CASE REPORT

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Commentaries:
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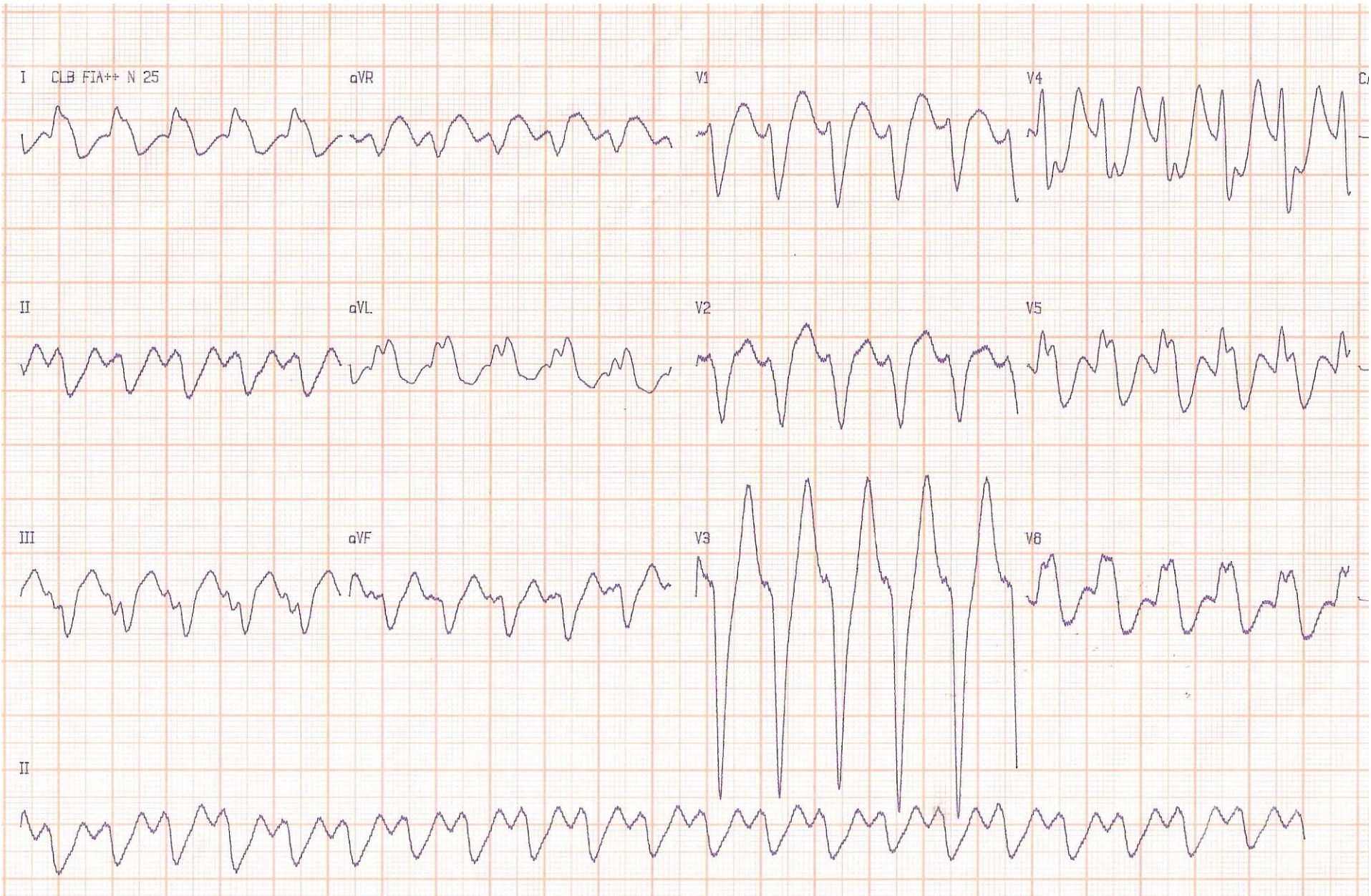
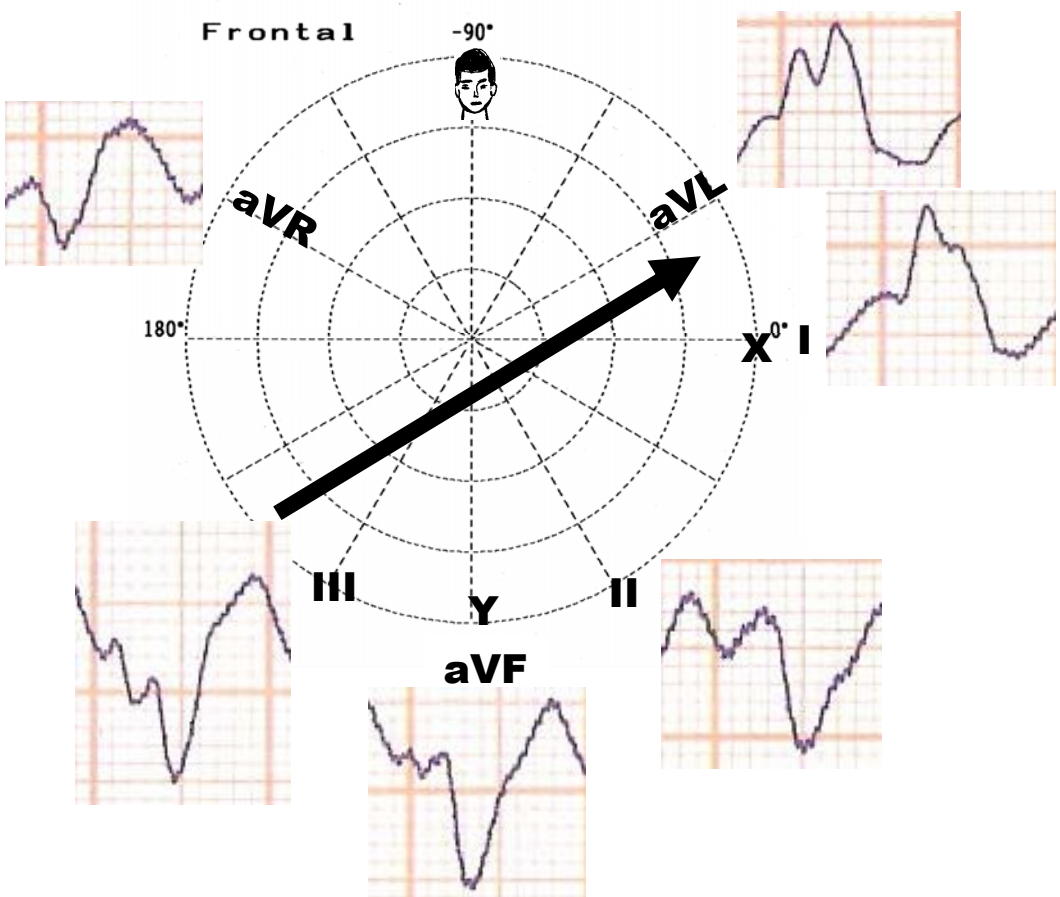
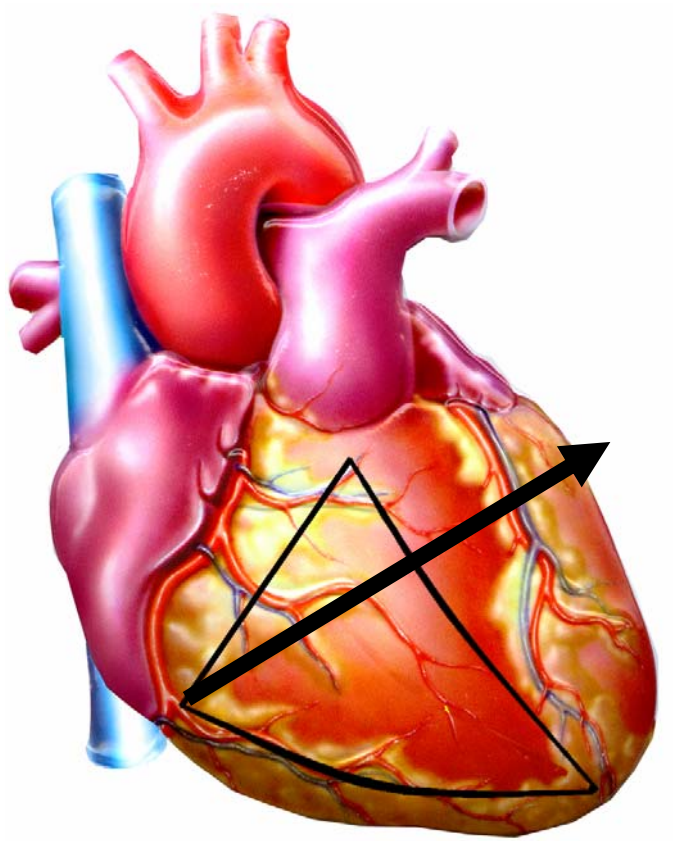
Dearest friend: these ECGs belong to a young man (29yo), with history of palpitations and near-syncope.
Negative familiar background.
The first ECG during the event with LBBB pattern
The second one during sinus rhythm.
Which is the possible diagnosis? And Why? Ground of diagnosis.
Suggestions for the approach?
Commentaries?
Thank in advance
Dr Barbosa de Barros from Fortaleza Brazil
Andrés Ricardo Pérez Riera.

