Young woman elite athlete with syncope consequence of wide QRS complex tachycardia (WCT)

Case report

A 18-year-old Caucasian woman, professional elite athlete of Women's Mixed Martial Arts (MMA), presented to the Emergency Room with a 3 - hour history of palpitations followed by syncope during training. There was no history of previous episodes. She had positive family background of arrhythmia, syncope and sudden cardiac death (SCD) in young first-degree relatives consequence of cardiomyopathy. (Which one?). Her brother referred that in the last 3 month she complained of weakness, foot, ankle and abdominal distension, and excessive urinating at night (nicturia).

Physical examination - signals of hemodynamic instability: hypotension (BP 85/40mmHg), tachycardia (HR 150bpm), tachypnea, diminished level of consciousness, pallor, and diaphoresis. With the patient in the position at 45° was observed signals of marked raise jugular venous pressure (jugular distention) and large positive venous pulse during "a" wave (Cannon "a" wave). The first heart sound had variation in intensity and a third heart sound, with gallop cadence at right side was heard.

Liver palpation: 3 cm below the right costal margin, tenderness, with texture and consistency firm, rounding and painful.

The admission ECG showed a sustained wide QRS complex tachycardia (Figure 1). This event was reverted with electrical cardioversion. Immediately after the event we performed the ECG shown in the Figure 2.

Later we performed transthoracic echocardiogram (TTE), signal-averaged electrocardiogram (SAECG), and cardiac magnetic resonance imaging (MRI). We also requested genetic testing in the patient (proposita) and in her first-degree relatives.

Electrocardiograms were asked in the relatives as well.

Questions:

1. Which is the diagnosis of the event?
2. Which is the ECG diagnosis after the event?
3. Which is the most probable clinical diagnosis?
4. Which is the appropriate approach?

Mulher jovem com síncope, consequência de taquicardia de QRS largo

Reporte de caso

Mulher caucasiana de 18 anos, atleta profissional de elite de Mixed Martial Arts (MMA), apresentou-se ao pronto Socorro com 3 horas de história de palpitações seguida de síncope durante o treinamento. Não havia história de episódios anteriores. Ela tinha antecedentes familiares positivos de arritmia, síncope e morte cardíaca súbita (MCS) em parentes jovens de primeiro grau consequência de cardiomiopatia hereditária (Qual?). Seu irmão referia que no último mês, ela se queixava de fraqueza, pés, tornozelos e abdômen distendidos e excessiva diurese à noite (nicturia). Exame físico: sinais de instabilidade hemodinâmica: hipotensão (PA 85 / 40mmHg), taquicardia (FC 150 bpm), taquipnéia, diminuição do nível de consciência, palidez e sudorese. Com o paciente a um ângulo de 45° foi observado sinais de marcada elevação da pressão venosa jugular (distensão jugular) e uma grande onda "a“ (onda em canhão). A primeira bulha tinha intensidade variável e uma terceira bulha, com cadência galope no lado direito foi ouvida.

Palpação do fígado: 3 cm abaixo da margem costal, de textura e consistência firme, arredondada e doloroso.

O ECG de admissão mostrou uma taquicardia sustentada de complexo QRS largo (Figura 1). O evento foi revertido com cardioversão elétrica. Imediatamente após o evento foi realizado o ECG mostrado na Figura 2.

Posteriormente, foi realizado ecocardiograma transtorácico, ECG de alta resolução (ECGAR) e ressonância magnética cardíaca (RMC). Também foram solicitados testes genéticos no paciente (proposita) e em seus parentes de primeiro grau. Eletrocardiogramas foram solicitados aos parentes também.

Perguntas:

Qual é o diagnóstico do evento?

Qual é o diagnóstico ECG após o evento?

Qual é o diagnóstico clínico mais provável?

Qual é a abordagem adequada?

Figure 1

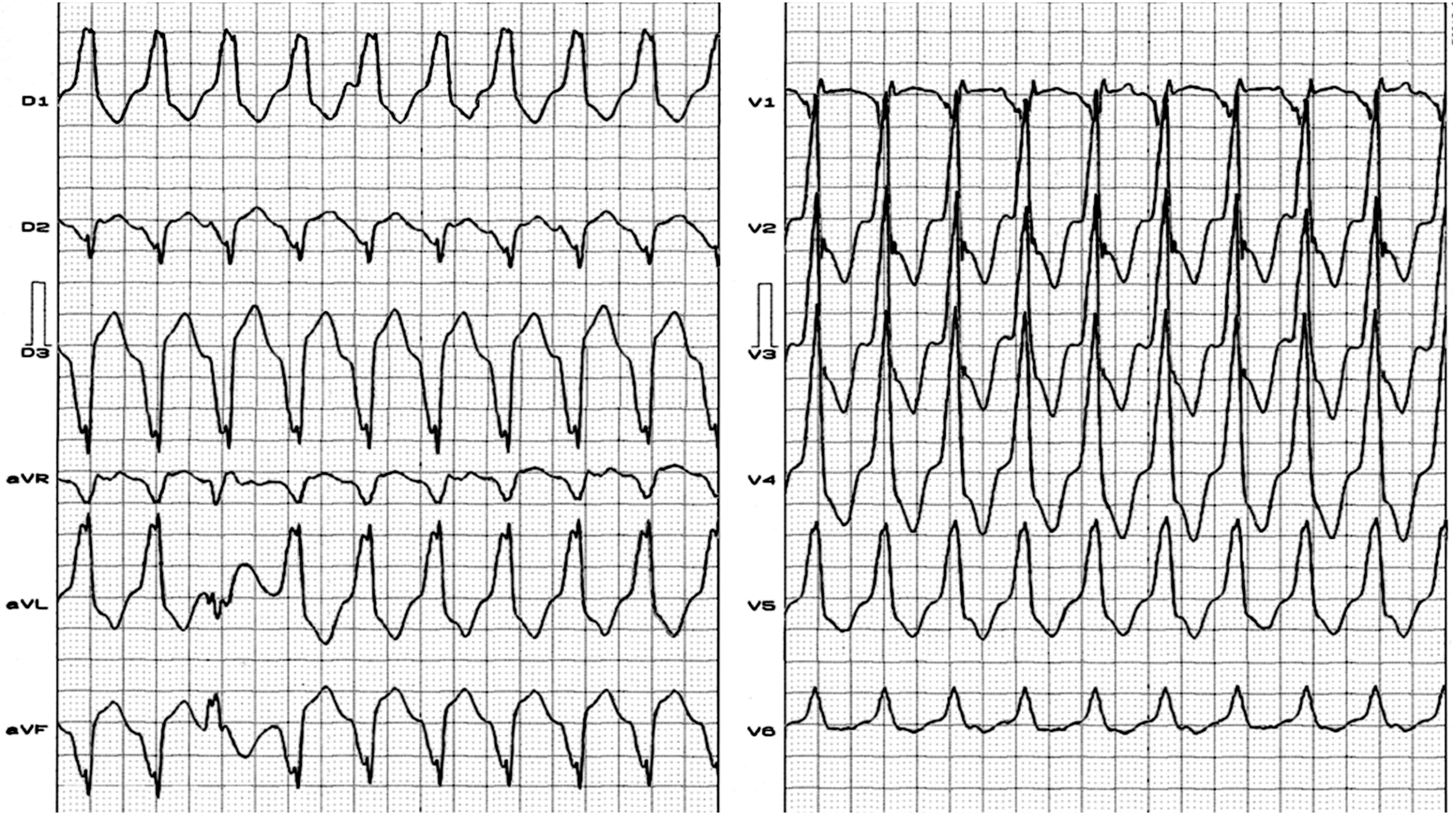
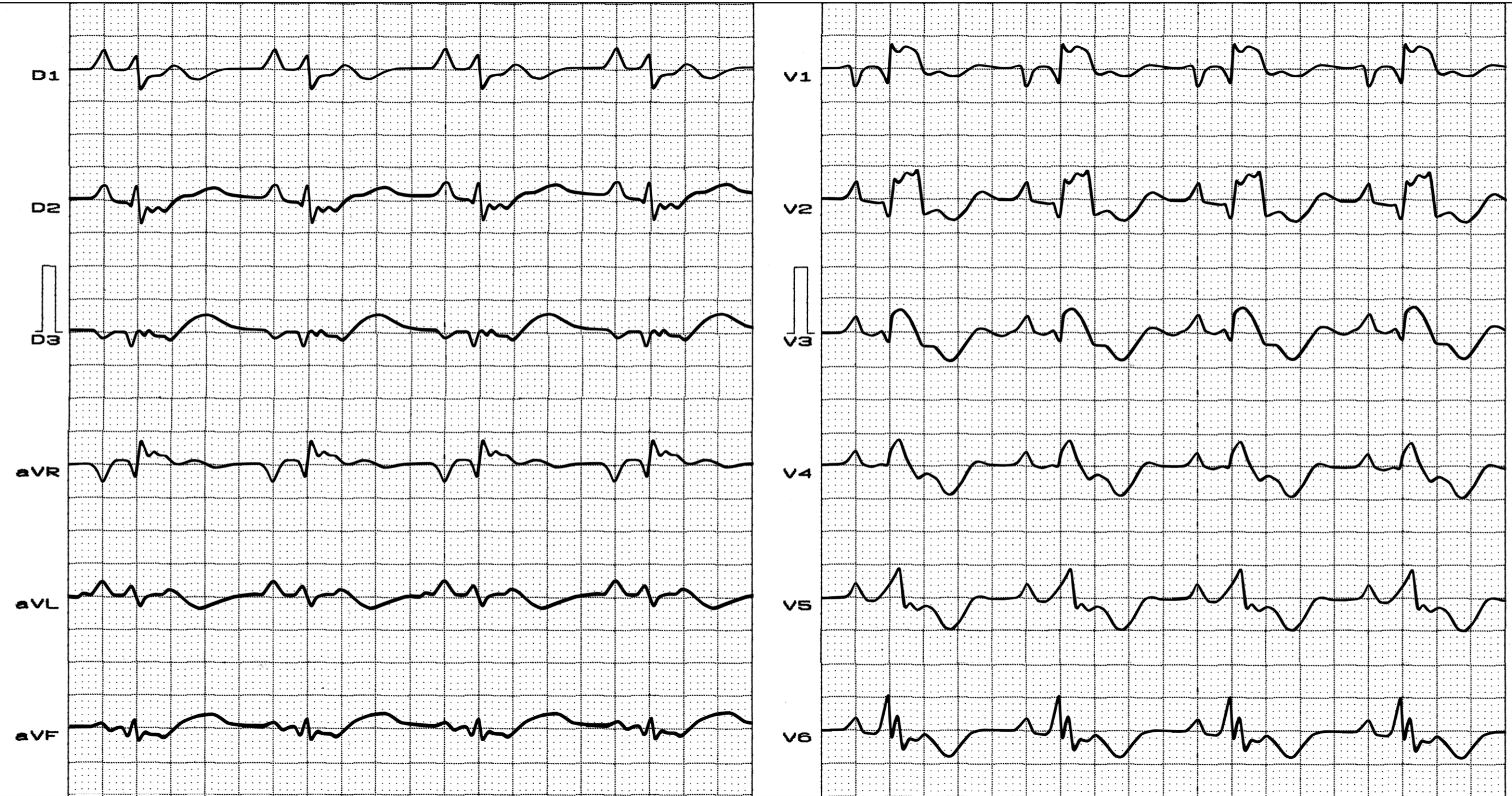
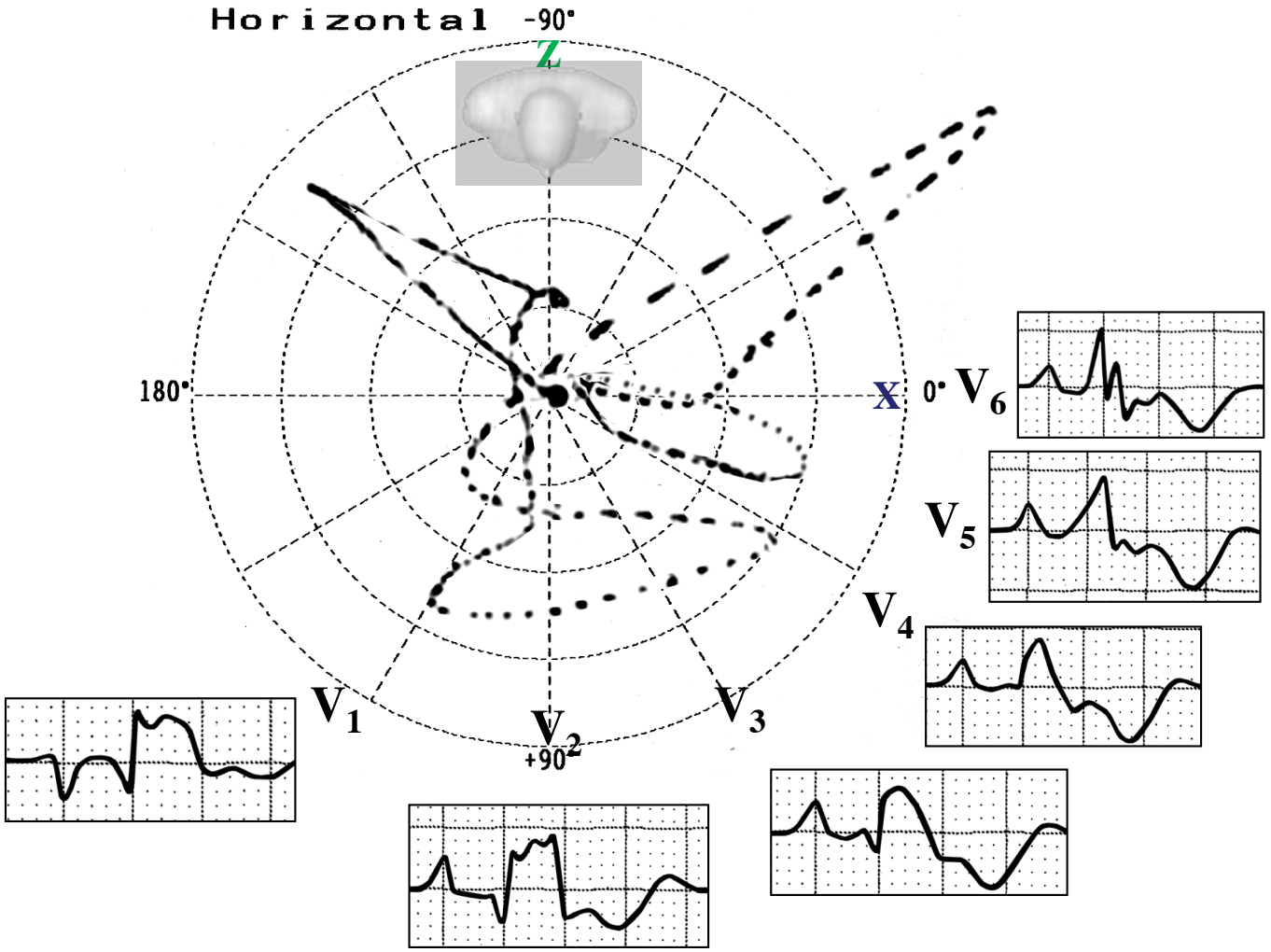


