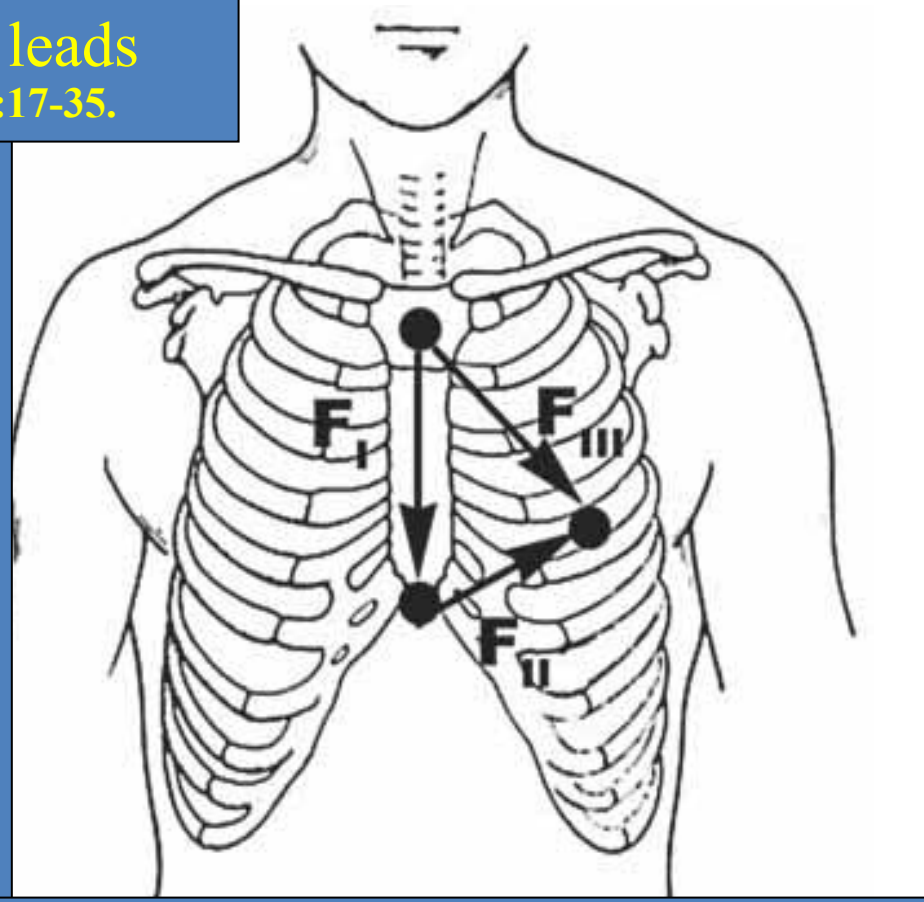
1. Fontaine G, et al. Annu Rev Med. 1999;50:17-35.

The Fontaine bipolar precordial leads are placed at the manubrium of sternum, xiphoid, and V4 positions using the right arm connection, left arm connection, and left foot connection, respectively.

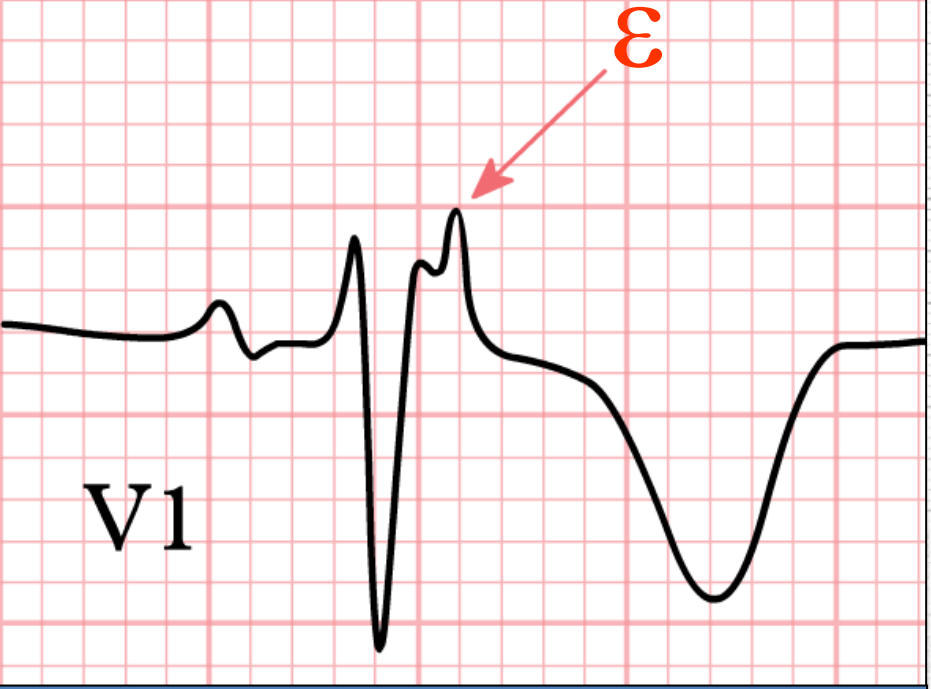
Epsilon waves are detected by:

1) **Standard 12-lead electrocardiography (S-ECG)**
2) **Right-sided precordial lead electrocardiography (R-ECG)**
3) **Fontaine bipolar precordial lead electrocardiography (F-ECG).**

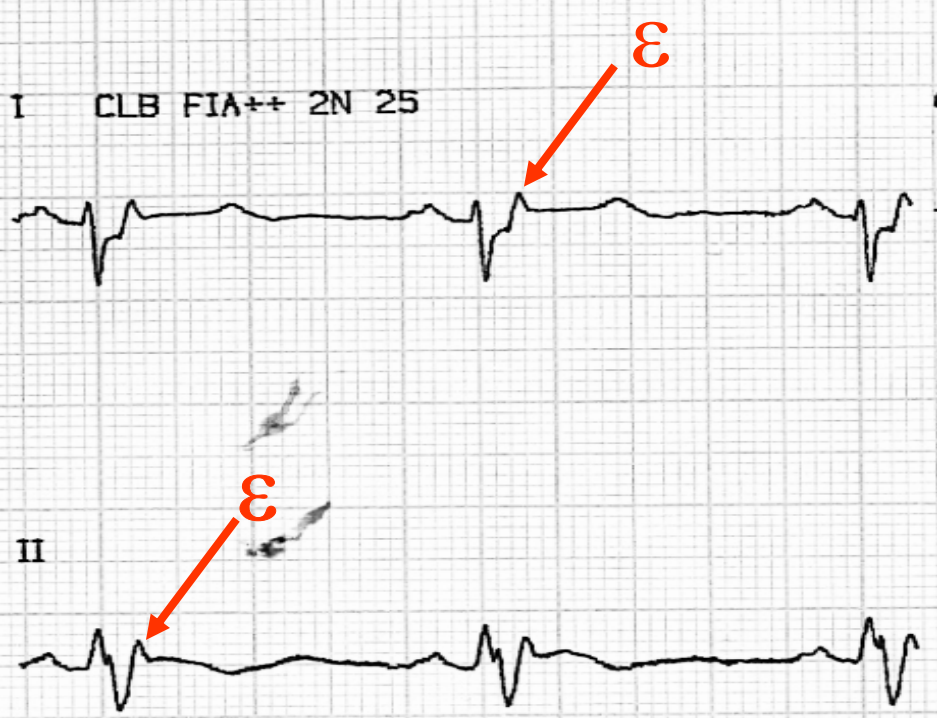
The detection rate using combined methods is significantly higher than that by S-ECG alone



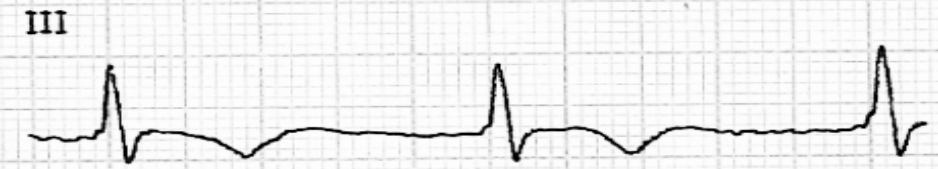
Fontaine bipolar precordial lead have the best sensitivity among the three options. the placement of the foot lead (positive) in position V_4 provides, instead of regular leads I, II, and III, three bipolar chest leads that can be called FI, FII, and FIII. Tracings are then produced by setting the machine on regular leads I, II,and III. This arrangement is used to record specifically the potentials developed in the RV, from the RVOT to the diaphragmatic area. The vertical bipolar lead FI, (similar to aVF lead), seems to be the most appropriate to record epsilon waves; it also magnifies the atrial potentials. As late potentials were supposed to be the result of late activation of a limited group of fibers, the term "post-excitation" looked logical, since it was observed after the main excitation of the ventricle, leading to the QRS complex. The term "epsilon“ was appropiate, because it occurs in the Greek alphabet after delta; thus, delta represents the preexcitation and epsilon the post-excitation phenomenon.



Source: ECG PEDIA.ORG



Fontaine bipolar precordial leads F-ECG (FI, FII, and FIII)



Characteristics of epsilon or Fontaine wave in ARVC/D

"Fontaine discovered and named the epsilon waves. He chose the epsilon because it follows delta in the Greek alphabet and is the mathematical symbol for smallness"[1].

Intrinsic features they are small notches or oscillations in variable quantities (1, 2, 3 or more).

Location: at the end of QRS in the J point or onset of ST segment (there is no consensus about this).

Leads: observed in right precordial leads; however Dr. Li Zhang et al, found the ε wave in the leads of the frontal plane, especially in inferior leads.