Prezado amigo Dr. Andrés gostaria de ouvir a sua opinião sobre estes ECGs de um homem,29 anos,com história de palpitações e pré-síncope.Não há relato de MS na família.O ECG de entrada revela TVMS com padrão de BRE .Após reversão ao ritmo sinusal observa-se BRD+inversão de T de V1-V3+onda epsolon em V2?+duração do QRS em precordiais(V1,V2 e V3) > V5 e V6.Estou pensando em displasia arritmogênica. O que você acha?

Abs
Raimundo Barbosa Barros

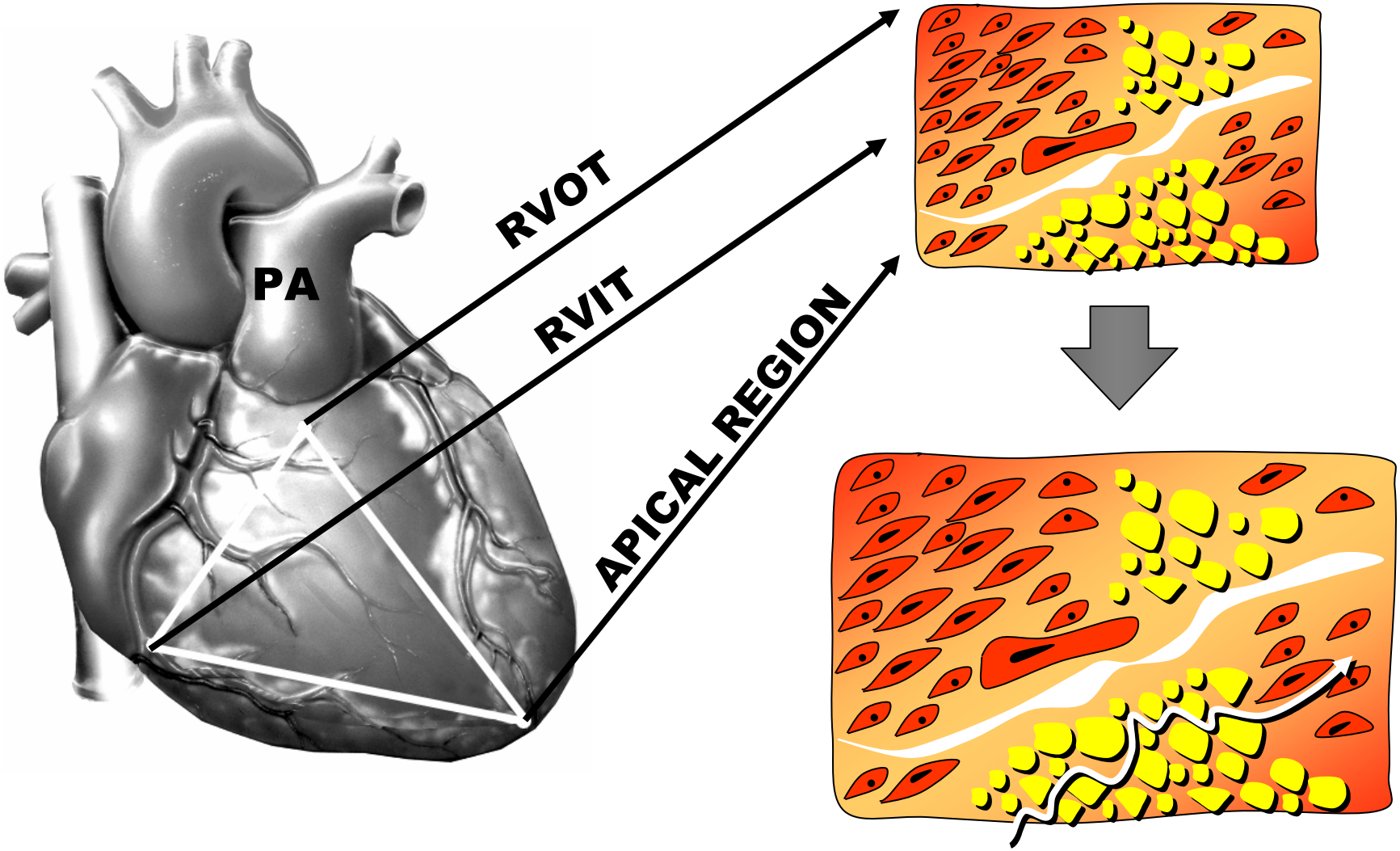

I CLB FIA++ N 25
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II



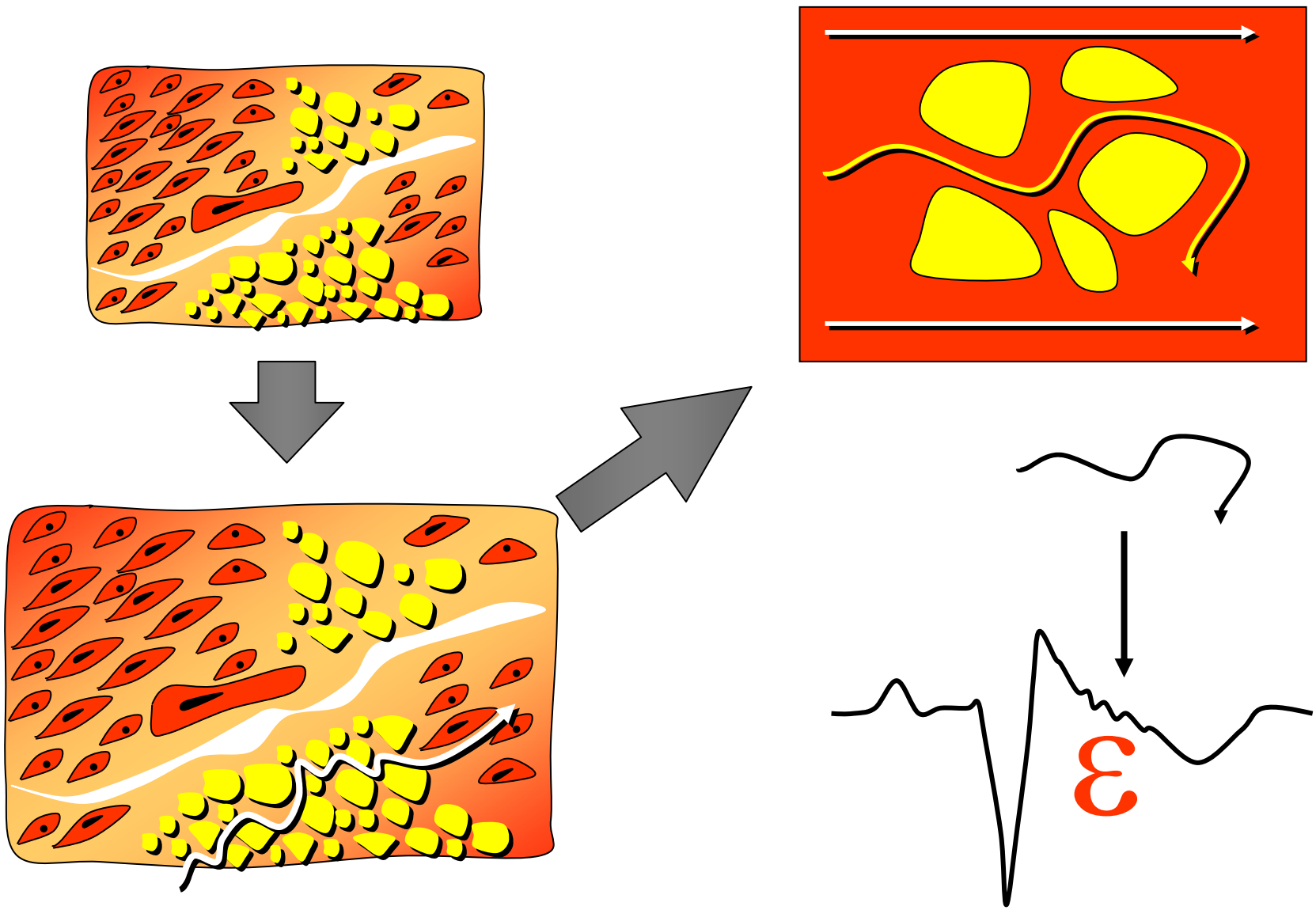


VT with LBBB pattern and extreme left axis deviation: origin from RVIT (dysplasia triangle). This origin is indicative of organic or structural heart disease.