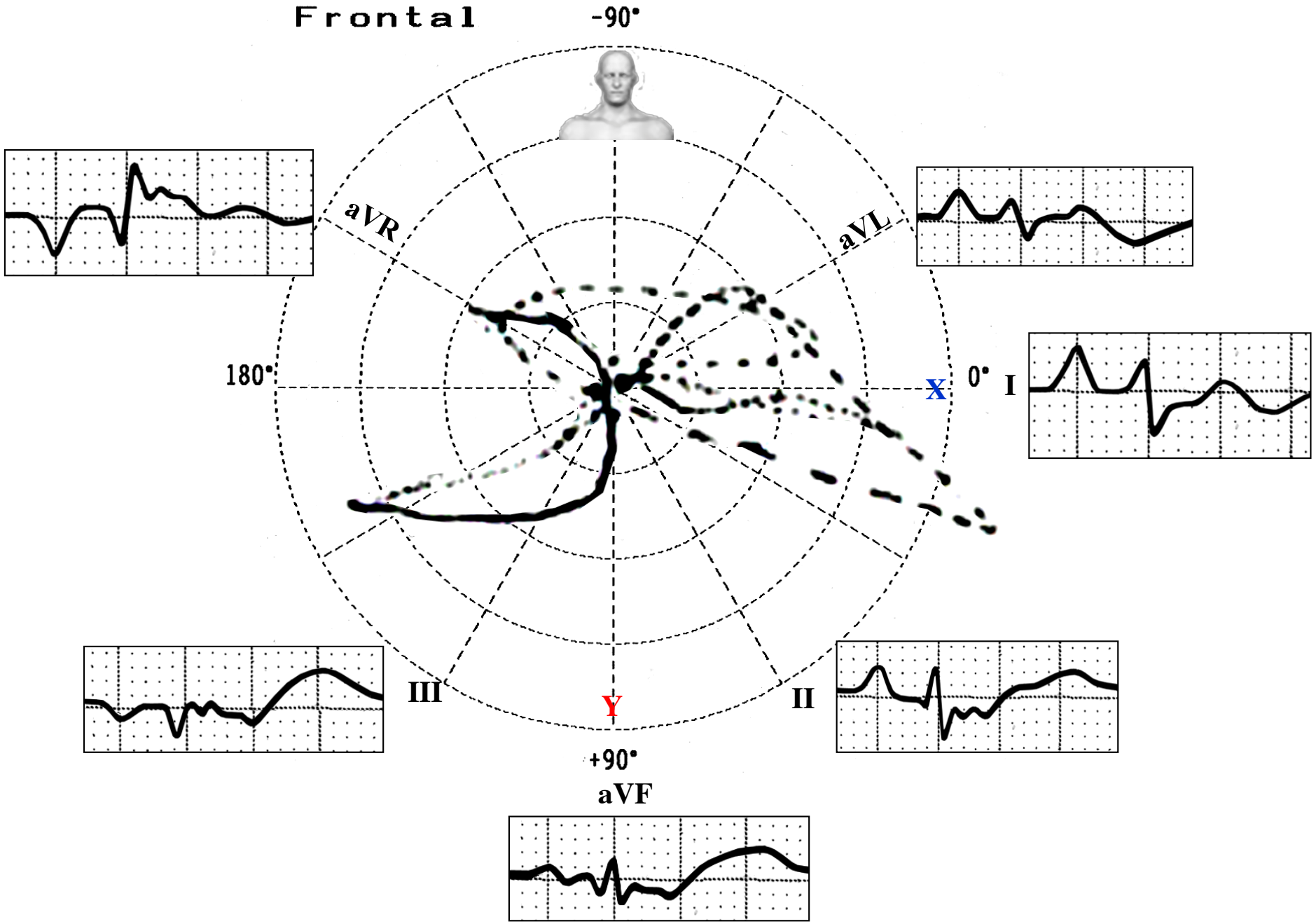
Figure 2 - Name: SFD.; **Sex:** Woman.; **Age:** 18 y.o.; **Race:** Caucasian .; **Weight:** 53 Kg .; Height: **1.52 m.; Biotype:** mesomorphic.



ECG/VCG correlation horizontal plane



ECG/VCG correlation frontal plane



Colleagues opinions

Great case demo dear Andres!
In my two cents the ECG Dx recorded during cardiac event is RV-VT, perhaps an inflow track VT.
With a positive family Hx, I assume Chagas disease is ruled out. As such I would head to the direction of inherited arrhythmias.
In sinus rhythm the 12-lead ECG shows the signs of ARVD, perhaps in the advanced stage. Such suspicion requires additional information to confirm the diagnosis.
If it were in the advanced stage, echo should show the RV abnormalities. I suspect her LV is also involved. If so the EF may be impaired. MRI will provide more details if the family could afford the test.
VT ablation should be considered.
ICD is recommended by following the guidelines if ARVD could be confirmed and if she is indeed a high risk individual after risk stratifications.
Unfortunately she should discontinue her athletic training otherwise it may speed up the disease progression.
Family screening and genetic testing can help identify additional affected members.
Thanks,

Li Zhang, MD
Associate Professor, Jefferson Medical College
Director, Cardiovascular Outcomes Research
Center for Clinical Cardiology
Lankenau Institute for Medical Research
Lankenau Medical Center
R129A, 100 Lancaster Avenue
Wynnewood, PA 19096

Hello.
Arrhythmia: Probably ventricular tachycardia (P waves foe example in V1 without temporal relationship to the QRS).
ECG. P terminal force in V1. Broad QRS, nonspecific intraventricular conduction delay. Q waves in V1-V3, suspicion of delta wave (V5). Strange QRS axis in extremity leads.
Diagnosis: hypertrophic cardiomyopathy (with pre-excitation).
Therapy depends on echo, MRI findings (EF…). Probably ICD.
Best regards
Kjell Nikus

The most likely diagnosis is arrhythmogenic right ventricular dysplasia. She is a young lady that presented with an hemodynamically unstable ventricular tachycardia originating from the basal and inferior portion of right ventricle. Both the ECG and physical exam were consistent with A-V dissociation. The ECG during sinus rhythm shows right atrial enlargement and a right bundle branch block and possibly an Epsilon wave at the end of the QRS. There are Q waves in V1-V3 consistent with involvement of the septum.
Genetic testing will help to identify relatives a risk.
She should avoid strenuous exercise.
Sotalol should be the best antiarrhythmic agent.
She will need an ICD to reduce the risk of sudden death.
Another possibility although very rare is Uhl's anomaly. MRI will confirm differentiate Uhl's anomaly from ARVD.

Muchas gracias,

Thank you,
Mario Gonzalez MD
Gonzalez@hmc.psu.edu
Penn State Hershey Heart and Vascular Institute
500 University Drive
Hershey, PA 17033 USA

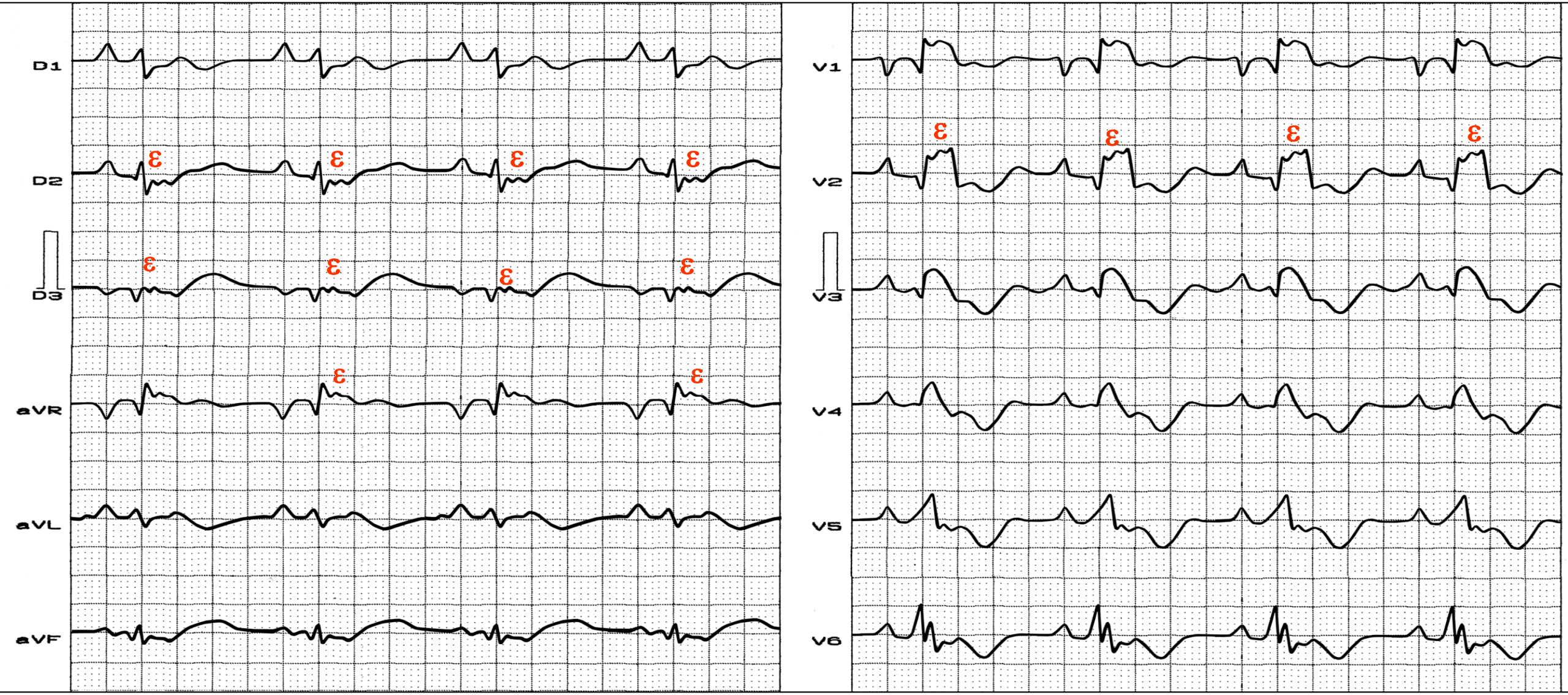
Final Comments

Andrés Ricardo Pérez-Riera M.D.Ph.D.[1]; Luiz Carlos de Abreu P.h.D.[2]; & Raimundo Barbosa-Barros M.D[3].

https://ekgvcg.wordpress.com/

1. Post-Graduates Advisor at Design of Studies and Scientific Writing Laboratory in the ABC Faculty of Medicine - ABC Foundation - Santo André – São Paulo – Brazil
2. Visiting Scientist at Program in Molecular and Integrative Physiological Sciences (MIPS), Department of Environmental Health | Harvard T.H. Chan School of Public Health.
3. Chief of the Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes. Fortaleza - Brazil

Name: SFD; **Sex:** F;**Age:** 18 y/o; **Race:** white; **Weight:** 53 Kg; **Height:** 1.52 m; **Biotype:** Mesomorphic



Clinical diagnosis: Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia. Severe right heart failure with left ventricular involvement
ECG diagnosis: sinus rhythm, HR: 60 bpm; **P wave:** SAP near +10º, voltage: 3 mm, duration: 130 ms; negative deep final polarity in V1 and high positive in V2, qR patern in V1 and V2: biatrial enlargement? or right ventricular mega enlargement? QRSd: 230 ms (CRBBB); **ε** waves are observed in inferior leads and aVR and right precordials.