Frequency in ARVD: approximately 15-30% of cases in 12-lead ECG. This percentage increases if we use the ECG with the modified protocol.

Value of criterion: considered to be a major criterion for diagnosis by the Task Force for ARVC/D diagnosis(2;3)

High resolution ECG: observed more frequently with this method.

Pathognomonic character: in spite of the characteristics in ARVC/D, they are not pathognomonic, since they have been described in other diseases associated with myocardial damage: RV infarction, inferior or dorsal**4**, sarcoidosis**5**, sickle cell anemia**1**, etc.

Meaning: late posterior potentials (PP) that occur in the RV free wall in patients with ARVC/D.

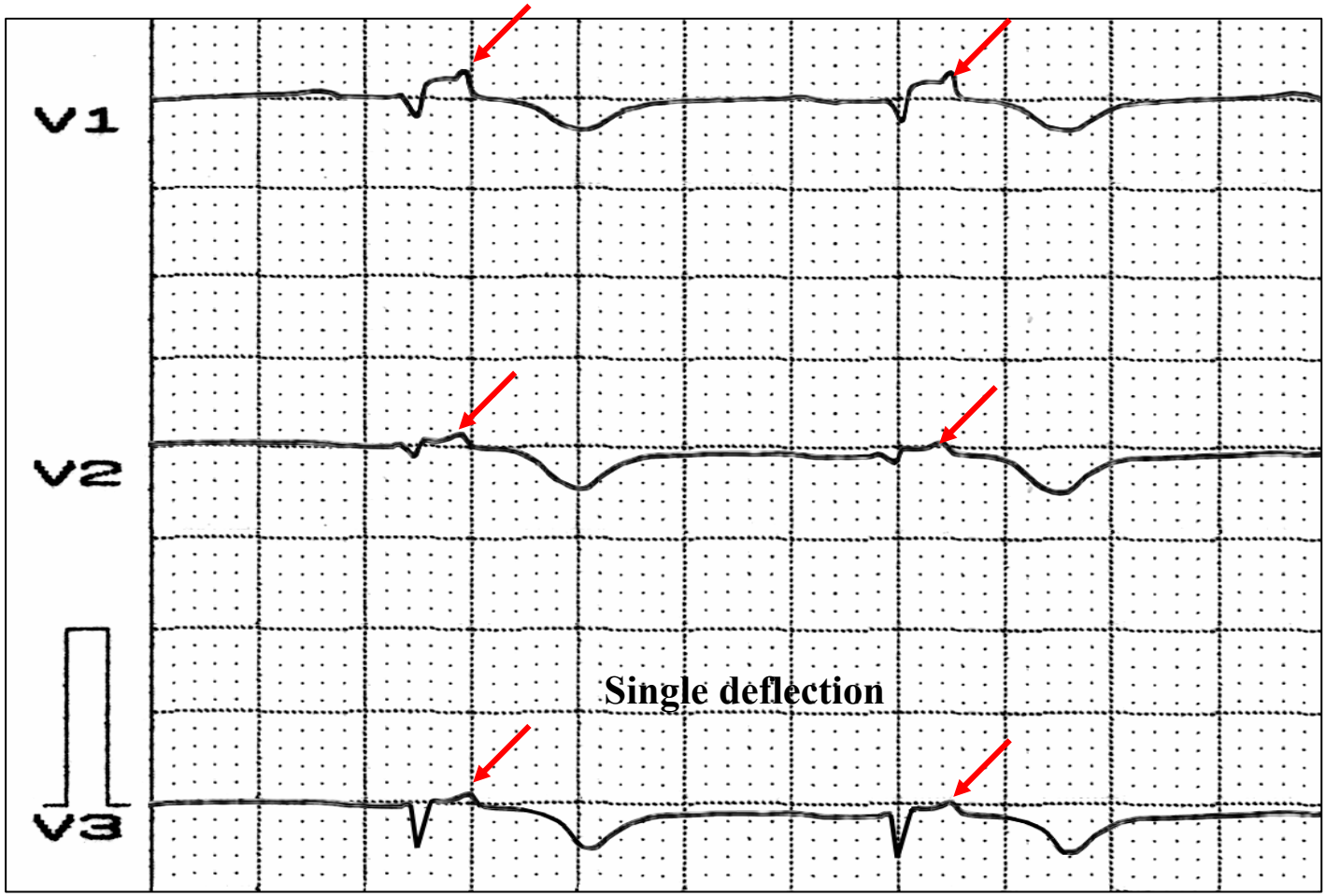
Inversion of T wave in leads V1-V3 and/or **ε** wave found in 70% of patients with ARVC/D. Epicardial electrophysiological studies in dysplastic areas reveal the LP that occur at the end of the QRS complex, in the J point, and at the onset of the ST segment, explained by fibro-fatty substitution of myocardial tissue**6**.

1. Hurst JW. Circulation 1998: 98, 1837-1942.
2. McKenna WJ, et al. Br Heart J 1994;71:215-218.
3. Fontaine G, et al. Annu Rev Med 1999;50:17-35
4. Zorio E, et al. Pacing Clin Electrophysiol. 2005; 28:245-247.
5. Santucci PA, et al. J Cardiovasc Electrophysiol. 2004; 15:1091-1094.
6. Fontaine G, et al. Jpn Circ J. 1984; 48:515-538.

Characteristics of epsilon or Fontaine wave in ARVC/D

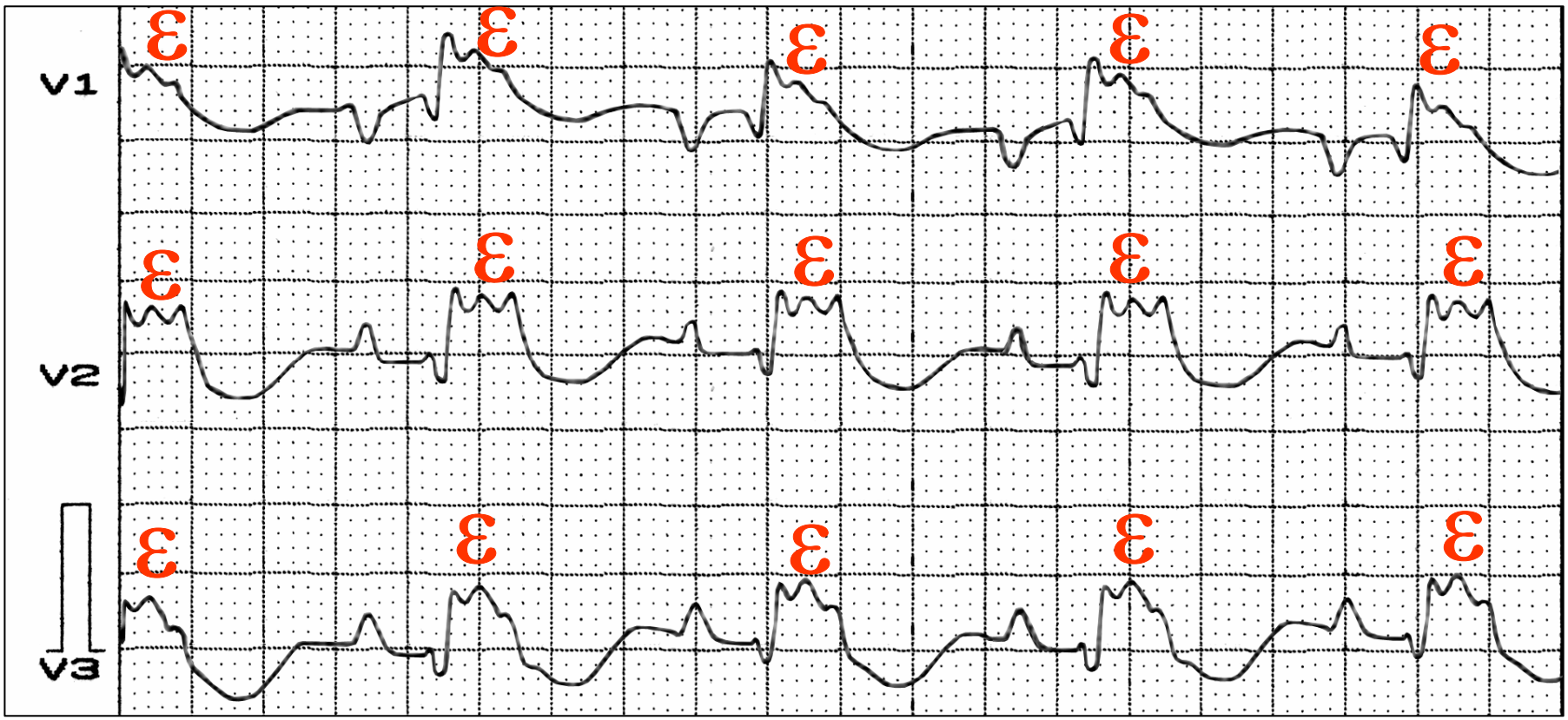
Epsilon wave and relationship to VT: the simple presence of these waves indicate slow and fragmented conduction, which favors reentry circuits, which in turn result in M-VT runs with CLBBB morphology by originating in the RV**1; 2**.

MORPHOLOGICAL CLASSIFICATION OF EPSILON WAVE



1) Aldakar M, et al. Presse Med. 1998; 27:1893-1996.
2) Sajeev CG, et al. Int J Cardiol. 2004; 93:315.