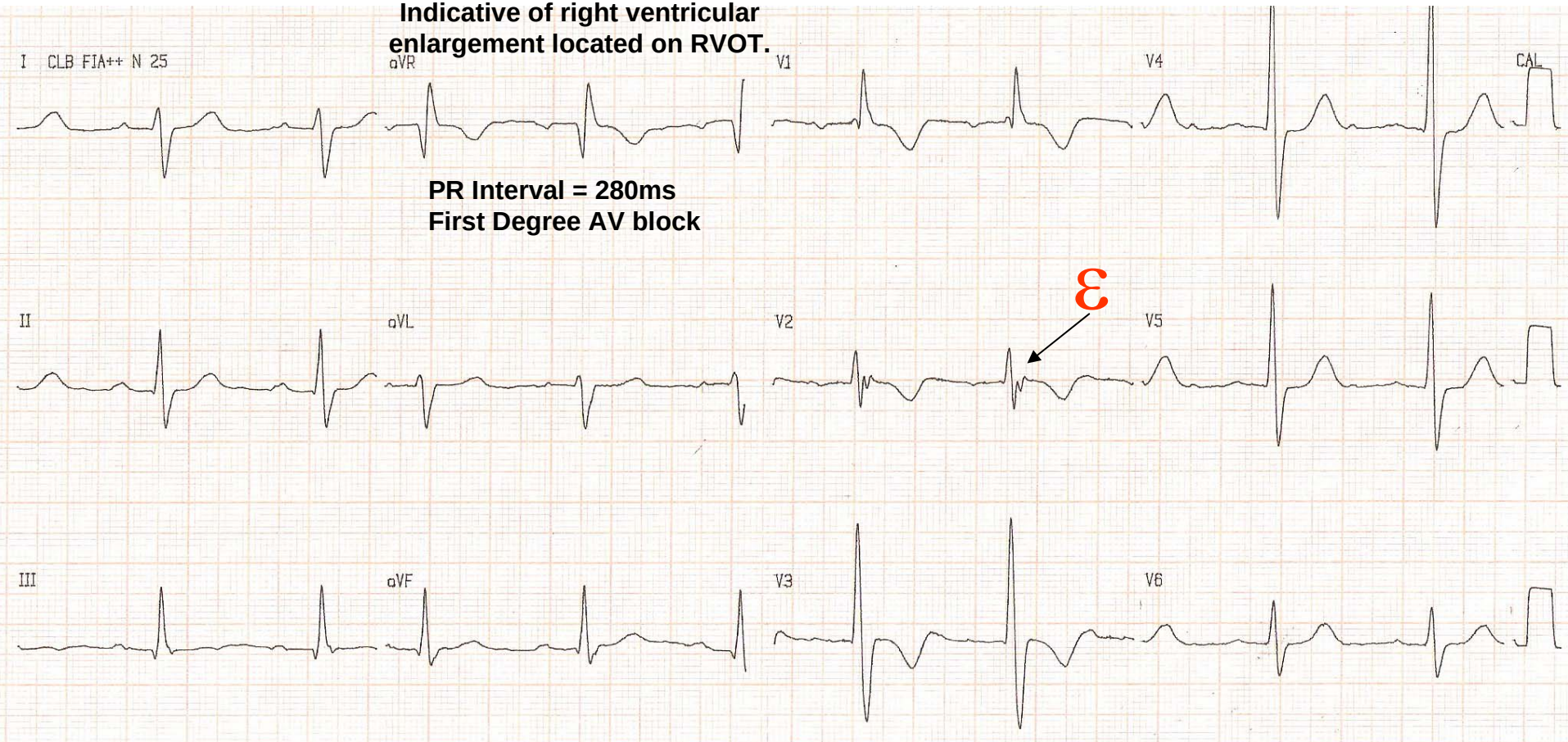
TRIANGLE OF DYSPLASIA IN ARVD



TRIANGLE OF DYSPLASIA



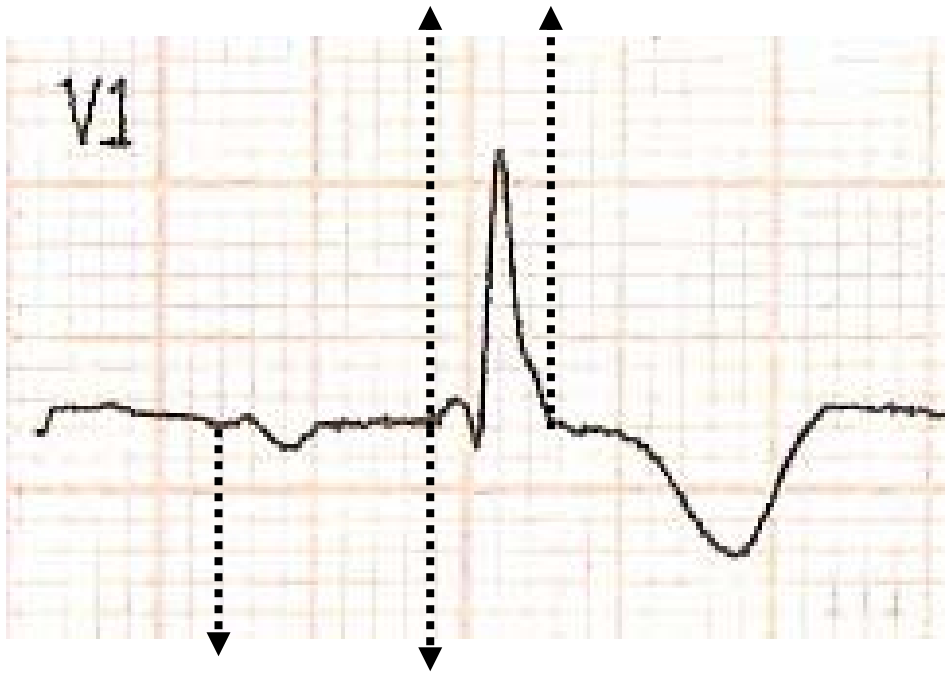
ECG After Event



QRS Axis = +125°: Another criteria of probable Right Ventricular Enlargement.

Left Atrial Enlargement (LAE)
By Morris' Criteria

QRS Duration = 160ms: Complete-RBBB



PR Interval = 280ms
First Degree AV block

Increase in depth and duration of final negative component of the wave in V_1 (Morris index); slow and deep of P in V_1 or V_1-V_2. PTFV1.P terminal force in lead V1 equal or more negative than 0,04mm/seg Greater than 0.03 mm/sec: product of the duration of the final negative