The epsilon (ε) wave clinical characterization and electrophysiological significance

I. **Other denominations (synonymous)** Epsilon **(ε)** potentials (**Peters 2007**), ventricular post-excitation waves (**Maia 1991**), post excitation **ε** waves (**Okano 1995**) and with the eponymous Fontaine wave (**Fontaine 1977**). "Fontaine discovered and named the **ε** waves. He chose the **ε** because it follows delta (δ), in the Greek alphabet and is the mathematical symbol for smallness" (**Hurst 1998**). In ≈ 30% of the most severe cases of arrhythmogenic right ventricular cardiomyopathy /dysplasia (ARVD/C), this deflection may be observed in the ECG, in most of cases located after the J point on ST segment. It is a late depolarization of right ventricular fibers of right ventricular free wall (dysplasic triangle) seen mainly in V_1-V_4 leads. These oscillations are best seen in the ST segments of leads V_1 and V_2 different from J wave seen in V_5, V_6 and inferior leads which origin is not so clear.

II. **Semantic discussion:** The reason that led this author to choose **ε** name is not clear enough. Could it be because its shape reminded him of the Greek letter ε as suggested by Surawicz e Knilans in their classical book on electrocardiography. If this was the case, it should be stated that the **ε** -like wave is in a horizontal position: The tracing shows in the location of the J point and the beginning of the ST segment, an indentation that reminds of the Greek letter **ε**, however, in a horizontal position. Dr. Fontaine could be considered following the Greek alphabet sequence?: α; β; δ and **ε**? If the additional wave observed in ventricular pre-excitation is located at the beginning of QRS complex is called delta wave (δ), the following additional wave in the Greek enumeration should be called with the following letter: **ε**. Faced with this doubt, I decided to ask the author of this nomenclature, Dr. Fontaine himself, who replied to me thus: "**Dear Dr. Pérez-Riera, Thanks for your documents. The naming of the ECG waves and the reason of their choice is a long story. Dr. Willis Hurst (Hurst 1998) in Circulation has published a summary of these some years ago. I have strongly contributed to this paper as indicated by Dr. Hurst. Best regards**." Dr. Hurst wrote: "**Fontaine discovered and named the ε waves. He chose the ε because it follows δ, in the Greek alphabet and is the mathematical symbol for smallness**. "The term "**ε** " was nice, because it occurs in the Greek alphabet after δ, ; thus, δ, represents the pre-excitation and **ε** the post-excitation phenomenon. In addition, **ε** is also used in mathematics to express a very small phenomenon. It was quite exciting to demonstrate that these late potentials (LPs) located on the free wall of the RV of patients with ARVC/D could be recorded on the surface by SAECG and in some circumstances by increasing the magnification of ECG recording.

To conclude, even with the great respect I feel for Dr. Boris Surawicz and Dr. Timothy Knilans, I have to comment that they made a mistake by thinking that the reason of the name was morphological and not the sequence of the Greek alphabet.

Fontaine discovered and named the ε wave. He chose the ε because it follows δ in the Greek alphabet

Dr Guy Fontaine discovered and named the ε waves
Hopital de la Salpêtrière, Université Pierre et Marie Curie, Paris
Cardiologie, Electrophysiologie cardiaque, Cardiomyopathies

Professor Guy Fontaine was born in Corbeil Essonnes, a suburb of Paris. He is the son of a bank worker who was responsible for the department of international affairs. His primary school was in the city of Bordeaux, in a Loyola institution, and he moved to the secondary school at the Lycte Montesquieu in Bordeaux and then moved to Paris (**Marcus 1998**). During World II, he lived in the city of Orleans at the time his father was a prisoner of war. After the end of World War II he entered second school in Paris.

He works at the Hôpital Jeam Rostand in Ivry, France, where he is co-director of the University Department of Clinical Electrophysiology. He has for the past 35 years, been continuously expanding the frontiers of electrophysiology. In 1976, he published **The Essential of Cardiac Pacing**, which was co-authored by his mentors and colleagues, Profs. Y Grosgogeat and JJ Welti. Together with his talented and thoughtful surgical colleague, Dr G Guiraudon, Fontaine and his colleagues were the first Europeans to perform successful surgical treatment of an accessory pathway. Fontaine and his associate, Dr. Robert Frank, perfected the technique of epicardial mapping, which permitted them to obtain the first recordings of epicardial delayed potentials in humans. His work lead to the discovery of **"arrhytmogenic right ventricular dysplasia"** which resulted in the publication of some of the first clinical descriptions of this conditions.

III. Definition

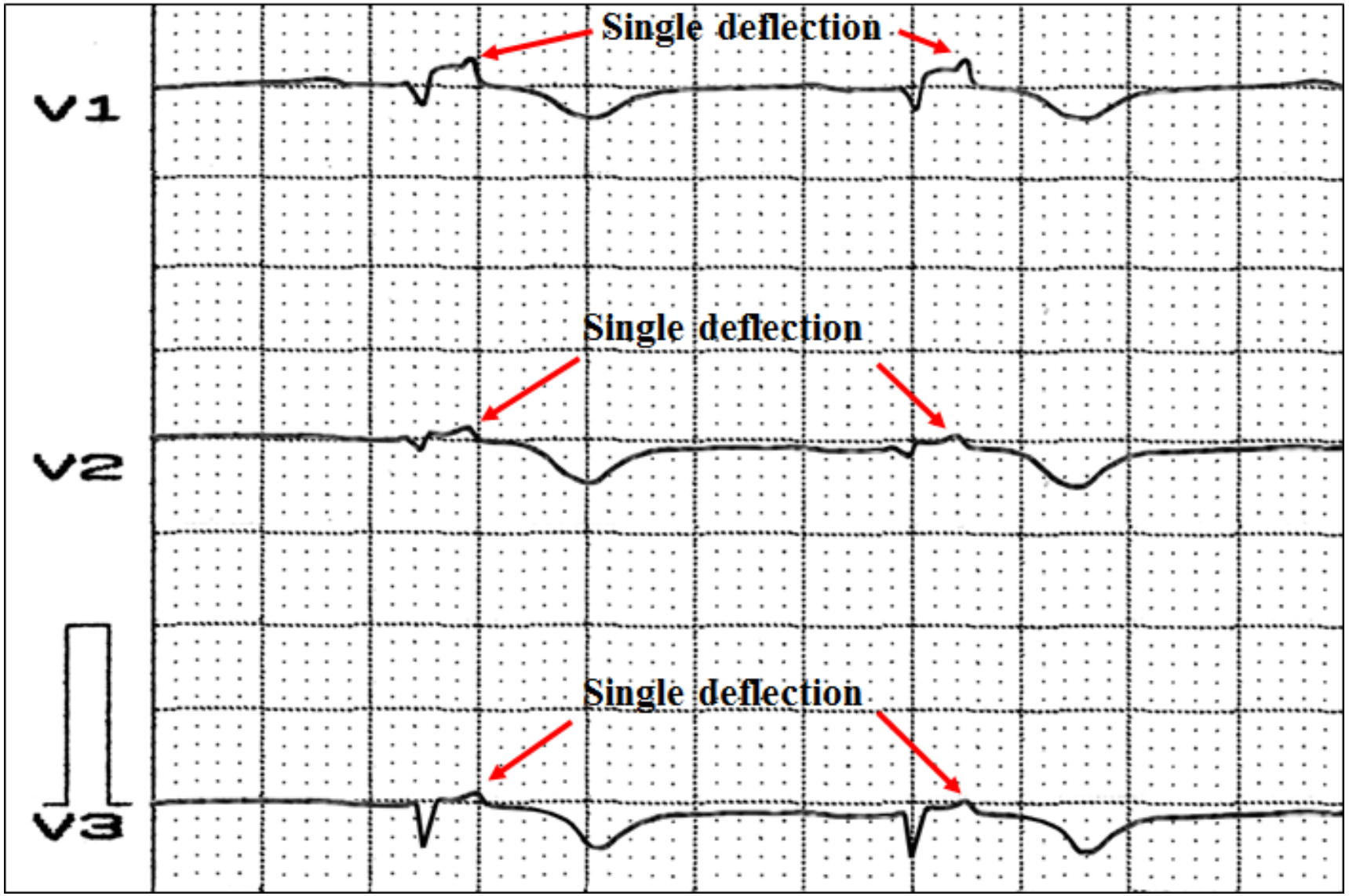
I. **Classical concept:** ε waves have been defined as any potential manifested as a distinct waves of post-excitation with small squiggles, small notches or oscillations (**Khaji 2013**) amplitude that occupy mainly the beginning of the ST segment after the end of the QRS complex (J point) (**Wang 2010**) in other words after the depolarization between the end of the QRS complex and the beginning of the ST segment .**ε** waves are caused by post excitation of the myocytes in the right ventricle free wall due to myocardial scaring. On ECG, they are small notches, oscillations, wiggles, or smoth potential waves in variable quantities (one single deflection, 2, 3 or more). The **ε** wave was defined as wiggler, small spike wave and smooth potential located between the end of the QRS complex and the beginning of the ST segment (**Wang 2009; 2010**):

   I. Small spike waves: The most common type. They are divided into 2 subtypes, upward and downward.
   II. Wiggle waves
   III. Smooth potential waves.

ε waves are late potentials (LPs) that occur in the RV free wall in patients with ARVC/D and rarely in others physiological and pathological scenarios. As LPs 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 **ε** was nice, because it occurs in the Greek alphabet after δ, thus, δ, represents the pre-excitation and **ε** the post-excitation phenomenon. In addition, **ε** is also used in mathematics to express a very small phenomenon.

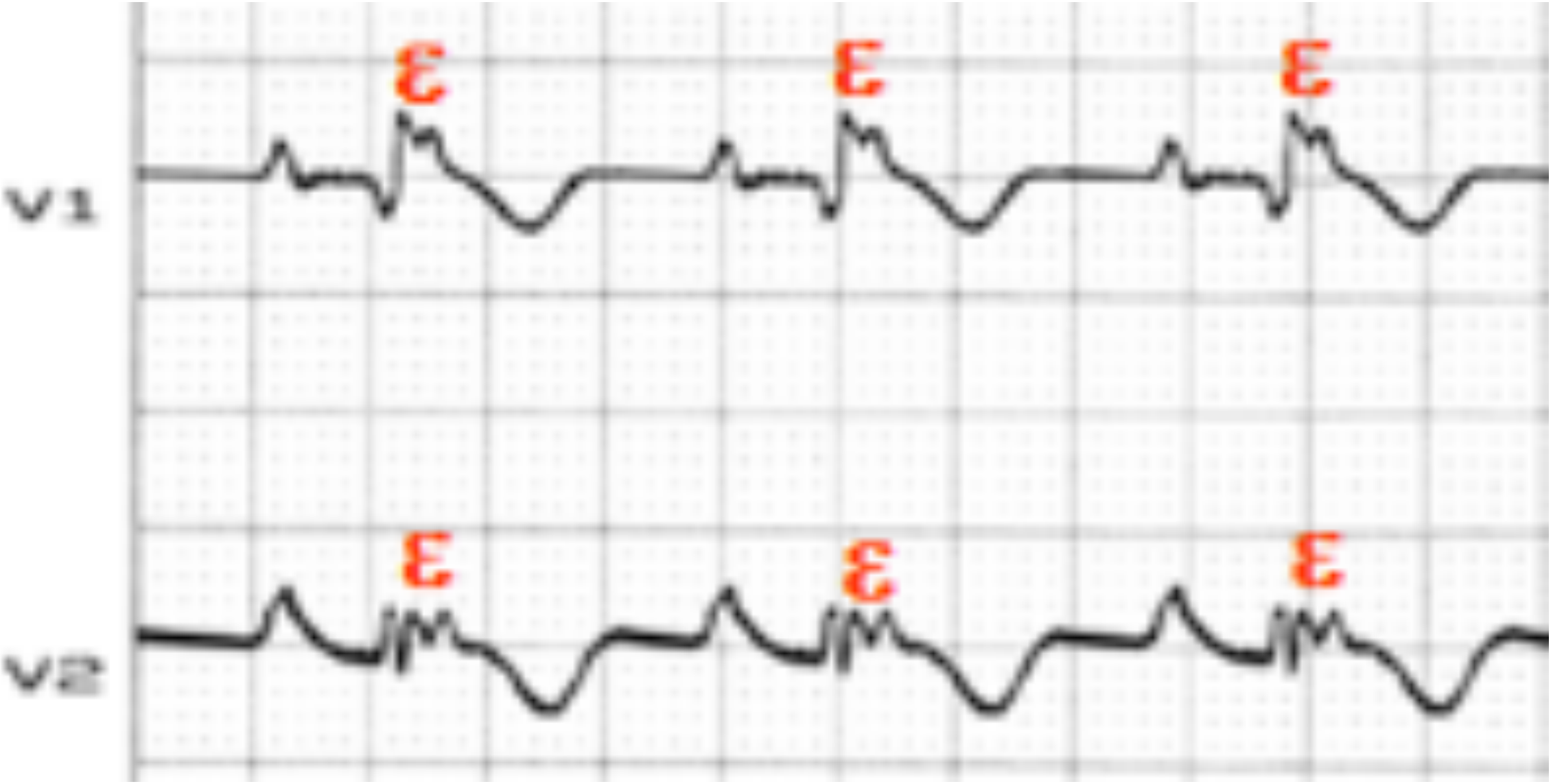
The proximity of the right ventricle to the anterior precordial leads V_1 to V_4 explains why the characteristic ECG abnormalities are most prominent in those lends. The following ECG shows **ε** waves with 1 (single deflection, 2, or multiple waves)