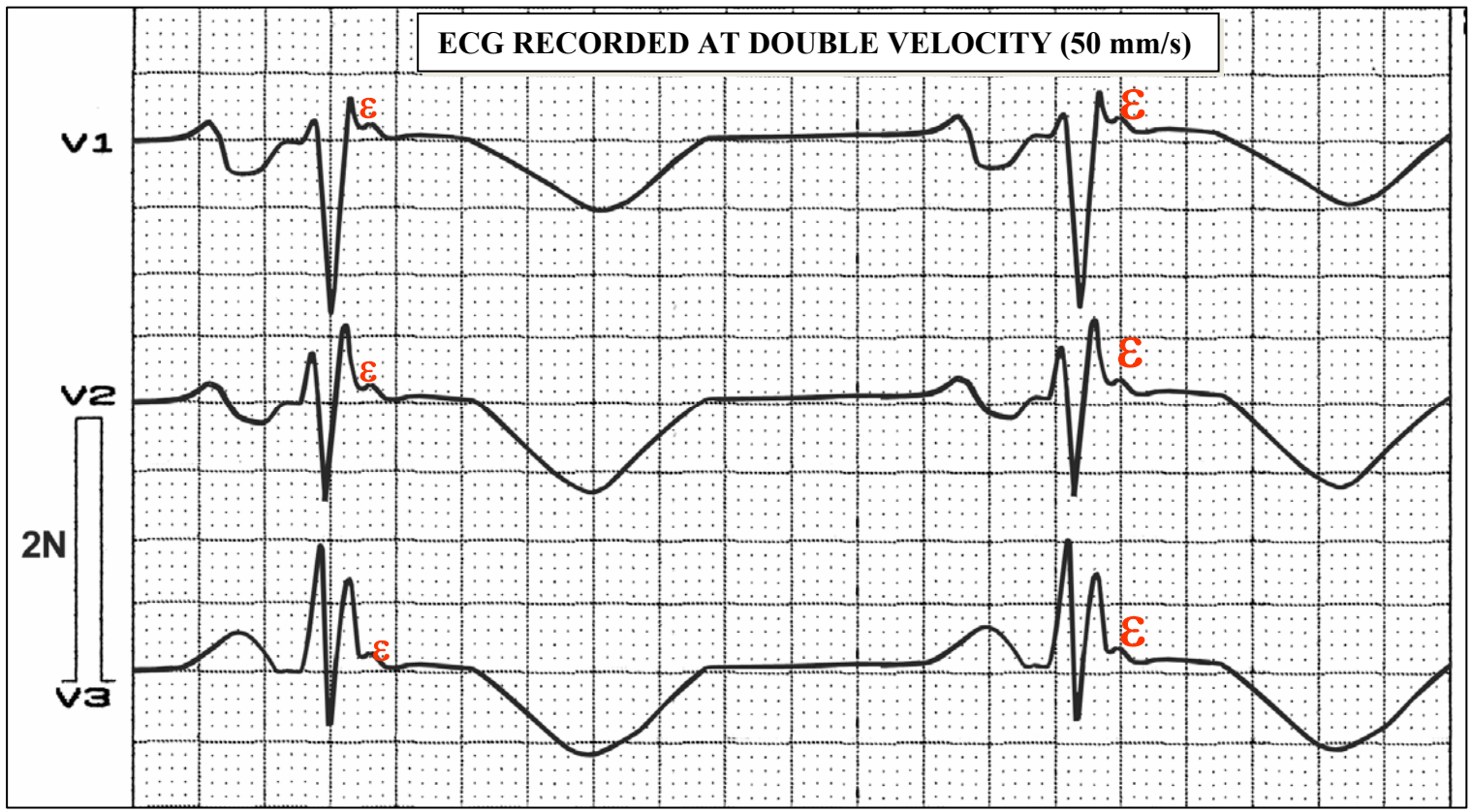
EPSILON WAVE WITH MULTIPLE DEFLECTIONS



Epsilon wave characteristics in ARVC/D.

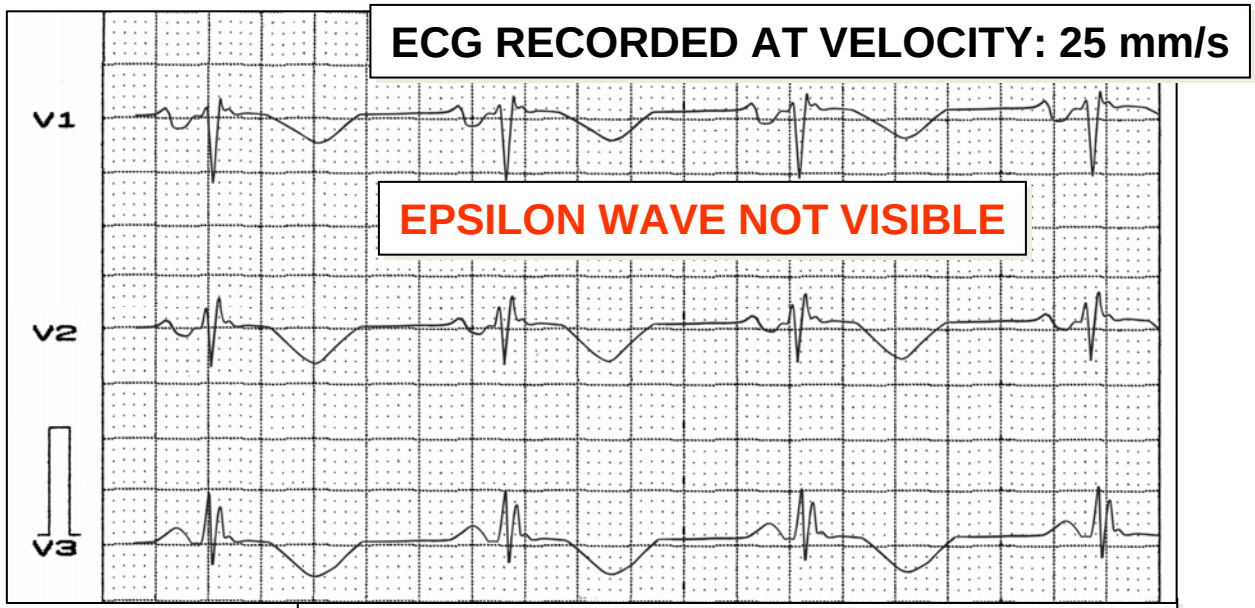
EPSILON WAVE (ε)

Double amplitude (20 mm/mV)

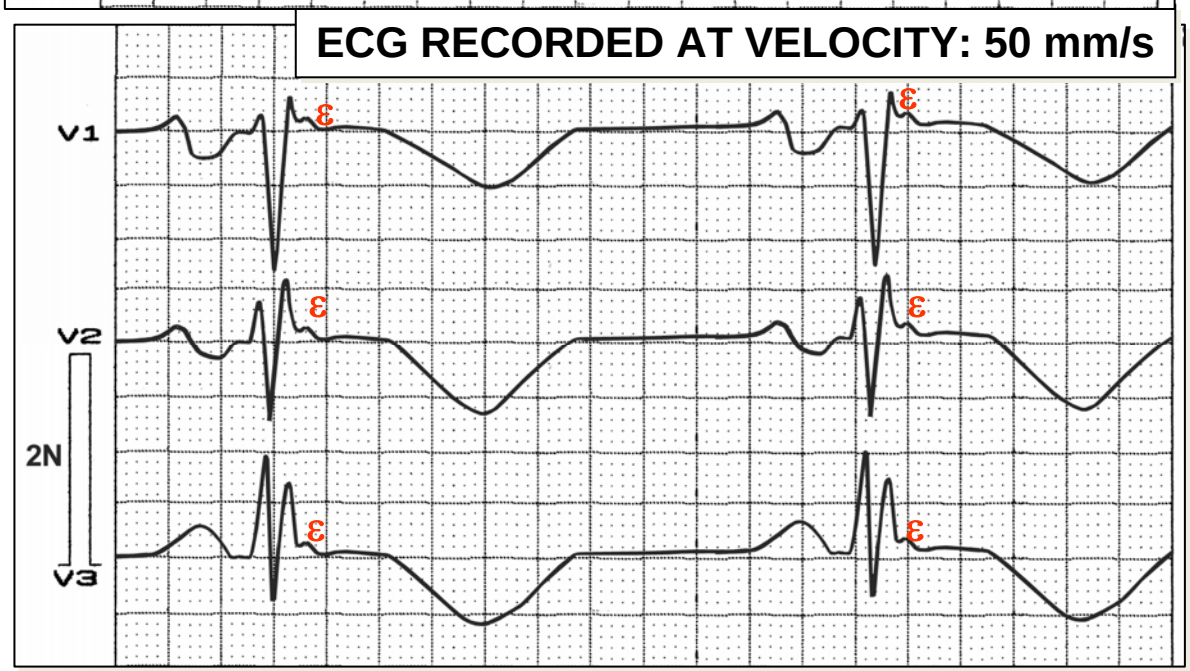


Epsilon wave characteristics in ARVC/D.