component (duration expressed in seconds); while depth is expressed in mm. Values above 0.03 mm per second constitute a highly sensitive criterion for diagnosis of LAE.

FINAL ECG DIAGNOSIS

1. Left Atrial Enlargement
2. Probable Right Ventricular Enlargement or Hypertrophy:
   QRS axis deviation: + 125°.
   Prominent final R wave in aVR ≥ 5mm.
3. Complete Right Bundle Branch Block: QRSd = 160ms + rsR'
4. Epsilon Wave in V2

Commentaries about this wave: "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 ARVD diagnosis[2;3].

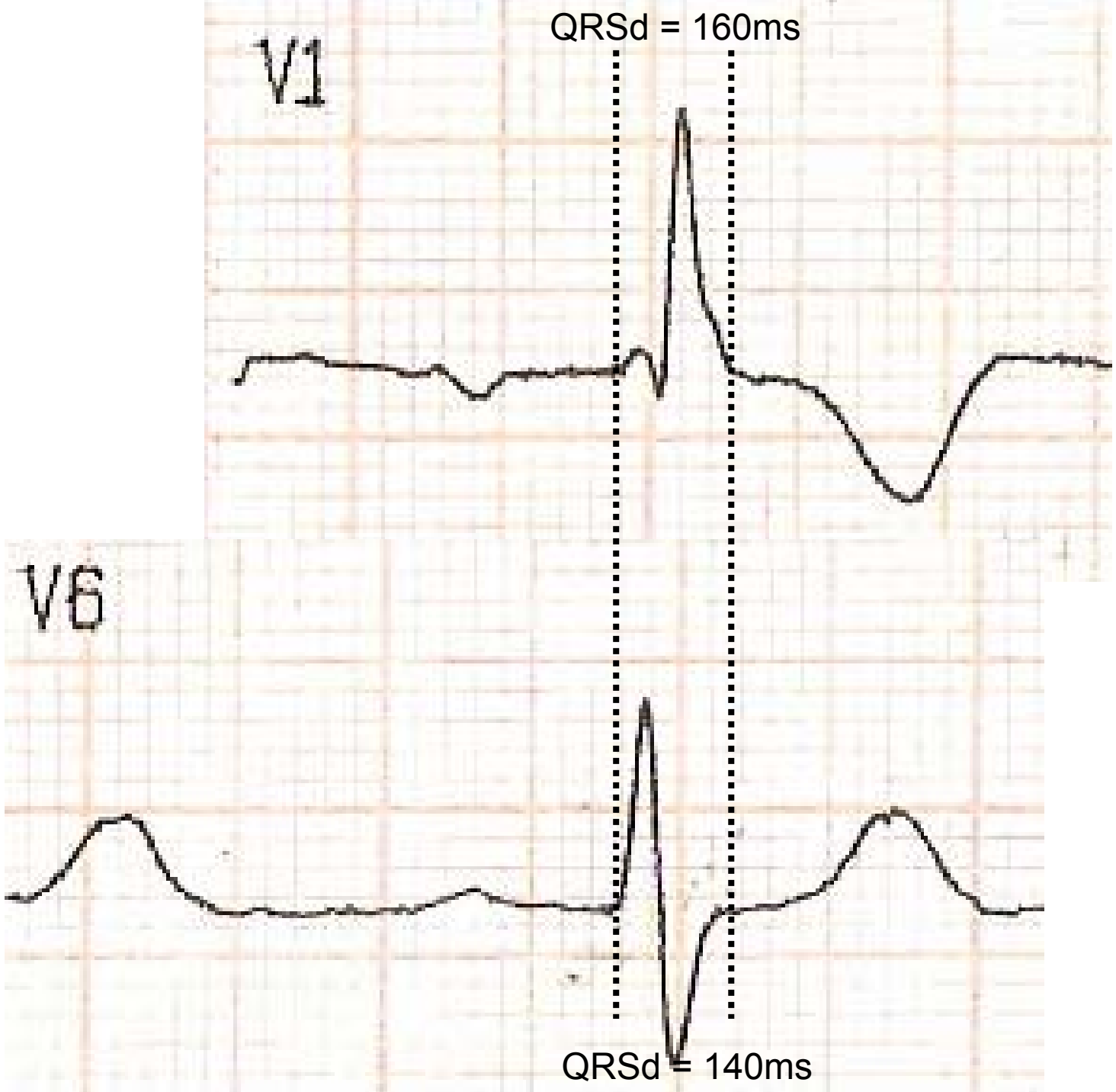
High resolution ECG: observed more frequently with this method.