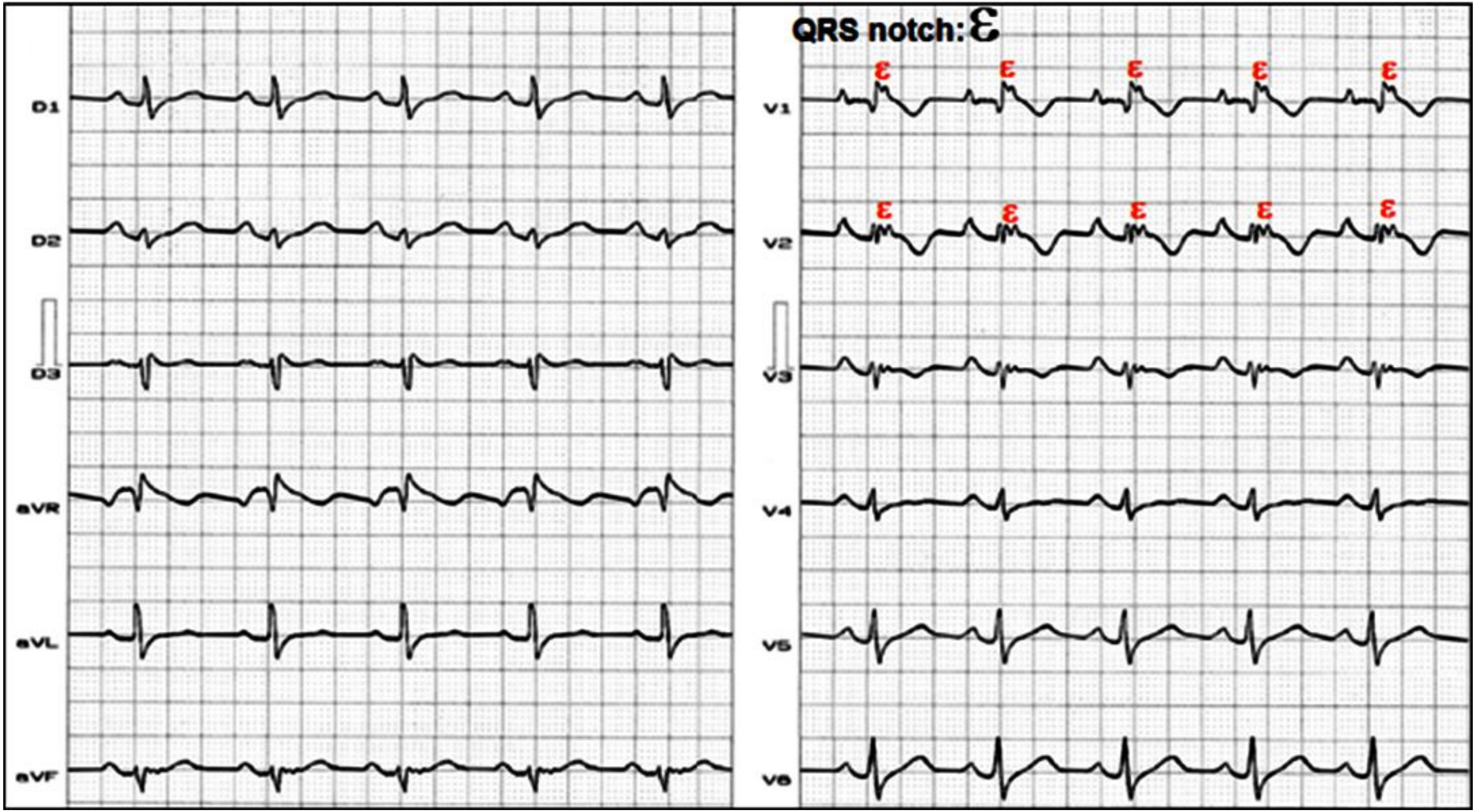
ε waves with a single deflection



We observe prominent upright deflections (red arrows) after the QRS complex in right precordial leads V1–V3 associated with negative T waves. **ε** waves are one of the major depolarization diagnostic criteria of ARVC/D following the last task force (**Marcus 2010**). **ε** waves can be recorded using 12 lead ECG during sinus rhythm, and are useful for establishing a diagnosis of ARVC/D (**Anan 2002**).

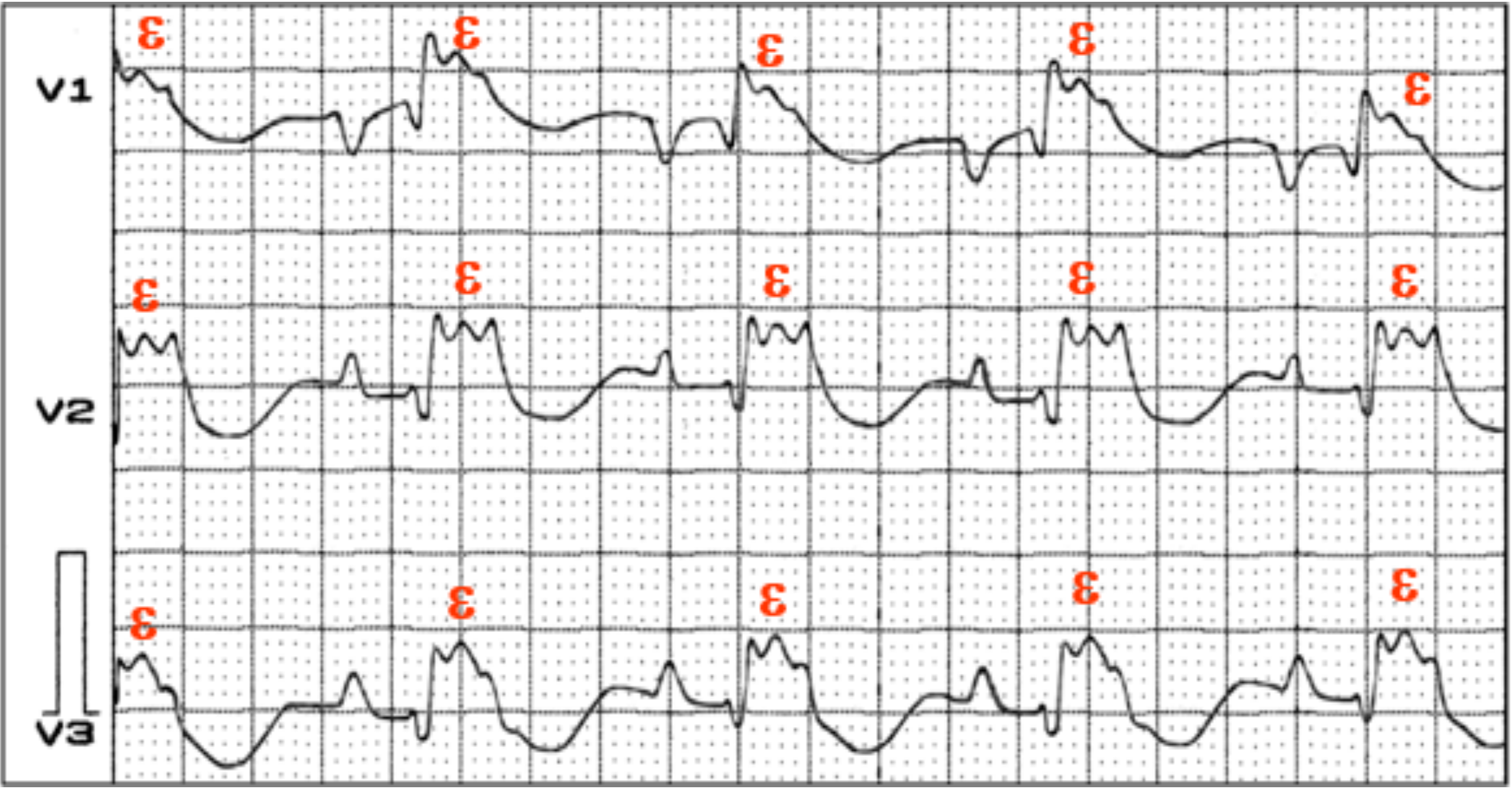
Example of ε waves with two deflections located inside of QRS complex(pre,-top-) fragmented QRS (fQRS)



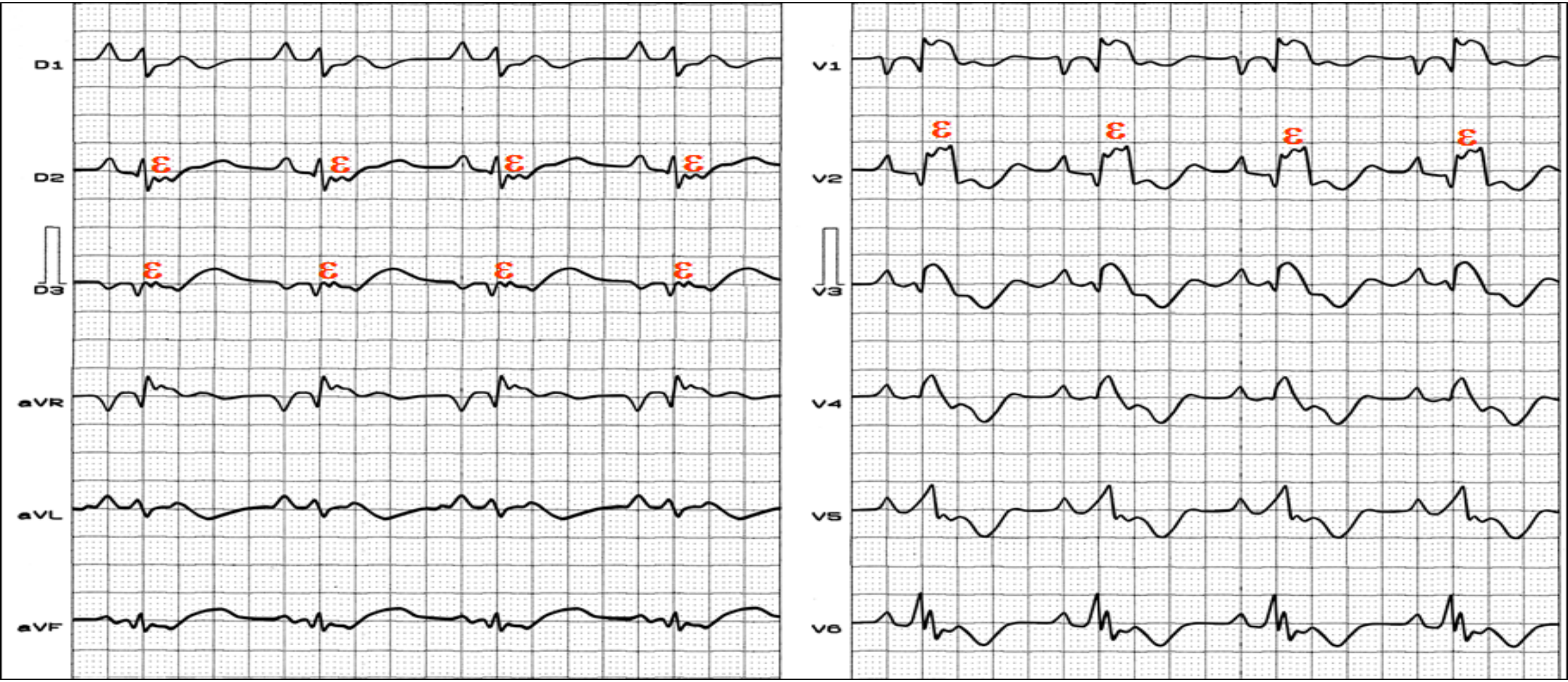


Sinus rhythm, right atrial enlargement, bizarre complete RBBB, terminal notch located in the J point (ε wave). The ε wave could be the result of delayed activation in the RV. It is visible from V1 to V3 and in the frontal plane leads. T wave inversion is observed in V1 to V3, characteristic of ARVC/D.

Example of ε waves with multiple deflections inside of the QRS complex



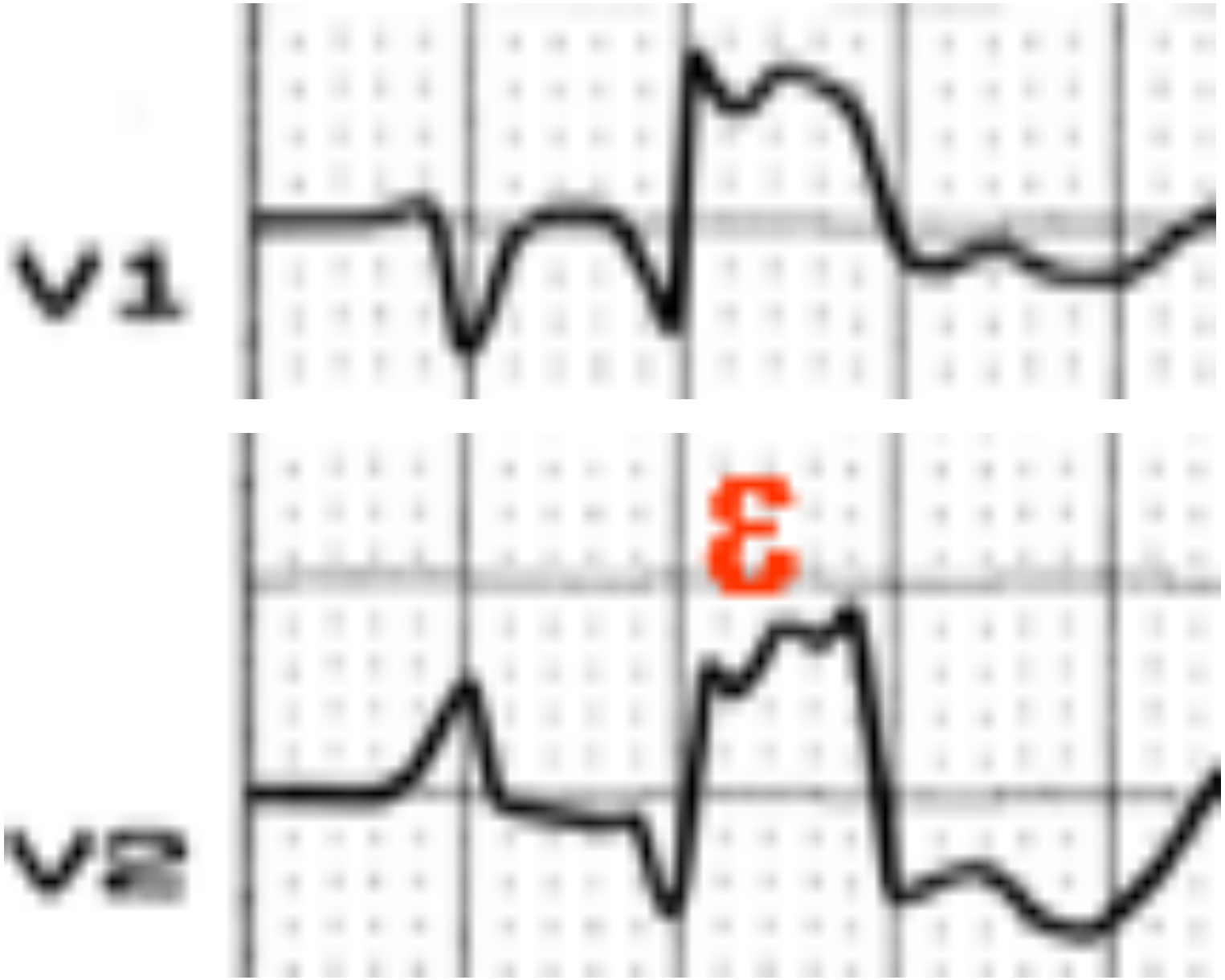
Name: SFD; **Sex:** F; **Age:** 18 y/o; **Race:** Caucasian; **Weight:** 53 Kg; **Height:** 1.52 m; **Biotype:** Normal; **Date:** 05/03/2006



Clinical diagnosis: Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Severe right heart failure.