Amplitude
(10 mm/mV)

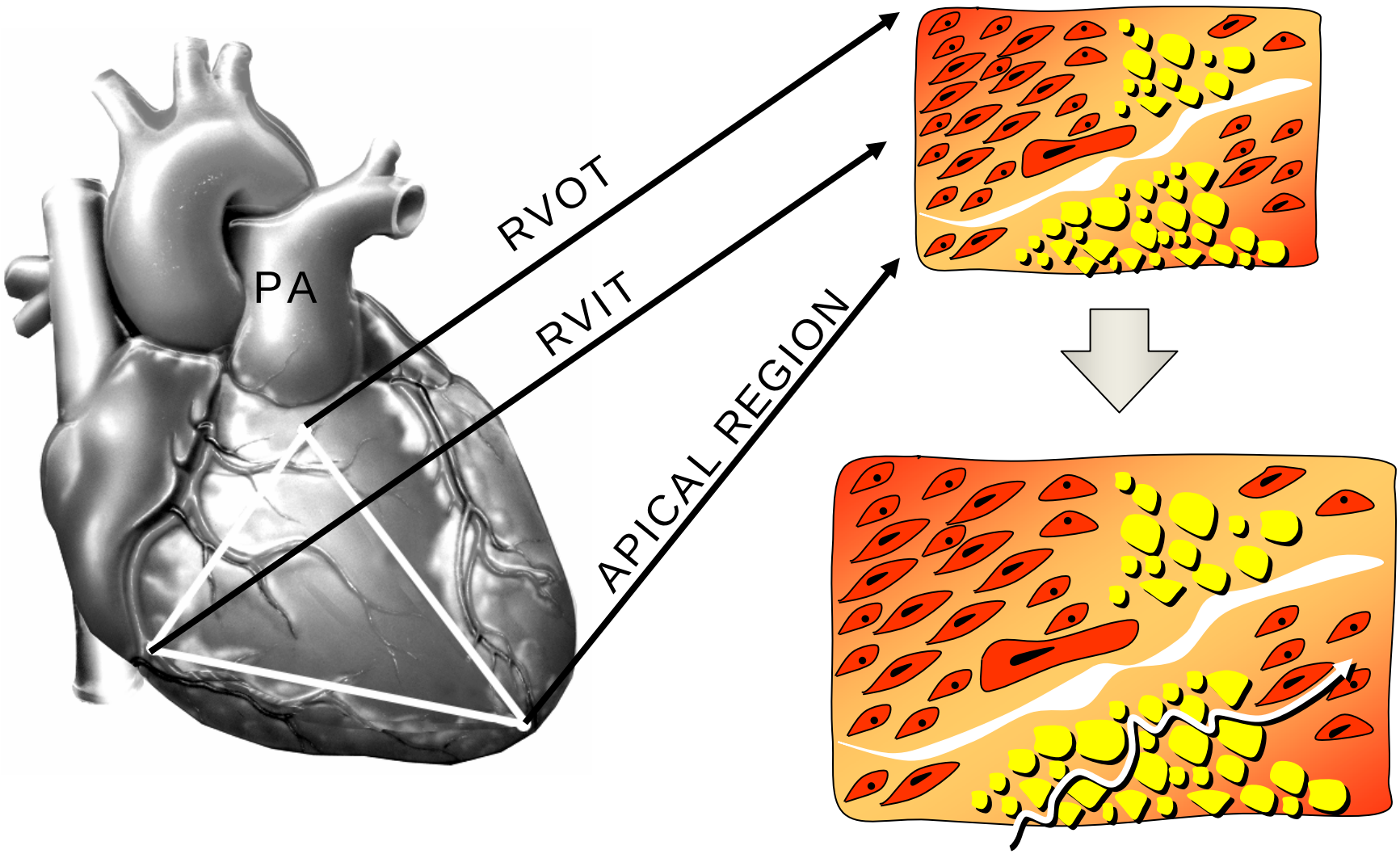


Double amplitude (20 mm/mV)



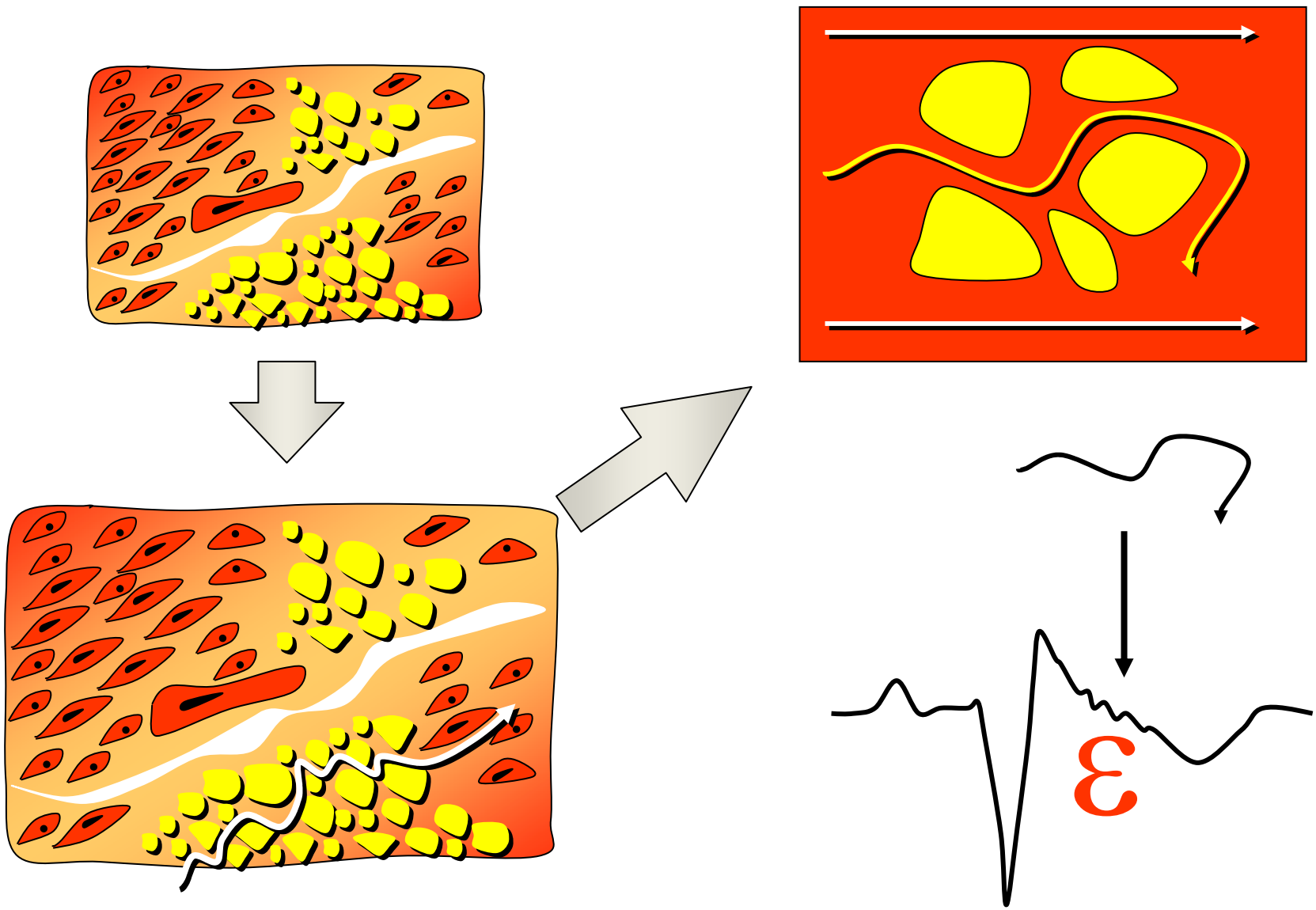
Epsilon wave characteristics in ARVD.

TRIANGLE OF DYSPLASIA IN ARVD

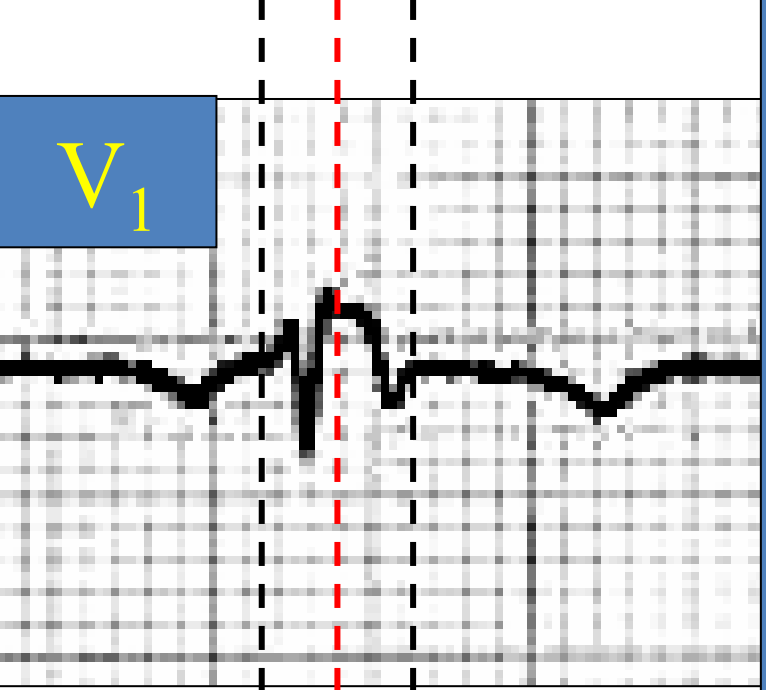


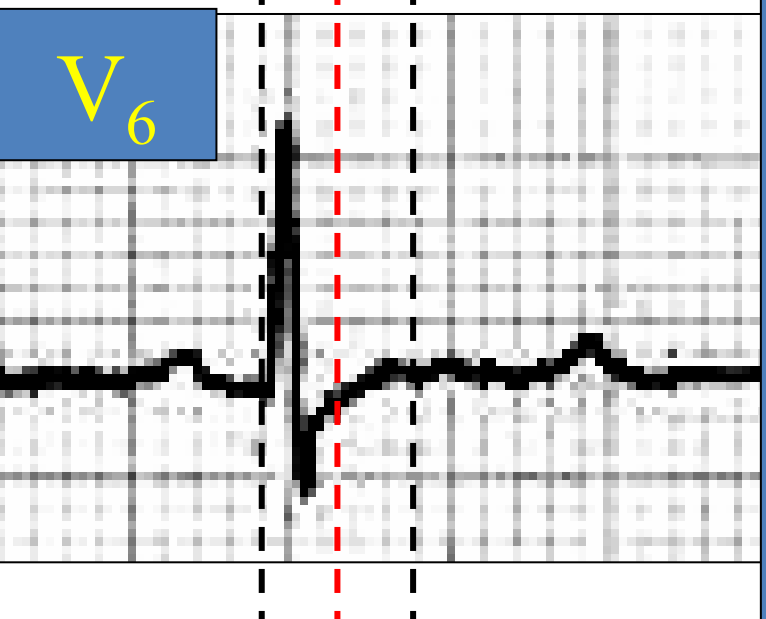
Triangle of dysplasia (ARVC/D).