Pathognomonic character: in spite of the characteristics in ARVD, 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[6], etc.

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

Inversion of T wave in leads V1-V3 and/or ε wave found in 70% of patients with ARVD.

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) Hurst JW. Circulation 1998; 98: 1837-1942.


QRSd = 160ms
V1
V6
QRSd = 140ms

ECG IN ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

Abnormalities in depolarization and repolarization in ECG are common in cases of ARVD.

Abnormalities in depolarization/conduction in ECG

Prolongation of QRS complex (110 ms) located in precordial leads (V1-V3) 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 (PVS).

ECG IN ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

Prolongation in S wave duration in antero-septal leads of ECG (V1-V3) is a significant marker for ARVD diagnosis in patients.

Automated medication in S wave duration (Marquette Mac12, Mac15 or MacVue) in the surface of ECG leads V1-V3, 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 ARVD.

Available ECGs were assessed in the initial and final phase in patients carriers of ARVD, obtained respectively at ages 11.6 ± 3.9 and 14.3 ± 3.4 years old.

ARVD was diagnosed in children with VT and CLBBB morphology, using diagnostic criteria already published for adult patients, carriers of ARVD or who had typical findings in biopsy.

ECG IN ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

The result from the addition of QRS complexes duration from V1 + V2 + V3 when divided by the addition of the duration of QRS complexes from V4 through V6 (V4 + V5 + V6). When this equation results in a value ≥ than 1.2, it constitutes a sign of high sensitivity for ARVD diagnosis, since it is present in 98% of patients carriers of this cardiomyopathy.

A recent research showed that the sign is not specific of ARVD 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 ARVD.
Possibly QRS complexes may be of low voltage, which is observed when the disease is diffuse or there is participation with the conduction system.

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

ECG IN ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

In ARVD there is evidence of peripheral right branch blocks, as the author Guy Fontaine proved some time ago: topographic IRBBB or CRBBB occurs in the fascicular portion of the right branch and/or in the right ventricle free wall after the trunk of the branch splits at the base of the papillary muscle of the tricuspid valve and, this mechanism seems to be due to the participation of dysplasia in the free wall, in RVOT, in RVIT or in the apical region (Triangle of Dysplasia), area where we find dysplasia[1].

Pattern of CRBBB[2;3;4] (15% of cases), IRBBB or ECD (18% of cases).

1) Fontaine G, et al. Arch Mal Coeur Vaiss. 1984; 77:872-879.
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) Marcus FI. e col. Circulation, 1982 65:384

ECG IN ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

- **Alterations of depolarization and conduction.**

  (1-a) Epsilon waves (ε): (30%) late potentials or low amplitude and short duration oscillations near the J point (before or immediately after): major criterion: if the addition of QRS complexes duration in V1+ V2+ V3 / V4+ V6+ V6 is ≥ than 1.2;
  (1-b) Increase in QRS complex duration (>110º) in V1, V2 and V3, in absence of CRBBB: parietal block. Major criterion: if the addition of QRS complexes duration in V1+ V2+ V3 / V4+ V6+ V6 is ≥ than 1.2;
  (1-c) Prolongation in the ascending ramp of S wave from V1 to V3, in absence of CRBBB (prolonged S wave upstroke): distance from the nadir of S wave up to the isoelectric line ≥55 ms[1].

1) Buffo Sequeira I, et al. Utility of ECG precordial S-wave duration in diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) in pediatric patients canadian. Cardiovascular Congress 2003 Abstrac 504.

Dear Andres,

I don't know how many times you tricked me with a Chagas. If it is already ruled out I would say the ECG features of this young man fit arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). If image tests showed dilated or regional dilatition of the RV wall further investigations (gene screening and molecular pathology evaluation of cell junctional structure) are recommended since it is a rare inherited condition. If image tests showed a RV hypertrophy rather than a wall thining, that would be another story...