ECG diagnosis: sinus rhythm, HR: 60 bpm; P wave: SAQRS near 0º, voltage: 3 mm, duration: 130 ms: negative polarity in V1 and positive in V2, q wave in V1 and V2: biatrial enlargement? Or right ventricular mega enlargement? QRSd: 230 ms (CRBBB **ε** waves are observed in numerous leads inside and outside of the QRS.

Example of P-wave morphology with biatrial enlargement (BAE)

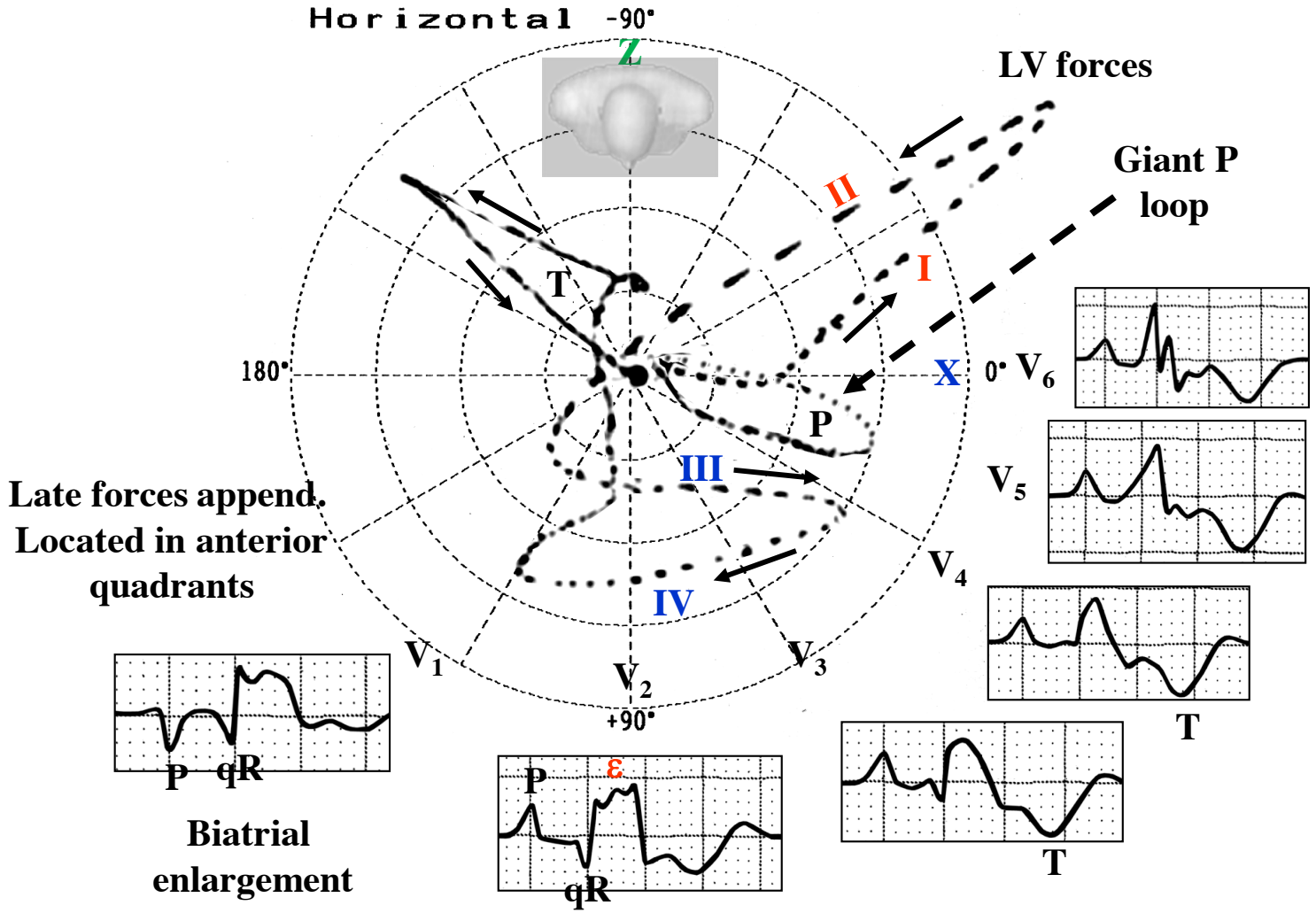


V1: Final slow and deep negative component > 1 mm in depth and 40 ms in duration.

P voltage ≥1.5 mm in V_2

ECG/VCG correlation in the Horizontal Plane

ECG/VCG sequence of a patient carrier of ARVC/D and severe right CHF.

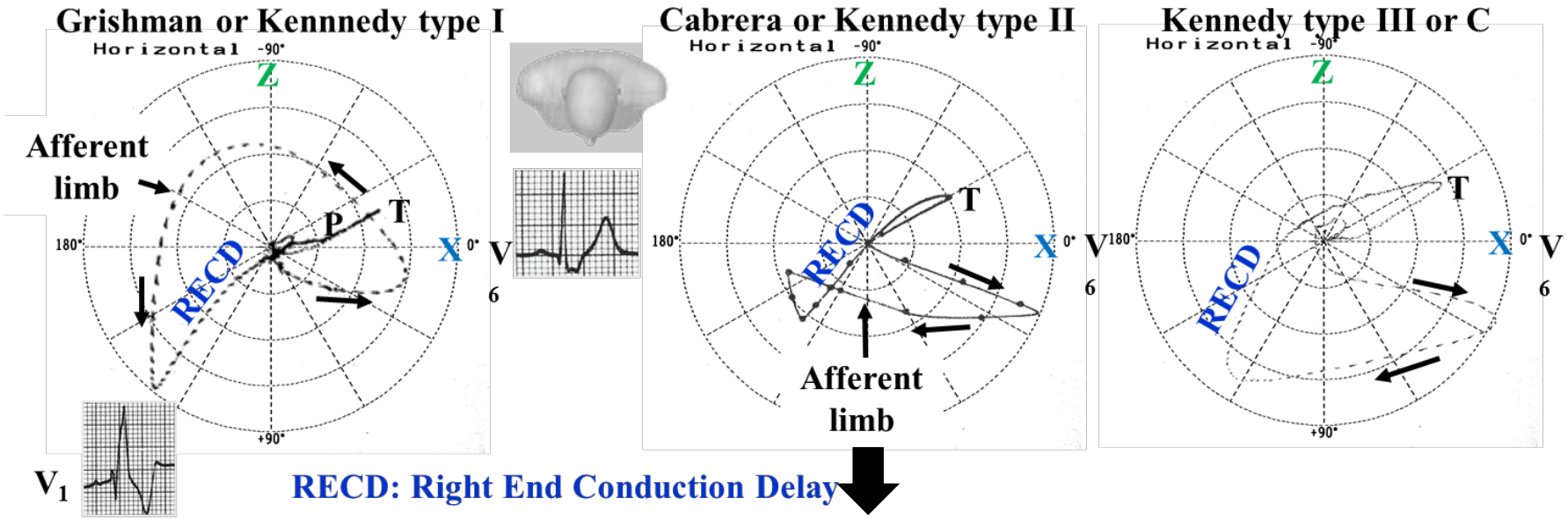


I – Efferent limb: initial delay Anteroseptal fibrosis? or indirect signal of right atrial enlargement? (Sodi-Pallares's signal?) see next slide

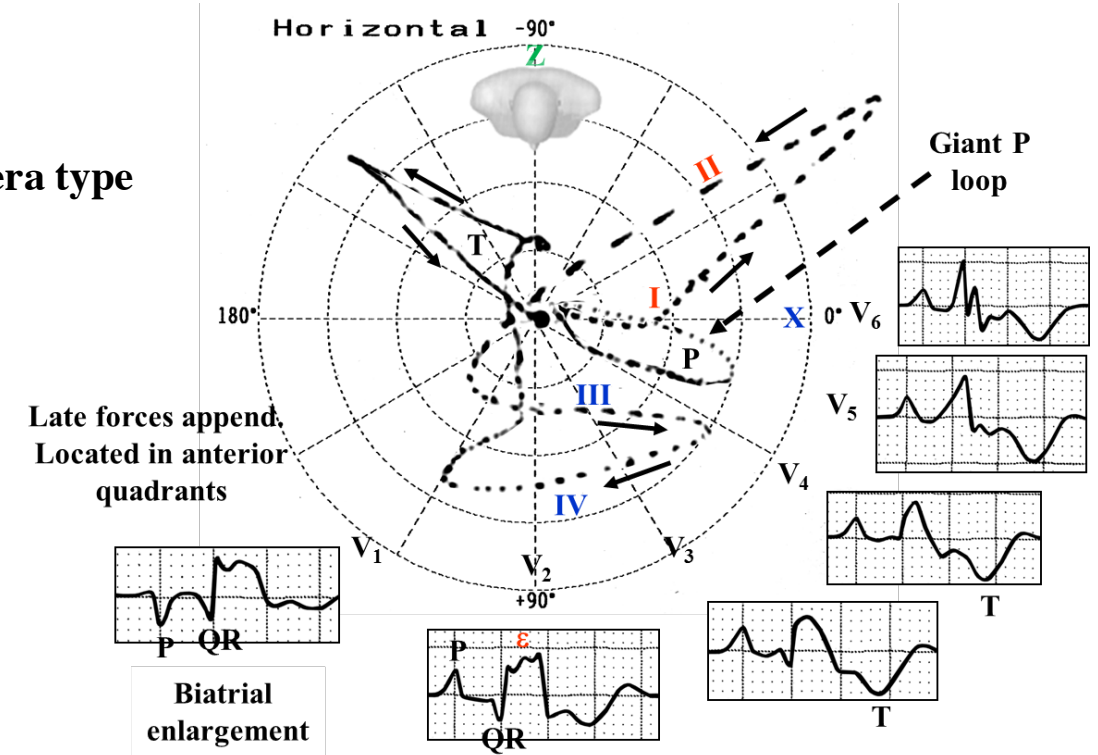
II – Afferent limb

III, IV – Late forces appendix o anterior quadrants: CRBBB. The terminal dots are close together, reflecting end conduction delay of RBBB.