TRIANGLE OF DYSPLASIA



Outline of Epsilon wave in ARVC/D.





QRS duration (QRSD) in V_1 = 170ms
QRS duration (QRSD) in V_6 = 90ms

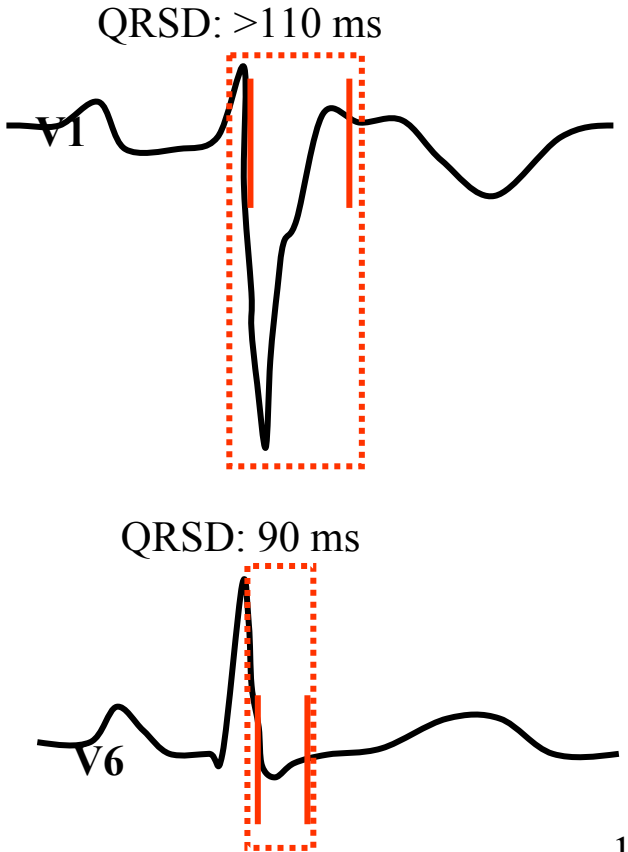
QRSD of $^{V1+V2+V3}$ / $_{V4, V5 \text{ and } V6}$ or ≥ 1.2 in approximately 65% of cases. QRS prolongation located in right precordial leads1.

QRSD ≥ from V1 to V3 with 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVD2.

The mechanism of the right conduction defects is not disease of the bundle branch itself but a distal block probably situated in the RV wall. This hypothesis is supported by the histological appearances of the dysplastic zones(3)

1) **Nasir K, et al. Circulation. 2004; 110:1527-1534.**
2) **Nasir K, et al. Pacing Clin Electrophysiol. 2003; 26: 1955-1960**
3) **Fontaine G et al. Arch Mal Coeur Vaiss. 1984; 77:872-879.**

QRSD V_1, V_2 and V_3 / QRSD V_4, V_5 and V_6 relationship



QRSD of V_1+V_2+V_3 /V_4,V_5, V_6 or ≥ 1.2 in approximately 65% of cases. QRS prolongation located in right precordial leads[1].

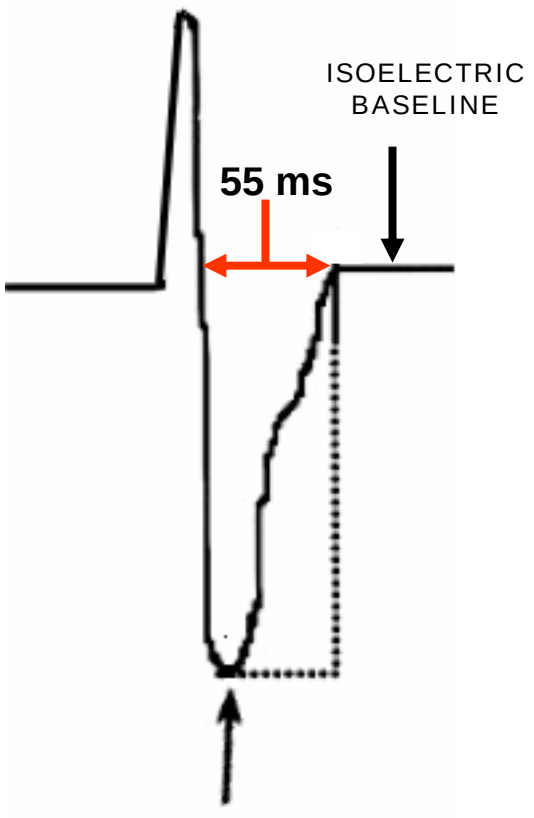
QRSD ≥ from V_1 to V_3 with 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVD[2].

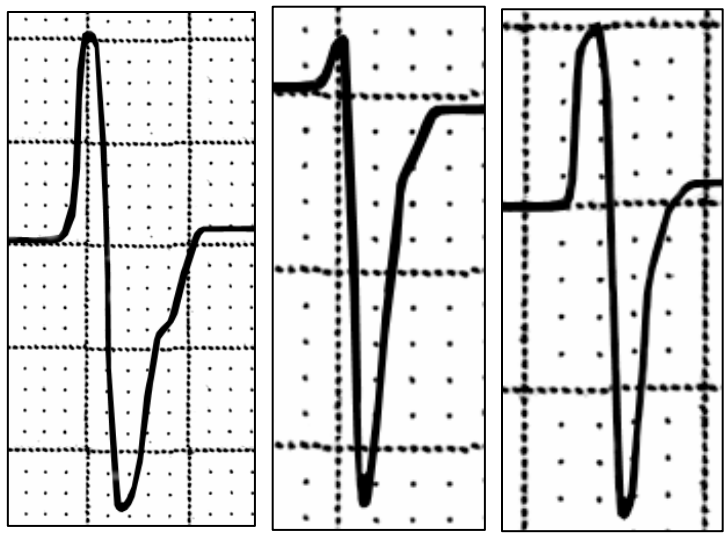
Brugada syndrome may display prolongation in QT interval duration from V_1 to V_3 and subsequently prolongation of QTc interval in right precordial leads[3].

1) Nasir K, et al. Circulation. 2004; 110:1527-1534.
2) Nasir K, et al. Pacing Clin Electrophysiol. 2003; 26: 1955-1960.
3) Pitzalis MV, et al. J Am Coll Cardiol. 2003; 42:1632-1637.

Electrocardiographic features in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D).

Among those without RBBB, a prolonged S-wave upstroke in V_1 through V_3 ≥ 55 ms was the most prevalent ECG feature (95%) and correlated with disease severity and induction of VT on EPS. This feature also best distinguished ARVD/C (diffuse and localized) from RVOT(1)





1. **Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004; 110:1527-1534**.