ECG info could be limited. It is wise that treatment strategy should be based on the correct clinical Dx.

Thanks much for sharing and I look forward to hearing from you and ARVC/C experts opinions.

Li Zhang from USA

Estimado Andrés:

No sé cuántas veces Usted me engañó con un ECG de Chagas. Si ya está descartado yo diría que el ECG de este joven tiene características y se adapta a una miocardiopatía arritmogénica del ventrículo derecho / displasia (MAVD / D). Si las pruebas de imagen mostraron dilatación o dilatación regional de la pared del VD nuevas investigaciones (detección de genes y la evaluación de la patología molecular de la estructura de la unión celular) se recomiendan, ya que es una rara enfermedad hereditaria. Si las pruebas de imagen mostraron una hipertrofia del VD en lugar de un adelgazamiento de la pared, eso sería otra historia ...

La información del ECG podría ser limitada. Es aconsejable que la estrategia de tratamiento se debe basar en el Dx clínico correcto.

Gracias por compartir y espero con interés escuchar de usted y opiniones de expertos en MAVD / C.Li Zhang

Dear Prof. Andres Riera

The case of 29 yo man could fit with ARVD/C but the role of ECG could be limited until some other exams (ECHO, MRI) will be performed. I think the cause of RV hypertrophy should be determined/excluded in this case.
My best wishes
Peter Kukla from Poland

Must exclude ARVD.The broad QRS and notching favor ARVD VT rather than Atrio fascicular tachycardia or aberration.
In addition there is epsilon wave in V2.Needs echo,MRI signal averaged ECG to confirm diagnoses.In case of ambiguities suggest invasive studies including RV angiogram,endocardial voltage mapp and VT induction and possible ablation even though another focus may arise in follow up.Would suggest AICD if he has ARVD/C.

Scheinman, Melvin scheinman@medicine.ucsf.edu

I am pleased to see that all these smart people are nicely interconnected

Guy
Prof, Dr Guy Fontaine, from Paris, France

International Task Force of the European Society of Cardiology and the International Society and Federation of Cardiology criteria for diagnosis of ARVD/C

GROUP	Mayor	Minor
Global and /or regional dysfunction and structural alterations	Sever dilatation and reduction of right ventricular ejection fraction with no (for only mild) left ventricular involvement Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging).	Mild global right ventrucular dilatation and or ejection fraction reduction with normal left ventricle. Mild segmental dilatation of the right ventricle Regional right ventricular hypokinesia.
Tissue characteristics of walls	Fibrofatty replacement of myocardium on endomyocardial biopsy	
ECG depolarization/conduction abnormalities	Epsilon waves or localized prolongation (≥110ms) of the QRS complex in the right precordial leads(V1-V3)	Late potentials seen on signal averaged electrocardiography
ECG repolarization abnormalities		Inverted T waves in right precordial leads (V2-V3) in people >12 years old and in the absence of right bundle branch block.
Arrhythmias		Sustained or nonsustained left bundle branch block type ventricular tachycardia documented ona the electrocardigraphy Holter monitoring , or during exercise testing.
Family history	Familial disease confirmed at necropsy of surgery	Family history of premature sudden deat (<35years) due to suspected ARVD/C Family history (clinical diagnosis based omn present criteria.

Diagnosis of ARVC in probands is made when two mayor criteria or one mayor plus two minors or four minors criteria for different groups are met. According to the proposed revision, the diagnosis of probable ARVD in a first degree family member would be fulfilled by the presence of a single minor criteria from groups 2, 3, 4 and 5

In red color, the positive features of the present case report

1. **Corrado D, Fontaine G, Marcus FI, McKenna WJ, Nava A, Thiene G, Wichter T. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. Study Group on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy of the Working Groups on Myocardial and Pericardial Disease and Arrhythmias of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation. Circulation. 2000 Mar 21;101(11):E101-6.**

ARVD/C: Differential Diagnosis

1. Right Ventricular Outflow Tract (RVOT) ventricular tachycardia with no structural heart disease

2. Brugada syndrome caused by nonstructural heart disease

3. Catecholaminergic ventricular tachycardia with no structural heart disease

4. Myocarditis, in which replacement fibrosis is associated with clusters of adipocytes, which can mimic ARVD, except that the transmural pattern is absent

5. Idiopathic dilated cardiomyopathy with ventricular tachycardia involving the right ventricle and pesenrvation of left ventricular function

6. Sarcoidosis, which can mimic ARVD[1], although the concomitant presence of the two disease has been reported.

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

Classification of cardiomyopathies

The first classifications of cardiomyopathies from 1980 and 1996 described them as heart muscle diseases, with dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), and nonclassifiable cardiomyopathies. Furthermore, the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) classification from 1996 listed among the specific cardiomyopathies inflammatory cardiomyopathy as a new and distinct entity, which was defined histologically as myocarditis in association with cardiac dysfunction. Infectious and autoimmune forms of inflammatory cardiomyopathy were recognized. Viral cardiomyopathy was defined as viral persistence in a dilated heart without ongoing inflammation. If it was accompanied by myocardial inflammation, it was termed inflammatory viral cardiomyopathy (or viral myocarditis with cardiomegaly). This entity was further elucidated in a World Heart Federation consensus meeting in 1999 by quantitative immunohistological criteria (< 14 infiltrating cells/mm(2)) and the etiology by molecular biological methods, e.g., polymerase chain reaction, as viral, bacterial, or autoimmune (= nonmicrobial). The development of molecular genetics, with the discovery of a genetic background in several forms of cardiomyopathies previously alluded to as "of unknown origin", was the origin of a debate on a new classification based on genomics. A genomic/postgenomic classification was postulated taking the underlying gene mutations and the cellular level of expression of encoded proteins into account, thus distinguishing cytoskeleton (cytoskeletalopathies, e.g., DCM or ARVC), sarcomeric (sarcomyopathies as in HCM and RCM) and ion channel (channelopathies, e.g., long or short QT syndrome and Brugada's syndrome) cardiomyopathies. Such a classification of cardiomyopathies was proposed in 2006 by the American Heart Association (AHA), which took the rapid evolution of molecular genetics in cardiology into account. It also introduced several recently described diseases, and is unique in that it incorporated ion channelopathies even without hemodynamic dysfunction as a "primary" cardiomyopathy.