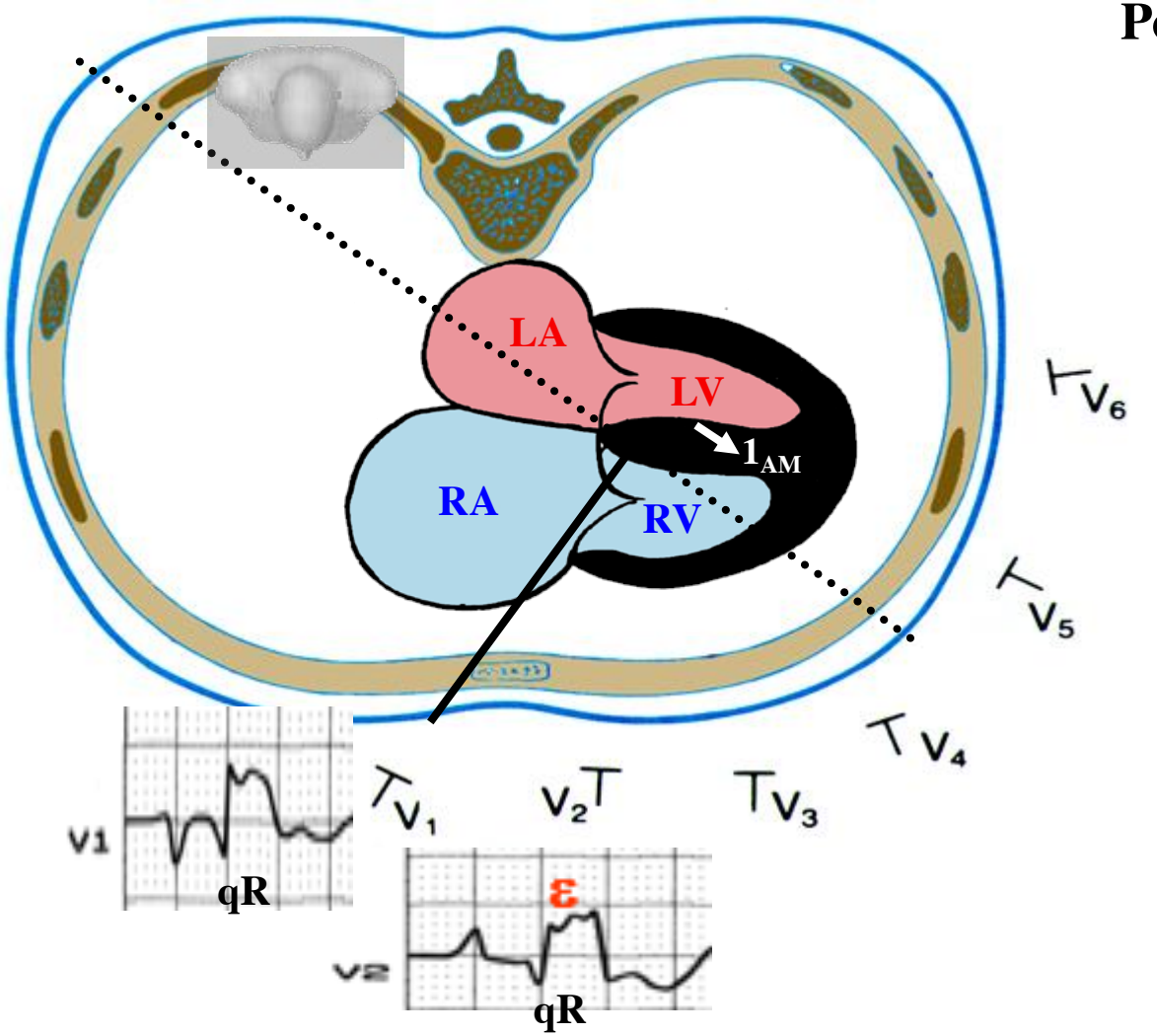
VCG classification of Complete Right Bundle Branch Block in the HP



Bizarre RBBB VCG Cabrera type



Significant dilatation of Right Atrium: Indirect sign of Right Atrial Enlargement(LAE) conditioning qR pattern in V_1 and V_3R (Sodi-Pallares' sign) (Sodi-Pallares 1952)



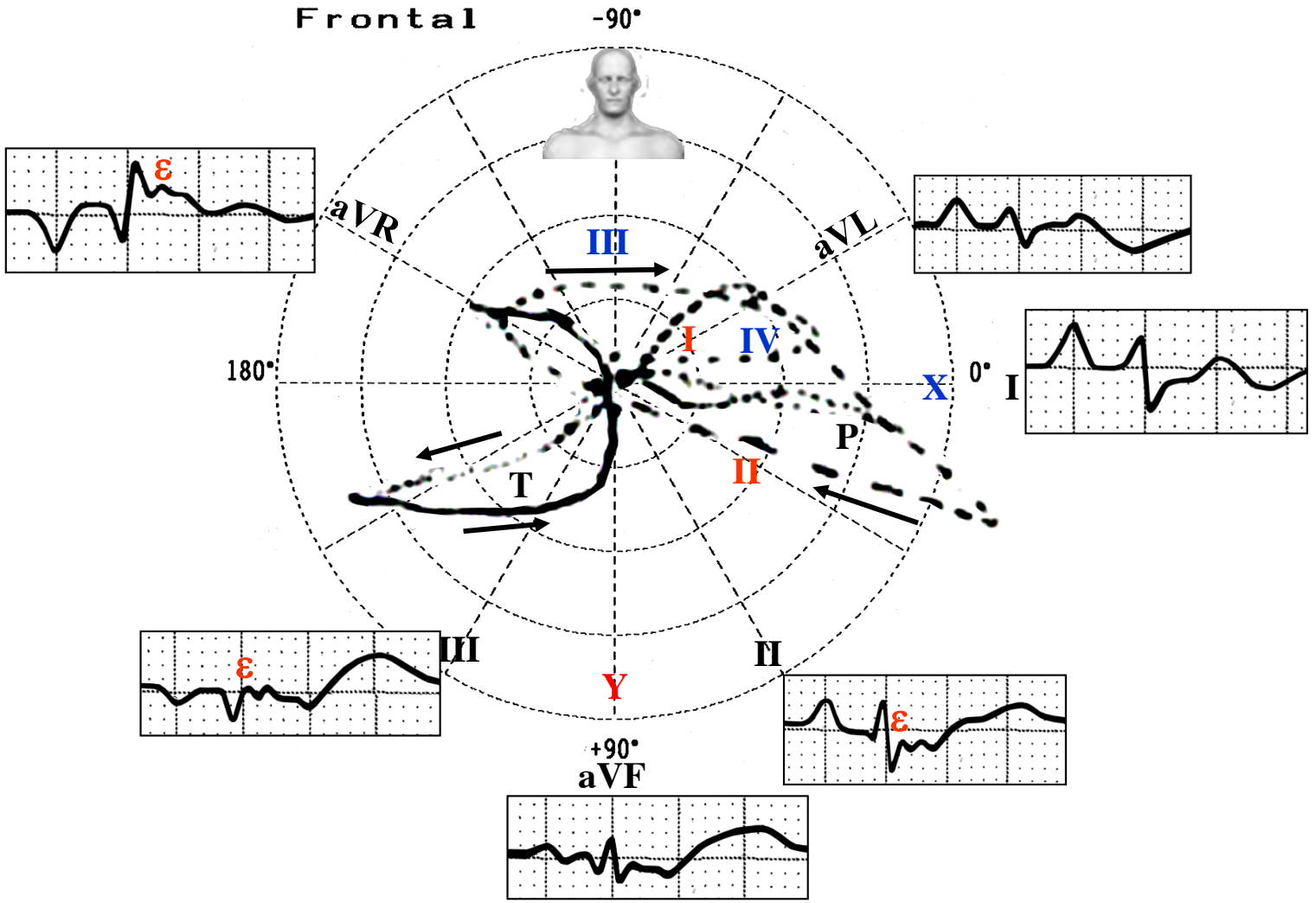
Possible causes of qR pattern in the right precordial leads

1. Systolic RVH with strain pattern: supra-systemic right intraventricular pressure. E.g.: PS with the form of a point or severe (see the previous ECG).
2. Severe dilatation of the right atrium: e.g.: Ebstein's anomaly (Lowe 1968) and tricuspid insufficiency. The volumetric increase of the RA gets it closer to the exploring electrode of V_1, registering negatively initial q wave in these lead, because the electrode records the epicardial morphology of the RA. See figure beside.
3. RBBB associated to anterior myocardial infarction.
4. RBBB with isoelectric initial r wave in V_1
5. Situs inversus: ventricular inversion; inverted septal activation.
6. Pectus excavatum

Outline that explains the indirect sign of RAE: qR pattern in V_1 or V_1-V_2 and V_3R (Sodi-Pallares's sign). The volumetric increase of the RA, gets closer to the exploring electrode V_1, recording initial QRS negativity in this lead, because this electrode records the epicardial morphology of the right atrium.

ECG/VCG correlation frontal plane

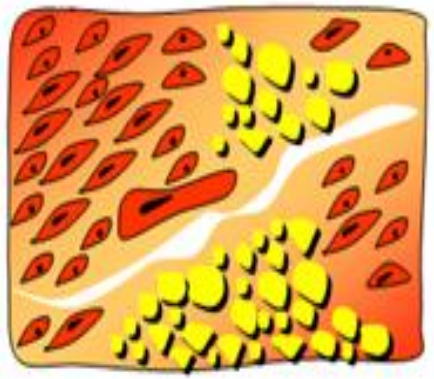
ECG/VCG sequence of a patient carrier of ARVD and severe right CHF.



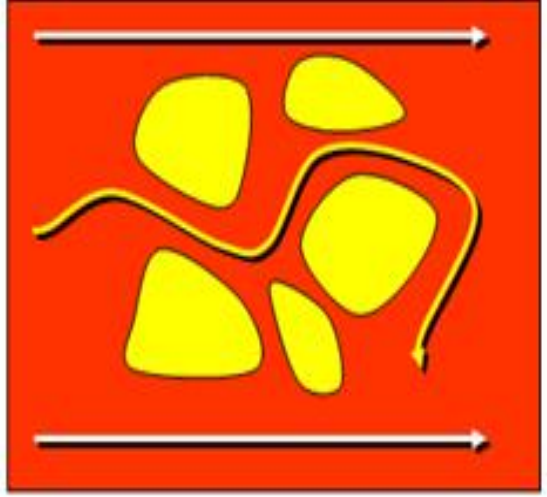
I – Efferent limb **II** – Afferent limb . **III, IV** – Late forces appendix on superior quadrants. The terminal dots are close together, reflecting end conduction delay. **Biatrial enlargement/ Giant P loop. P axis +12°.**

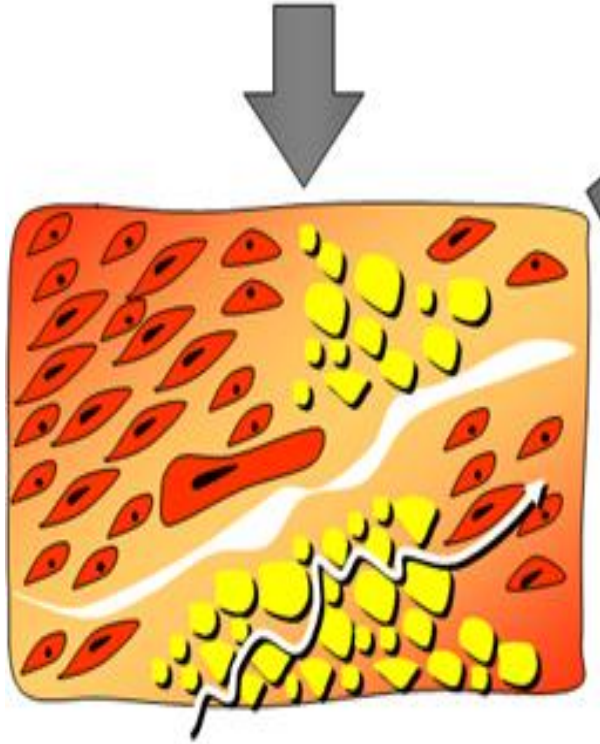
II. **New concept:** in many cases the definition of e waves/ **ε** potentials remains difficult because some authors consider that these waves may be inside of the QRS complex, manifested as QRS fragmentation or QRS notching (**Hoffmayer 2013**). In ARVD/C fragmented QRS (fQRS) has a high diagnostic value similar to **ε** potentials by a highly amplified and modified recording techniques, such as right precordial leads ECG (R-ECG) and Fontaine leads (F-ECG) (**Peters 2008**). fQRS refers to the 'slurs or notches' appeared on the R or S wave or if the total QRS complex had ≥ 4 spikes. fQRS can be registered as a normal variant mainly in seniors endurance athlete heart if it appeared randomly in just a few leads. fQRS presenting in multiple leads is more likely pathologic. The underlying cause is the regional delay in propagation of ventricular depolarization (**Monta 2008**). fQRS is highly prevalent in ARVC/D patients when applied to amplified and modified ECG recording techniques, including the use of the Fontaine Leads System (**Peters 2008; Hurst 1998**). In real world practice, nevertheless, most ECGs available from ARVC/D patients and family members were obtained by using only the standard ECG recording technique. fQRS is easily recognizable from standard ECGs (S-ECG) and they are much more common in ARVC/D patient when compared with control subjects. Among them a notch before the end of R or S wave is characteristic, seen in 51% of ARVC/D vs 26% in controls. In ARVC/D, fQRS is often seen in multiple leads (**Zhang 2014**). Such changes, however, are common in control subjects as well. In the latter, the QRS complex is wider (**Dechering 2013**). fQRS complex, with various morphology, has been described as a diagnostic criterion of ARVC/D. Since fQRS is also prevalent in other types of cardiomyopathies (both ischemic and non-ischemic) (**Das 2006;2010**). fQRS is induced by radiotherapy in patients with breast cancer (**Adar 2015**), and in normal subjects, its use in ARVC/D diagnosis is limited.

The figure of next slide shows the two admitted possibilities of **ε** waves.