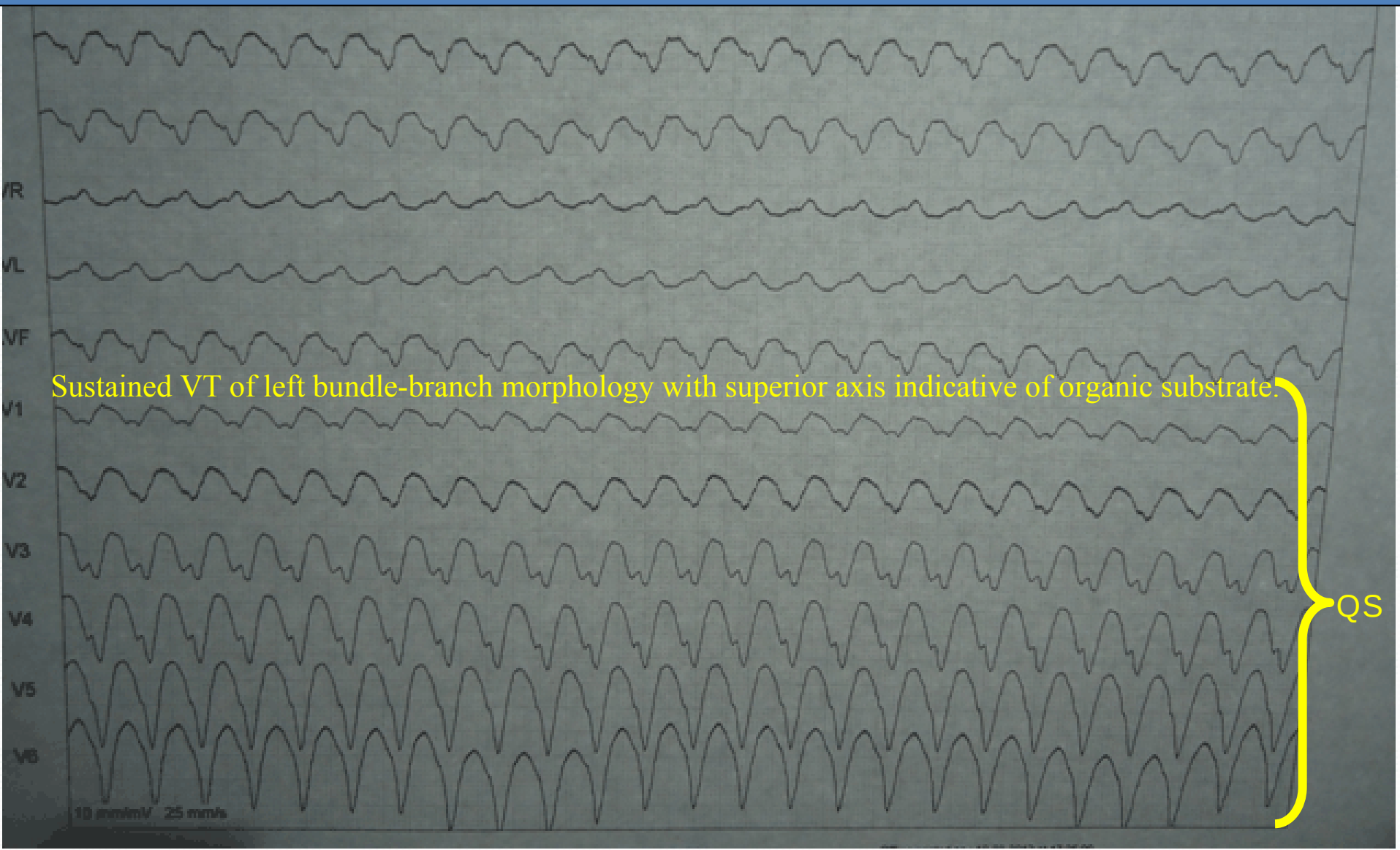
CHARACTERISTIC OF VT IN ARVC/D

1) Non-sustained or sustained VT of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL) is considered a major criteria in The Revised Task Force Criteria for ARVD / ARVC(1)
2) Non-SVT or S-VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
3) >500 PVCs per 24 hours (Holter). Items 2 and 3 are considered minor criteria in The Revised Task Force Criteria for ARVD / ARVC(1)
4) Monomorphic VT with CLBBB morphology, sustained or not, and frequent premature ventricular contractions (>100º in 24h).(2)
5) If SAQRS of MVT with CLBBB morphology has inferior axis: it originates in RVOT.
6) If SAQRS of MVT with CLBBB morphology has superior axis is indicative of organic substrate.
7) Multiple morphologies of VT during the electrophysiological study and abnormal angiogram of RV are suggestive of ARVC/D diagnosis.
8) QRST interval mapping reflects disparities in ventricular repolarization, which lead to vulnerability to arrhythmias. Integral mapping of QRST interval is considered an appropriate method to assess ventricular repolarization dispersion in patients with ARVC/D.(3)
9) ARVC/D associated to a high and significant incidence of inducibility for Supraventricular Tachyarrhythmias in the control population.
10) Supraventricular Tachyarrhythmias may precede induced VT.

1) Marcus FI, T, Heart J. 2010 Apr;3:806-814.
2) Scognamiglio R, et al. JACC 1997;29:744-753.
3) Navarcikova S, et al, Bratisl Lek Listy. 2005;106:212-215

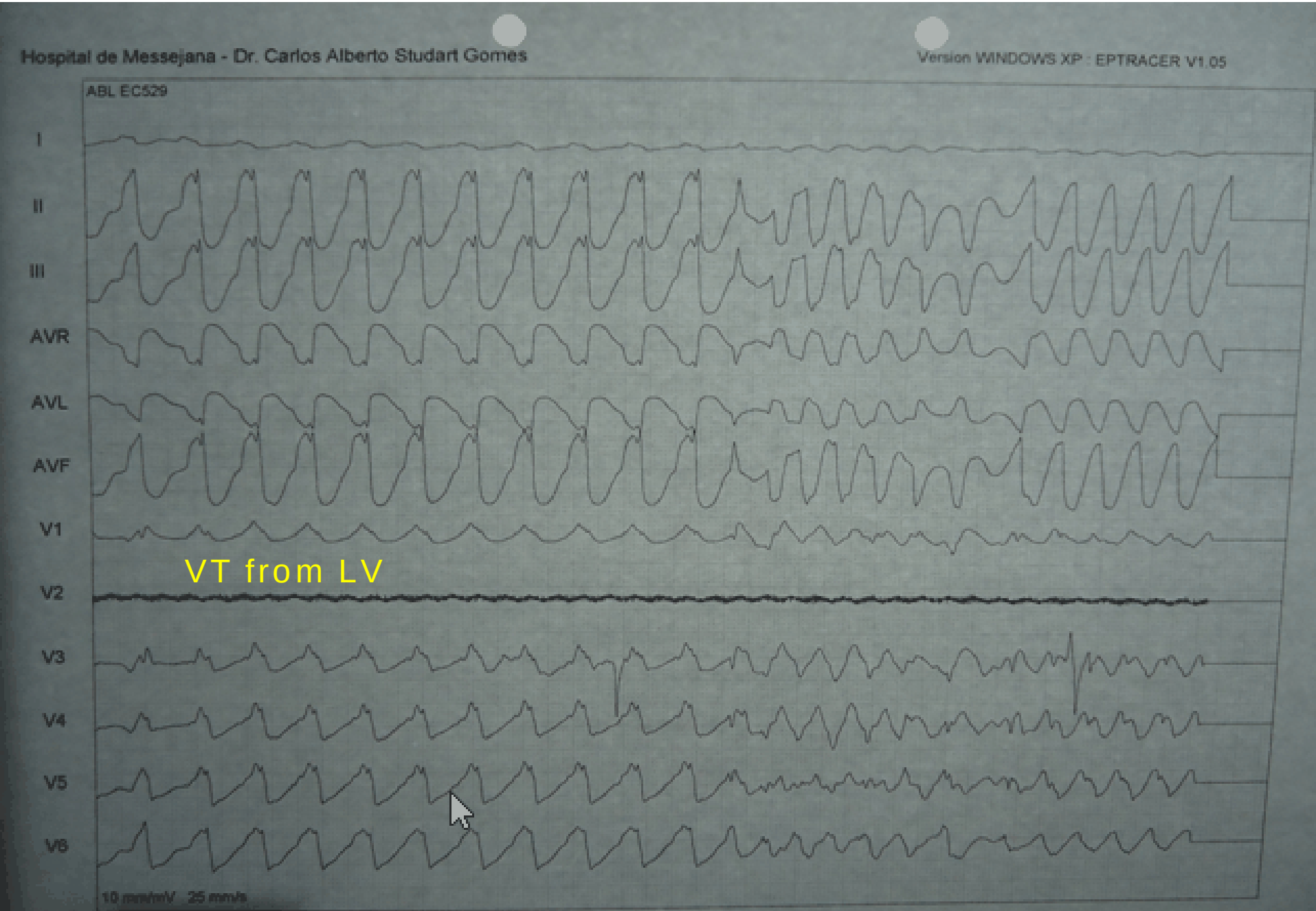
SMVT during EPS

SM-VT induced in the lab are from different foci because the QRS axis is superior. Additionally, QRS complexes on precordial leads are enterely negative: PRECORDIAL CONCORDANCE It is a strong indicator of VT.



Evoluiu para TVP e FV

It evolve in to PVT and VF



ARVC/D is a predominantly genetically determined and heritable form of cardiomyopathy that is characterized pathologically by the replacement of myocytes by adipose and fibrous tissue and leads to right ventricular failure, arrhythmias, and sudden cardiac death. The estimated prevalence of ARVC/D in the general population ranges from 1 in 2,000 to 1 in 5,000, men are more frequently affected than women, with an approximate ratio of 3:1. ARVC/D can be inherited as an autosomal dominant disease with reduced penetrance and variable expression, autosomal recessive inheritance is also described. There have been 12 genes identified which are linked to A RVC/D, encoding several components of the cardiac desmosome.

Designation-Pattern of inheritance	Chromossomal locus	Gene mutation
ARVC/D 1 AD	14Q23-Q24	Transforming growth factor TFD-β3
ARVC/D 2 AD	1q42-q43	Cardiac Ryanodine receptor RyR2
ARVC/D3 AD	14q12-q22	?
ARVC/D4 AD	2q32.1-q32.3	?
ARVC/D5 AD	3p23	Transmembrane 43 (TMEM43)
ARVC/D6 AD	10p12-p14	?
ARVC/D7 AD	10q22	?
Naxos disease AR	17q21	Plakoglobin (JUP)
ARVC/D8 AD	6p24	Desmoplakin-2(DSP)
ARVC/D9 AD	12p11	Plakophilin-2 (PKP2)
ARVC/D10 AD	18q12.1	Desmoglein-2 (DSG2)
ARVC/D11AD	18q12.1	Desmocollin-2(DSC 2)
ARVC/D 12 AD	17q21	Plakoglobin (JUP)

Dysfunctional desmosomes resulting in defective cell adhesion proteins, such as plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP-2), and desmoglein-2 (DSG-2) consequently cause loss of electrical coupling between cardiac myocytes, leading to myocyte cell death, fibrofatty replacement and arrhythmias. Diagnosis is based on the finding a combination of characteristic abnormalities in family history, electrocardiography, cardiac imaging, angiography as well as endomyocardial biopsy (original task force criteria). The differential diagnosis for the ventricular tachycardia due to ARVD include:

Congenital heart disease: Repaired tetralogy of Fallot, Ebstein's anomaly, Uhl's anomaly, atrial septal defect, partial anomalous venous return

Acquired heart disease: Sarcoidosis, idiopathic RVOT tachycardia, Myocarditis, Fat dissociation syndrome(1) tricuspid valve disease, pulmonary hypertension, right ventricular infarction Bundle-branch re-entrant tachycardia, pre-excited AV re-entry tachycardia and idipatic dilated cardimyopathy with VT involving the RV and preservation of LV function.