The ESC (European Society of Cardiology) Working Group on Myocardial and Pericardial Diseases has deliberately taken a different approach based on a clinically oriented classification in which heart muscle disorders were grouped according to morphology and function. This obviously remains the clinically most useful approach for the diagnosis and management of patients and families with heart muscle disease. In the ESC position statement published in 2008, cardiomyopathies were defined as myocardial disorders in which the heart muscle is structurally and functionally abnormal, and in which coronary artery disease, hypertension, valvular and congenital heart disease are absent or do not sufficiently explain the observed myocardial abnormality. The aim was to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses. In parallel, a scientific statement on the role of endomyocardial biopsy in the management of cardiovascular disease was published at the end of 2007 making useful recommendations for clinical practice and providing an understanding for the use of endomyocardial biopsy in an individual patient. Taking the classification of cardiomyopathies and the statement on the role of endomyocardial biopsies in different clinical scenarios together, the clinician is now able to identify genetic, autoimmune and viral causative factors by using a thorough and logical approach to reach a diagnosis in patients with familial and nonfamilial forms of the underlying structural heart muscle diseases

1. Pankuweit S, Richter A, Ruppert V, Maisch B. [Classification of cardiomyopathies and indication for endomyocardial biopsy revisited] Herz. 2009 Feb;34(1):55-62.

PROPOSAL FOR NEW CLASSIFICATION OF CARDIOMYOPATHIES

Currently, cardiomyopathies are classified by dominant pathophysiology, or when possible, by etiological/pathogenic factors.

1) Dilated. (DCM), sarcomyopathies
2) Hypertrophic. (HCM) sarcomyopathies ,
3) Restrictive.
4) Arrhythmogenic RV dysplasia/cardiomyopathies(ARVC), .
5) Nonclassifiable cardiomyopathies
6) Specific.
7) Ion channel diseases: should they be considered as cardiomyopathies? channelopathies, e.g., long or short QT syndrome and Brugada's syndrome) cardiomyopathies.

Fontaine Classification of ARVD/C[1]

1) Arrhytmogenic Right Ventricular Dysplasia
2) Biventricular Dysplasia
3) Right Ventricular Dysplasia without Arrhythmia
   - Quiescent Form
   - Right Ventricular Dysplasia with congestive heart failure
4) Arrhytmogenic Right Ventricular Dysplasia with Superimposed Myocarditis
   - Quiescent Form
   - Hyper acute Form
   - Acute Form
   - Chronic Form
   - Chronic Active Form.
5) Naxos disease
6) Israelian Desmoplakin-Recessive Right Ventricular Dysplasia
7) Venetian Desmoplakin-Dominant Right Ventricular Dysplasia
8) Ul´s Anomaly
9) Arrhytmogenic Right Ventricular Dysplasia Mimicking Ul´s Anomaly
10) Biventricular Spongy Dysplasia
11) Catecholaminergic Ventricular Tachycardias
12) Brugada Syndrome(I didn't understand dear Prof. Fontaine. Why do you included this entity inside dysphasia's? Could you teach to us? Thank in advance Andrés.)
13) Right Ventricular Outflow Tract Tachycardia
14) Fat Dissociation Syndrome
15) Borderline Syndromes
   - Mitral valve prolapse
   - Carvajal-Huerta disease
   - Desmoplakin arrhytmogenic LV cardiomyopathy

1. Fontaine Guy and Charron Philippe. Arrhytmogenic Right Ventricular Cardiomyopaties In Cardiac Electrophysiology Zipes DP & Jalife J From Cell to Bedside Fight Edition. 2009. Chapter 64; pp: 689-698.

Chromosomal loci and disease-causing genes in ARVD/C

Pattern of inheritance	Chromosomal locus	Gene mutations
ARVD1(AD)	14q23-q24	Transforming growth factor-β3 (TGF β 3)
ARVD2(AD)	1q42-q43	Cardiac ryanodine receptor (RyR2)
ARVD3(AD)	14q12-q22	?
ARVD4(AD)	2q32.1-q32.3	?
ARVD5(AD)	3p23	Transmembrane 43(TMEM43)
ARVD6(AD)	10p12-p14	?
ARVD7(AD)	10q22	?
Naxos disease (AR)	17q21	Plakoglobin (JUP)
ARVD8(AD)	6p24	Desmoplakin (DSP)
ARVD9(AD)	12q11	Plakophilin-2(PKP2)
ARVD10(AD)	18q12.1	Desmoglein-2(DSG2)
ARVD11(AD)	18q12.1	Desmocollin-2(DSC2)
ARVD12(AD)	17q21	Plakoglobin (JUP)