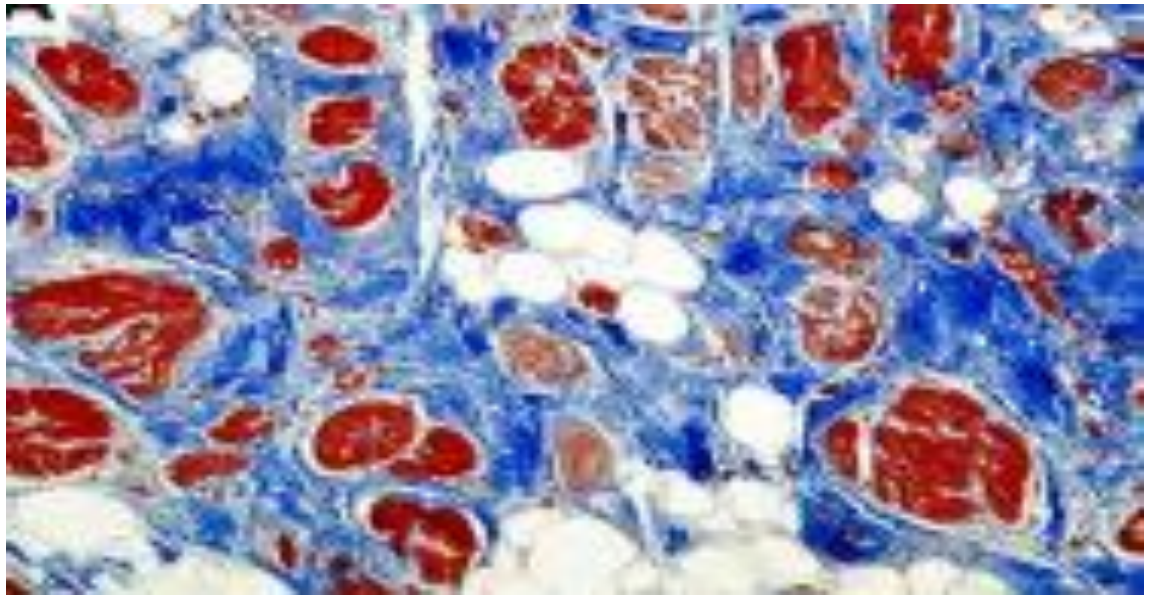


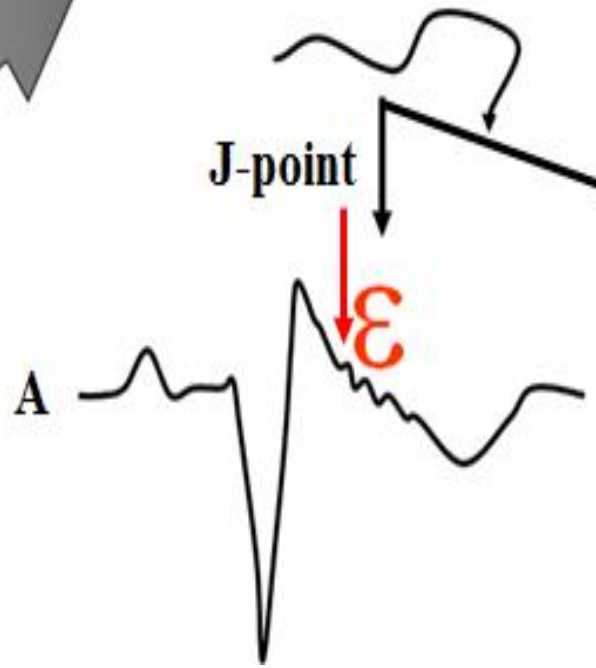
Fibro-fatty replacement of the RV myocardium

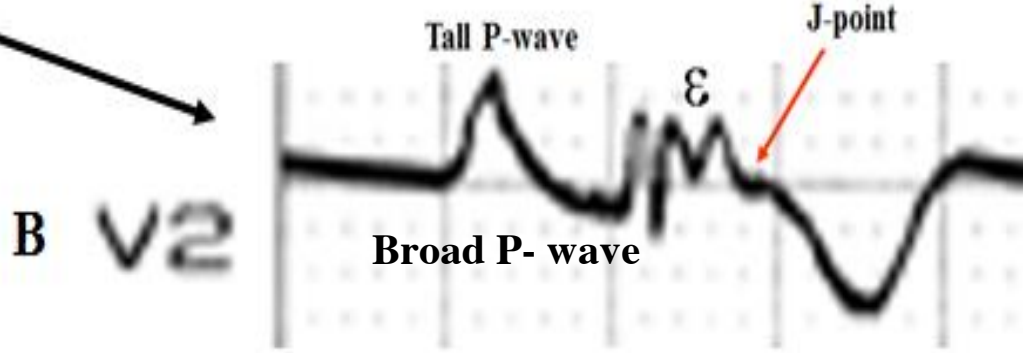




Residual myocytes entrapped within fibrous and fatty tissue







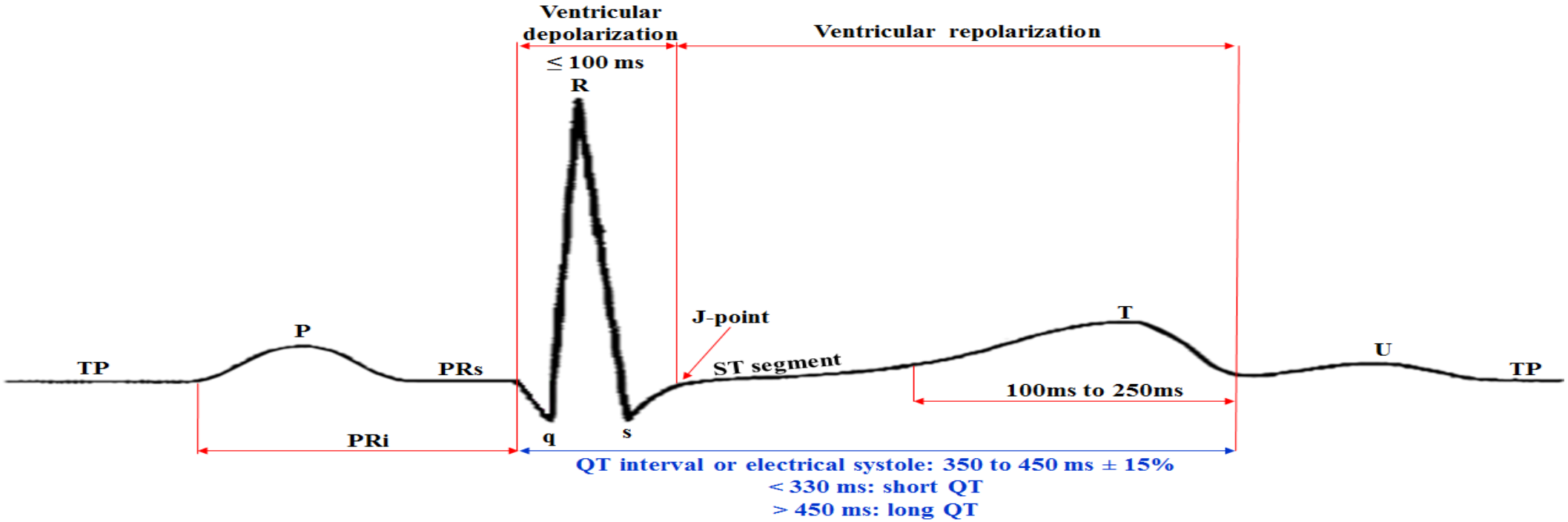
Biatrial enlargement+ bizarre CRBBB + ε waves inside of QRS complex

The figure shows the two admitted possibilities of ε waves location

A. Oscillations registered after J-point at the beginning of ST segment.

B. Oscillations registered inside the QRS complex. In this case, ε waves are indistinguishable of fQRS.

Evidence of slow fractionated conduction is present as **ε** waves. The signal averaged ECG may show exceedingly long and low late potentials (**Marcus 2000**). Tanawuttiwat et al (**Tanawuttiwat 2016**) studding 30 ARVC/D patients underwent endo and epicardial electroanatomical activation mapping in sinus rhythm. The ECGs were classified into 5 patterns: 1. Normal QRS (11 patients); 2. Terminal activation delay (TAD) (3 patients); 3. Incomplete right bundle branch block (IRBBB) (5 patients); 4. **ε** wave (5 patients); 5. Complete RBBB (CRBBB) (6 patients). Timing of local ventricular activation and extent of scar was then correlated with surface QRS. Earliest endocardial and epicardial RV activation occurred on the mid anteroseptal wall in all patients despite CRBB pattern on ECG. Total RV activation times increased from normal QRS to prolonged TAD, IRBBB, **ε** wave, and CRBB, respectively (103.9±5.6, 116.3±6.5, 117.8±2.7, 146.4±16.3, and 154.3±6.3, respectively, $P<0.05$). Total epicardial scar area (cm^2) was similar among the different ECG patterns. Median endocardial scar burden was significantly higher in patients with **ε** waves even compared with patients with CRBBB (34.3 vs.11.3 cm^2). Timing of **ε** wave corresponded to activation of the subtricuspid region in all patients. **ε** waves are often associated with severe conduction delay and extensive endocardial scarring in addition to epicardial disease. The timing of **ε** waves on surface ECG correlated with electrical activation of the sub-tricuspid region. If we considered that **ε** waves are located after the J-point at the beginning of ST segment only, the phenomenon theoretically could not be a depolarization criterion because ST segment occur during the repolarization. The following figure explains depolarization and repolarization intervals on ECG.



I. **QRS complex**: Set of deflections that represent ventricular depolarization

II. **J-point:** Approximate point of convergence between the end of QRS complex and the onset of ST segment. It is considered the point at which the QRS complex finishes and the ST segment begins. The J-point is an essential landmark for measuring QRS duration and ST segment elevation and/or depression. J-point represents approximate the end of depolarization and the beginning of repolarization as determined by the surface ECG. There is an overlap of ≈10 milliseconds (**Mirvis 1982**). In the classical concept, **ε** waves are located after this point. In the embracing concept, the **ε** waves could be inside the QRS complex, consequently have the same meaning as fragmented QRS (fQRS). Okano et al (**Okano 1995**) observed that there is no difference in electrophysiologic findings in patients with or without **ε** waves. Negative potentials are present on the anterior chest in ST-T isopotential, ST-T and QRST isointegral maps in all of the patients. The area of these negative potentials was closely correlated with RV dilatation and dysfunction. It is concluded that **ε** waves are not the direct counterpart of delayed potentials, but the reflection of the peripheral conduction delay, and that primary change seems to play large part of the genesis in negative T waves of ARVC/D.

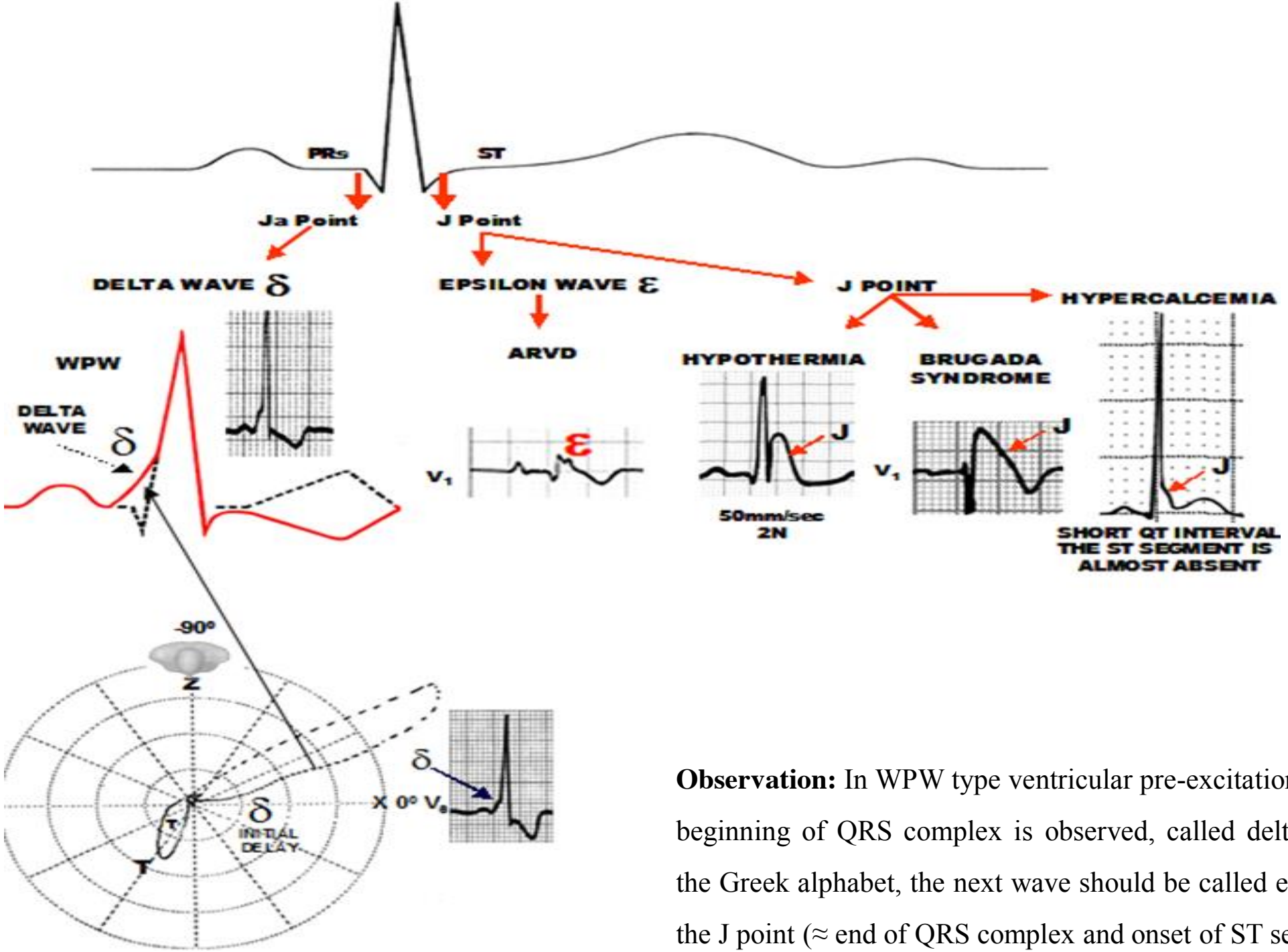
IV. **ST segment:** it stretches from the from the J point (union of ST with the end of QRS complex) until the onset of the T wave, which is usually hard to determine. In electrocardiography, the ST segment connects the QRS complex and the T wave and has a duration of 80 to 120 ms. The ST segment corresponds to phase 2 of action potential (AP).