With Naxos Disease). Carvajal Syndrome, israelian desmoplakin-recessive RV dysplasia(2)

Channelopathy: Catecholaminergic Ventricular tachycardias(3), Brugada syndrome (with Minor or Concealed Forms) : ARVC/D and BrS are distinct clinical entities which diagnostic criteria exclude their coexistence in individual patients. ARVC/D is a myocardial disorder characterized by fibro-fatty replacement of the myocardium and ventricular arrhythmias. In contrast, the BrS has long been considered a primary electrical disease or functional cardiac disorder: no gross structural abnormalities can be identified in the majority of patients and its ECG hallmark of coved-type ST-segment elevation ≥2mm followed by symmetrical negative T wave in right precordial leads is dynamic. Nonetheless, a remarkable overlap in clinical features has been demonstrated between these conditions.

1. **Macedo R,** AJR Am J Roentgenol**. 2007 May;188:W423-7.**
2. **Alcalai R, et al. J Am Coll Cardiol. 2003 Jul 16;42:319-27.**
3. **Tiso N, et al. Hum Genet. 2004 Mar;114(4):405.**

	ARVC/D	Brugada syndrome BrS
Prevalence	The estimated prevalence of ARVC/D in the general population ranges from 1 in 2,000 to 1 in 5,000. The prevalence is dependent of geographic circumstances. Endemic in Veneto area (Italy), Nova Scotia and Naxus Greek island.	Although this syndrome is observed worldwide and the exact prevalence is unknown, because the ECG pattern can be dynamic and is often concealed, it is difficult to estimate the true prevalence of the disease in the general population. It is more common in the Southeast Asian countries.The entity has an incidence ranging between 5 and 66 per 10,000. It is believed to be responsible for 4-12% of all SCD and around 20% of deaths in patients with apparent structurally normal hearts. Endemic in Southeast Asia as Thailand. The annual mortality rate in this country was estimated to be 26 to 38 deaths per 100,000 inhabitants. 4 to 10 SCD per 10,000 inhabitants per year was observed in areas like Thailand and Laos (Southeast Asia). Japan and Philippines also possess greater incidence in relation to the remaining portion of the world.
Annual rate of SCD	≈ 2.5% a year.	Higher. 10% per year.

Symptoms	Palpitations are the most common complaint. Syncope, dizziness or SCD. Frequently triggered by stress or exercise.	Syncope, dizziness or SCD more often occur at rest or during sleep when the vagal tone is predominant.
Circumstance	Effort	At rest
Pathology	Fibro fatty replacement	Normal or near normal
Sex (male/female)	M>F 3:1	M>F 8:1
Sinus node function	Frequently affected. Eventually: Prolonged sinus node recovery time Sick Sinus Syndrome Slowed atrial conduction	Frequent affected Eventually Prolonged sinus node recovery time Sick Sinus Syndrome Slowed atrial conduction
Symptoms	Palpitations are the most common complaint. Syncope, dizziness or SCD. Frequently triggered by stress or exercise.	Syncope, dizziness or SCD more often occur at rest or during sleep when the vagal tone is predominant.
Circumstances	Effort	At rest
P wave	Is possible giant P wave, very low amplitude, intra-atrial conduction defect, left atrial enlargement, right atrial enlargement or biatrial enlargement	Eventually slowed atrial conduction and atrial standstills when SCN5A mutation is present. Prolonged P duration

	ARVC/D	Brugada syndrome BrS
ECG Repolarization in right precordial leads	Inverted T wave	High take-off ST segment elevation followed by symmetrical negative T wave Symmetrical T wave on VCG loop(1)
ECG Depolarization	Parietal block, late potentials, epsilon waves	Right end conduction delay(1), LP, epsilon waves and parietal block are possible
AV conduction	Normal	50% PR prolongation/HV interval or split His
Supraventricular arrhythmias	Late and secondary	Early primary 25% of cases.
VT characteristics	M-VT with LBBB pattern	P-VT. Exceptional monomorphic
Mechanism of arrhythmias	Scar-related reentry predominance.	Phase 2 reentry
ECG Repolarization in right precordial leads	Inverted T wave	High take-off ST segment elevation followed by symmetrical negative T wave Symmetrical T wave on VCG loop(1)
Natural history	SCD Heart failure	SCD, repetitive syncope..

1. **Peréz-Riera AR**, et al, Europace. 2012 Jun;14(6):889-97.

	ARVC/D	Brugada syndrome BrS
Quinidine	No indicate	Great utility
Beta-blocker	Helpful	Ineffective
Amiodarone	Helpful	Ineffective
Isoproterenol	Contraindicated	Great utility in electric storm
Natural history	Sudden death and heart failure	Sudden death

A BrS patient without clinically detected cardiac structural abnormalities underwent cardiac transplantation for intolerable numbers of ICD discharges. The patient's explanted heart was studied electrophysiologically and histopathologically. Whole-cell currents were measured in HEK293 cells expressing wild-type or mutated sodium channels from the patient. The RVOT endocardium conduction delay slowing and was the origin of VF without a transmural repolarization gradient.. RVH and fibrosis with epicardial fatty infiltration were present. HEK293 cells expressing a G1935S mutation in the gene encoding the cardiac sodium channel exhibited enhanced slow inactivation compared with wild-type channels. Computer simulations demonstrated that conduction slowing in the RVOT might have been the cause of the ECG changes(1).

1. Coronel R, Circulation. 2005 Nov 1;112(18):2769-77.

DIFFERENTIAL DIAGNOSIS BETWEEN CARDIAC SARCOIDOSIS AND ARVC/D

	CARDIACSARCOIDOSIS	ARVC/D
Family history:	Absent	Present in 30% to 50% of cases. When the disease is identified, genetic screening should be conducted among 1st degree relatives
Gender (M/F):	1 to 1.	2.9 to 1
Mean age of presentation:	Young people or adults in intermediary age	Adolescents and young adults. Rarely in children.
Multi-systemic involvement	Yes	No
Precordial pain	Intense precordial pain is described	No
Clinical manifestations of restrictive cardiomyopathy:	Possible	No
Mitral valve insufficiency	Common	Only lately when it involves the LV.
ECG pattern of pseudo infarction:	Frequent in extensive forms	No
Chest X-rays	Bilateral hiliar lymphoadenopathy.	Possible right cardiomegaly.
Pulmonary involvement	Present in >90% of cases. Frequent COPD.	No
Pathological anatomy:	Non-cancerous granulomas that sometimes form fibrotic scars.	RV fibro-fatty substitution in the triangle of dysplasia.
Cardiac location involved more frequently:	LV free wall and interventricular septum.	RVOT, RVIT and RV apex.
Pericardial effusion:	Frequent	Absent
Improvement of symptoms shown by MNR with use of corticoids:	Yes	No
Corticosteroids, chloroquine, methotrexate or cyclophosphamide:	Sometimes prescribed	No

Riera AR.et al. Differential diagnosis between ARVD and Cardiac Sarcoidosis. Folia Cardiol. 2006; 13: 432-434.

Differential diagnosis with Carvajal Syndrome (With Naxos Disease)

The Carvajal Syndrome (1) is a familial, cardio-cutaneous, autosomal recessive entity, mapped to the short arm of chromosome 6 (6p24) and caused by a 7901delG mutation in exon 24 of desmoplakin. This is an intracellular protein that links desmosomal adhesion molecules to intermediate filaments of the cytoskeleton. It causes premature deletion of the codon located in the amino acid with number 18, causing truncation of the C-terminal domain in the region that interacts with intermediate filaments.

Desmosomes are major cell adhesion junctions, particularly prominent in the epidermis and cardiac tissue and are important for the rigidity and strength of the cells. The desmosome consists of several proteins, of which desmoplakin is the most abundant. Norgett et al.described the first recessive human mutation, 7901delG, in the desmoplakin gene which causes a generalized striate keratoderma particularly affecting the palmoplantar epidermis, woolly hair and a dilated left ventricular cardiomyopathy. A number of the patients with this syndromic disorder suffer CHF in their teenage years, resulting in early morbidity. All tested affected members of three families from Ecuador were homozygous for this mutation which produces a premature stop codon leading to a truncated desmoplakin protein missing the C domain of the tail region. Histology of the skin revealed large intercellular spaces and clustering of desmosomes at the infrequent sites of keratinocyte adhesion.

This suggests that the tail domain of desmoplakin is not required for establishing tissue architecture during development. (2)

1. **Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. J Am Acad Dermatol. 1998; 39:418-421.**
2. **Norgett EE, Hatsell SJ, Carvajal-Huerta L, Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet. 2000;9:2761-2766**

It is clinically characterized by: Woolly hair present since birth; Hyperkeratosis and palmoplantar keratoderma of early onset (approximately the first year of life); Dilated cardiomyopathy with systolic dysfunction that leads to CHF (1). This entity should not be considered part of ARVC/D, because it causes global dilated cardiomyopathy and not ARVC/D. The cardiomyopathy is characterized by ventricular hypertrophy and dilatation, focal ventricular aneurysms, and distinct ultrastructural abnormalities of intercalated disks; however, there is no evidence of fibrofatty infiltration or replacement of myocardium. There are markedly decreased amounts of specific immunoreactive signal for desmoplakin, plakoglobin and the gap junction protein, connexin 43, at intercalated disks. The intermediate filament protein, desmin, which is known to bind desmoplakin, showed a normal intracellular pattern of distribution but failed to localize at intercalated disks (2). It has a differential diagnosis with recessive Naxos disease, which affects the long arm of chromosome 17 (17q21) associated to non-epidermolytic palmoplantar keratoderma with wooly hair.
Immunohistochemistry of skin from the patients showed a perinuclear localization of keratin in suprabasal keratinocytes, suggesting a collapsed intermediate filament network. This study demonstrates the importance of desmoplakin in the attachment of intermediate filaments to the desmosome. In contrast to null DESMOPLAKIN: mice which die in early development, the truncated protein due to the homozygous 7901delG mutation in humans is not embryonic lethal.
Table in next slide shows the main differences between both entities.

1. **Duran M, Avellan F, Carvajal L. Dilated cardiomyopathy in the ectodermal dysplasia. Electro-echocardiographic observations in palmo-plantar keratoderma with woolly hair. Rev Esp Cardiol. 2000; 53:1296-1300.**
2. **Kaplan SR, Gard JJ, Carvajal-Huerta L, Ruiz-Cabezas JC, Thiene G, Saffitz JE. Structural and molecular pathology of the heart in Carvajal syndrome. Cardiovasc Pathol. 2004;13:26-32.**

DIFFERENTIAL DIAGNOSIS BETWEEN CARVAJAL SYNDROME AND NAXOS DISEASE

	CARVAJAL SYNDROME	ARVC/D NAXOS DISEASE
Inheritance pattern:	Recessive autosomal.	Recessive autosomal.
Affected chromosome	6 short arm. (6p24). Caused by a 7901delG mutation in exon 24 of desmoplakin.	Long arm of chromosome 17 (17q21) that codifies the desmoplakin protein. This protein is a key component of desmosomes and adherens junctions, and is important for the tight adhesion of many cell types, including those in the heart and skin.
Cardiac disease:	Global dilated cardiomyopathy.	RV predominance
Symptoms:	CHF	Unique form of RV cardiomyopathy. It presents a high prevalence of malignant ventricular arrhythmias, including SCD. CHF.
Geographic distributions	Spain. Ecuador. Others?	It appears in families descending from the Hellenic island of Naxos and Milos
Structural and molecular pathology of the heart:	Markedly decreased amounts of specific immunoreactive signal for desmoplakin, plakoglobin, and the gap junction protein, connexin43, at intercalated disks.	Progressive replacement of myocardial cells by fat and fibrous tissue on RV. Deletion in plakoglobin in ARVC suggests that the proteins involved in cell-cell adhesion play an important role in maintaining myocyte integrity. Thus, when junctions are disrupted, cell death, and fibrofatty replacement occur
Treatment:	Conventional for CHF.	ICD associated to drugs

1. **McKoy G, et. al. Lancet. 2000; 355:2119-2124.**
2. **Narin N, et al .Pacing Clin Electrophysiol. 2003; 26:2326-2329**
3. **Gatzoulis K, et al Pacing Clin Electrophysiol. 2000; 23:1176-178** .

The Revised Task Force Criteria for ARVD / ARVC(1)

Ⅰ. Global or regional dysfunction and structural alterations∗ Major/Minor

Major By 2D echo:	**Minor By 2D echo**
Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2) PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) *or* fractional area change ≤33%	Regional RV akinesia or dyskinesia *and* 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2) PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2) *or* fractional area change >33% to ≤40%
By MRI:	**By MRI**
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) *or* RV ejection fraction ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female) *or* RV ejection fraction >40% to ≤45%
By RV angiography:	
Regional RV akinesia, dyskinesia, or aneurysm	

II. Tissue characterization of wall

Major	Minor
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

III. Repolarization abnormalities

Major	Minor
Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBB QRS ≥120 ms)	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB

IV. Depolarization/conduction abnormalities

Major	Minor
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	•Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
	•Filtered QRS duration (fQRS) ≥114 ms

	Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
	Root-mean-square voltage of terminal 40 ms ≤20 μV
	Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block

V) Ventricular Arrhythmias

Major	**Minor**
Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	•Non-SVT or S-VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 PVCs per 24 hours (Holter)

VI. Family history

Major	**Minor**
•ARVC/D confirmed in a first-degree relative who meets current Task Force criteria	•History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
•ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative	•Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative

•Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation	ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

∗ Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

† A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. E.g.: in TMEM43, DSP, PKP2, DSG2, DSC2, JUP.

1. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W.Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria.Eur Heart J. 2010 Apr;3:806-814.

NATURAL HISTORY

Management of patients with ARVC/D is complicated by the incomplete information on the natural history of the disease and by the lack of risk stratification for SCD. (1) **Hulot JS, et ai. Circulation. 2004; 110:1879-1884.**). There is a long asymptomatic lead-time. The entity is characterized by a "concealed phase" in which ECG and imaging abnormalities are often absent, but patients may nonetheless be at risk for SCD. Detection at this stage remains a clinical challenge, underscoring the potential value of mutation analysis in identifying affected persons. Unfortunately, SCD may be the first symptom of the disease, even in subjects with borderline ARVC/D. (**Wlodarska EK, et al. Kardiol Pol. 2004; 60:1-14.**).Serial evaluation of patients with suspected ARVC/D is recommended as clinical features may develop during the follow-up period.(**Sen-Chowdhry S, et al. Am J Med. 2004;117:685-695**.). While this is a genetically transmitted disease, individuals in their teens may not have any characteristics of ARVC/D on screening tests. Many individuals have symptoms associated with VT, such as palpitations, light-headedness, or syncope. Others may have symptoms and signs related to RV failure, such as lower extremity edema, liver congestion with elevated hepatic enzymes. There are references of electrical storm (ES) as initial presentation in an elderly woman (**Barriales V, et al .Int J Cardiol. 2004; 94:331-333**.).ARVC/D is a progressive disease. Over time, the RV becomes more involved, leading to RV failure. The RV will fail before there is LV dysfunction. However, by the time the individual has signs of overt RV, there will be histological involvement of the LV. Eventually, the LV will also become involved, leading to bi-ventricular failure. Signs and symptoms of LV failure may become evident, including CHF, AF, and an increased incidence of thromboembolic events. Concomitant LV involvement is not rare and represents a late stage of the disease. Its natural history is modulated by the wide variety of antiarrhythmic therapies. Hemodynamically ill tolerated ventricular arrhythmia, LV involvement, sports, a younger age below 35, and uncontrolled therapy seem to predict an adverse outcome for these patients. (**Frank R, et al. Ann Cardiol Angeiol (Paris). 2005; 54:21-25.**. Risk factors significantly associated with adverse outcome were history of CHF, the presence of LV involvement on echocardiography , LA dilatation, prolonged PR interval, prolonged QRSd in V1, and BBB In multivariate analysis, history of CHF and presence of LV involvement were identified as independent risk predictors for an adverse outcome. (**Lemola k, et al. Heart. 2005;91:1167-1172.).**

Management

Pharmacological theraphy is the first choise treatment of patients wth well tolerated and not life-treatin ventricular arrhthmias. Sotalol or amiodarone alone or in combination proved to be highly effective in patients with ARVC/D and inducible as well as non-inducible VT; if it is ineffective in inducible VT response to other antiarrhythmic drugs is unlikely and therefore non-pharmacological therapy without further drug testing should be considered. No pharmacological theraphy is reserved for drug-resistance cases and for patients with previous arrhythmic arrest. Therapeutic options remain limited because of the progressive nature of ARVC/D. The progressive nature of ARVC/D suggests that RFCA would not be a long-term curative procedure. RFCA should be reserved for particular clinical condition such as drug refractory incessant VT or frequent recurrences of VT after CID implantation.Competitive athletics should be avoided. Patients with ARVC/D with a history of having been **resuscitated from SCD, patients with syncope, very young patients, and those who have marked RV involvement are at the highest risk for arrhythmic death and also, the presence of LV involvement is a risk factor**.(1) (DARVIN study. Defibrillator for ARVC/D In Italy and North America). On the contrary , theraphy with ICD did not improve survival in the subgroup of patients presenting with thermodynamically stable M-VT.

VF has been associated with active phases of myocite death occurring in younger affected patients with progressive disease, whereas thermodynamically well-tolerated MVT is caused by a reentry mechanism around a stable myocardial scar as the result of a healing process that occurs in a later stage of the disease course. Several authors concluded that patients who meet the Task Force criteria for ARVC/D are at high risk for SCD and should undergo ICD placement for primary and secondary prevention, regardless of EPS testing results. Prophylactic ICD theraphy may be also indicated in young patients with sever right ventricle dysfunction or advanced disease wit biventricular involvement(2)

1. Corrado D, Leoni L, Link MS,et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation. 2003 Dec 23;108:3084-91.
2. Basso C, Corrado D, Marcus FI et al. arrhythmogenic right ventricular cardiomyopathy. Lancet 2009:373:1289-1300.

Orthotropic heart transplantation is considered in patients with progressive HF and intractable recurrent ventricular arrhythmias. ARVC/D can develop malignant arrhythmias, severe ventricular dysfunction with right ventricular predominance, and SCD. Orthotropic heart transplantation must be considered as last therapeutic options in refractory cases of ARVC/D with malignant arrhythmias or refractory congestive heart failure and or intractable recurrent ventricular arrhythmias. because it is the only way to remit the symptoms and the disease.(1)

The role of EPS in ARVC/D

In DARVIN study the positive predictive value of PVS was 49%, the negative predictive value of PVS was 51% and the test accuracy was 49%(low predictive accuracy)
The type of VT inducible at EPS did not predict the occurrence of VF/flutter during follow-up
The risk of SCD is better determined on the basis of patient's clinical presentation rather than on the results of EPS with PVS

1. **Fiorelli AI, Coelho GH, Oliveira JL Jr, Heart transplantation in arrhythmogenic right ventricular dysplasia: case reports. Transplant Proc. 2009 Apr;41:962-964.**