V. **T wave:** Normal profile of T wave with slow ascending ramp and faster descending ramp. It is coinciding with phase 3 of AP. T duration is 100ms to 250ms (up to five times more than ventricular depolarization).

VI. **QT interval or electric systole:** interval between the first recognizable part of QRS up to the final recognizable area of the T wave (the latter may be hard to determine precisely).The end of T is defined as the return of the T wave to the T-P baseline.

VII. **U wave:** Last, inconstant and smallest deflection of ECG that is recorded immediately after T wave and before the P of the following cycle, of equal polarity to the preceding T, i.e. positive where T also is. Voltage of U is always lower than 50% of the width of the preceding T and generally between 5% and 25% of it. Usually it does not exceed 1 mm, being in average of 0.33 mm. If it reaches 1.5 mm or more, it is considered high, however, there may be normal U waves of up to 2 mm (0.2 mV) in II and from V2 to V4.

The figure of the next slide shows a comparative location and aspect of delta (δ), epsilon (ε), and J waves.

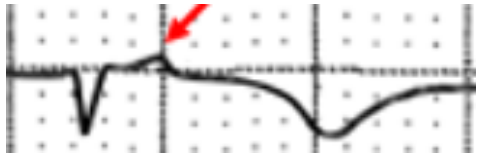


Observation: In WPW type ventricular pre-excitation, a wave located at the beginning of QRS complex is observed, called delta wave (δ). Following the Greek alphabet, the next wave should be called epsilon (ε), located near the J point (≈ end of QRS complex and onset of ST segment).

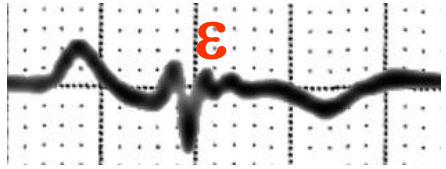
Proposed to classification for epsilon (ε) wave

I) Classification of ε wave by the number of deflections or oscillations

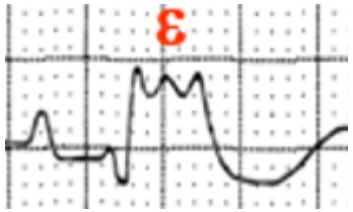
- Single (only one deflection) →



- Two deflections →



- Multiple deflections (termed "pre-, top-, and postsilons") (**Saguner 2014**) →



II) Classification of ε wave by the location related to the J-point

- After the J point: at the beginning of the ST segment
- Preceding the J-point: inside the QRS complex
- Concomitantly before the J-point (within the QRS) and after the J-point

II) Classification of ε wave according to the lead location

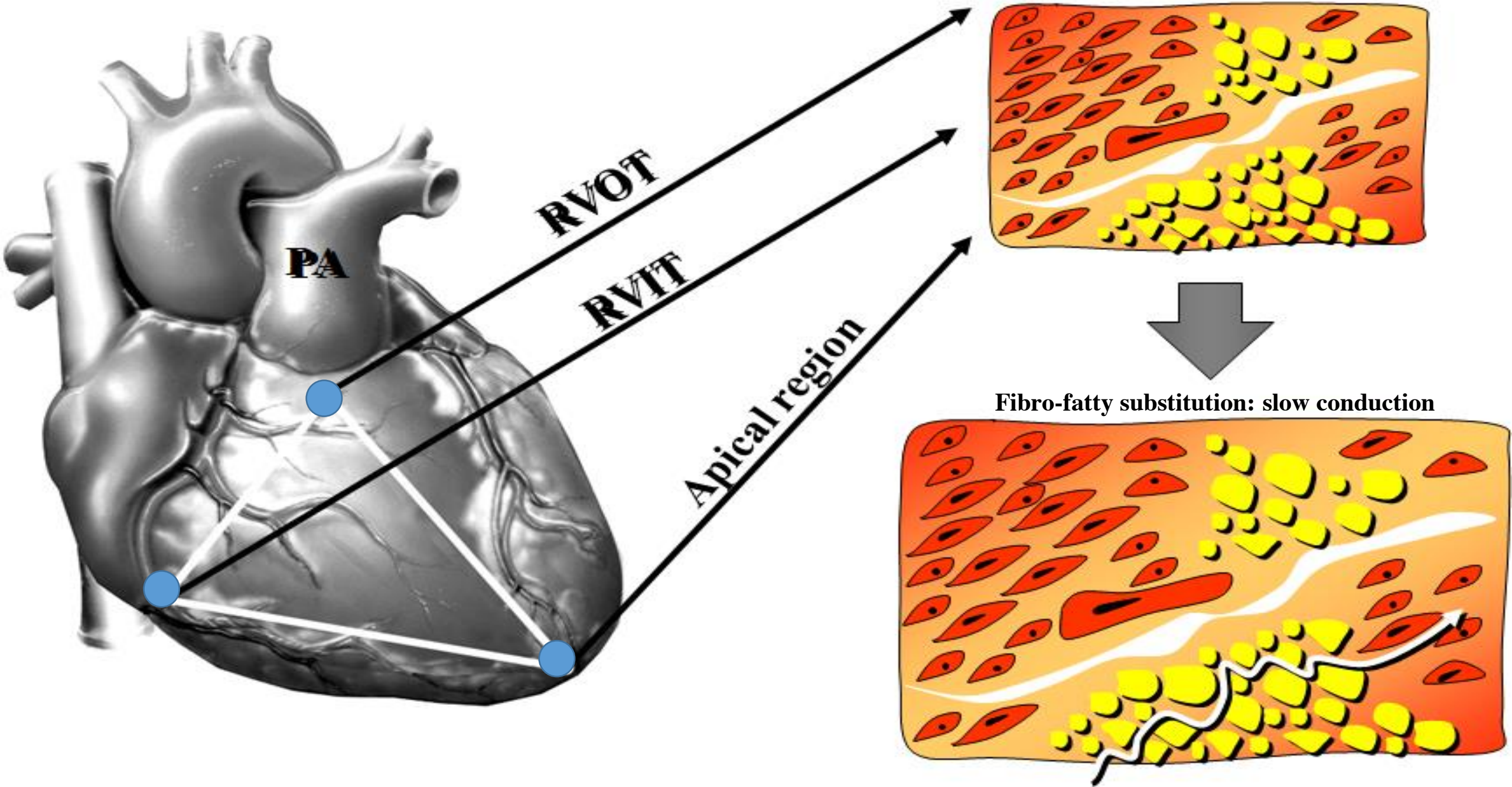
- In the right precordial leads: from **V_1** to **V_4**.
- In the inferior leads: **II, III** and **aVF**.
- In **aVR**.
- Concomitantly in right precordial leads and inferior leads.
- Concomitantly in right precordial, inferior leads, and aVR.

In the classical concept, **ε** wave is located at the end of QRS in the J point or onset of ST segment . **ε** waves have been defined as any potential after the depolarization between the end of the QRS complex and the beginning of the ST segment (**Wang 2010**). Consequently, the phenomena occur temporarily during the repolarization and not during depolarization. Kukla et al (**Kukla 2012**) commented that the definition of **ε** wave remains difficult because within the QRS complex are inscribed notches or deflections called fragmentation of the QRS complex (f-QRS). The fQRS at the beginning, on the top, and at the end of QRS complex (termed "pre-, top-, and postsilons") was proposed as typical extended definition of **ε** potentials.

Meaning of* ε *waves: **ε** waves and other depolarization abnormalities in the right precordial leads are thought to represent delayed activation of the right ventricular outflow tract in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). **ε** waves are a major depolarization criterion that represent in the right precordial leads delayed activation of the right ventricular outflow tract in ARVC/D (**Tanawuttiwat 2016**) but they are an insensitive sign when we use Standard 12-leads ECG (S-ECG). Right precordial **ε** potentials were found in 23% in S-ECG and in 75% in highly amplified and modified recording technique (**Peters 2003**). On the other hand, these waves represent a post-excitation phenomenon: delayed activation of "islands" of viable right ventricular myocytes interspersed in myocardium that does not depolarize normally (**Hurst 1998**).

Origin focus of* ε *waves: The figure of next slide shows the focus location of the **ε** wave on right ventricular free wall in the area called triangle of dysplasia. The angles of this triangle are: the right ventricle outflow track (RVOT), the right ventricle inflow track (RVIT) and the apex of the right ventricle.

Triangle of dysplasia: its angles are RVOT, RVIT and apex of RV.



Leads where ε waves could be observed

ε waves are observed mainly in right precordial leads from V_1 to V_3 however are also found the frontal plane, especially in inferior leads. The duration of the QRS complex may be a bit longer in leads V_1 and V_2 than in leads V_5 and V_6.

Sensitivity ECG for detection of ε waves Frequency in ARVC/D with S-ECG with F-ECG and with R-ECG

ε waves are observed in approximately 15-30% of the most severe cases of ARVC/D when is used the *standard* 12-lead *electrocardiogram* (S-ECG). This percentage increases if we use the ECG with the modified protocol such us Fontaine leads (F-ECG) (**Peters 2014**) and right precordial leads (R-ECG). Although the small wiggles may be seen in the routine ECG, they may be seen more readily in Fontaine leads (F-ECG) (**Gottschalk 2014**).

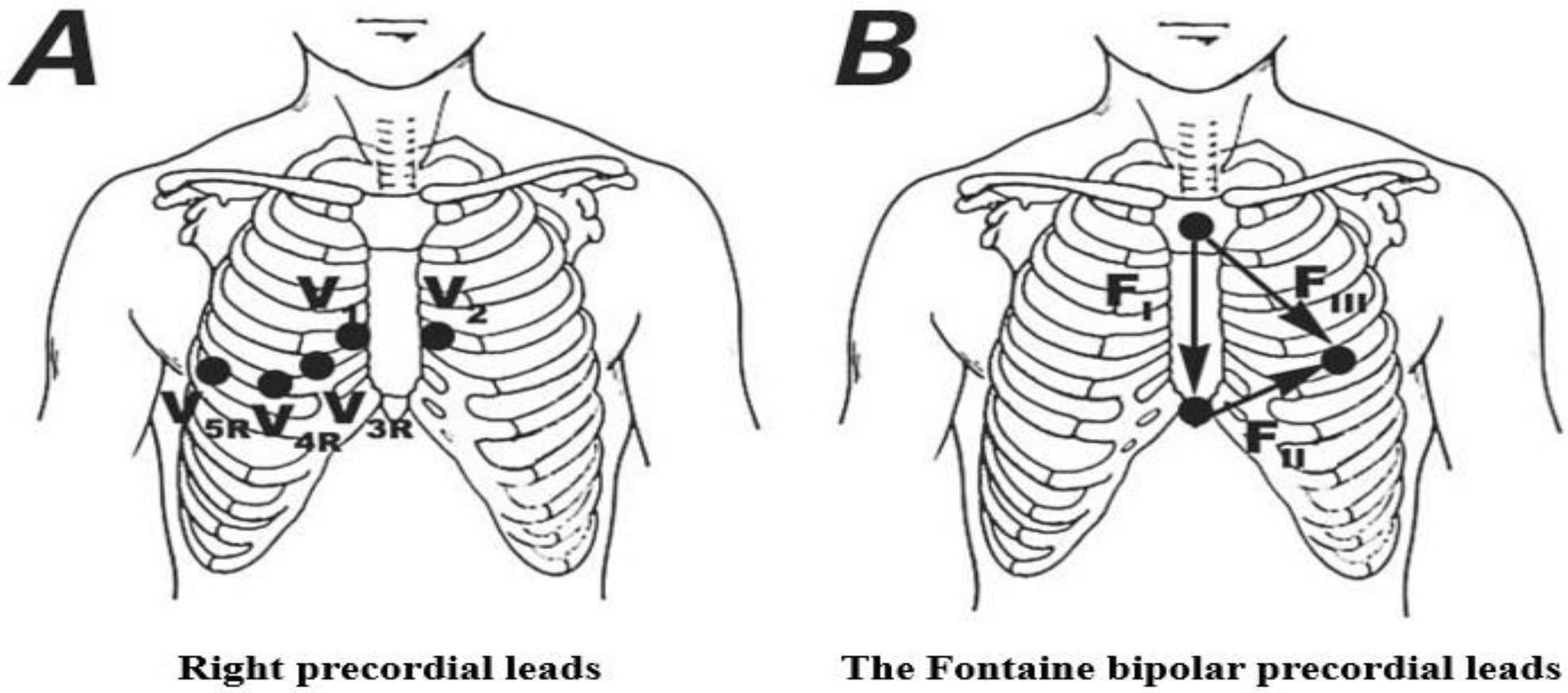
The presence of **ε** waves by the Fontaine lead system provide a high degree of suspicion for the disease (**Chiladakis 2010**). However, **ε** wave is more commonly seen on Signal Averaged Electrocardiography (***SAECG***).

Because these waves are of relatively low voltage and may go undetected by standard electrocardiography (S-ECG) or unnoticed by the interpreter (**Zorio 2005**).

Value of the Fontaine bipolar precordial leads

The tracing should be obtained from I and aVF at double velocity and amplitude, placing the electrode of the left arm on the xiphoid appendix, the one from the right arm on the manubrium sternum, and the one from the left leg on the rib at the fourth or fifth space with the aim of improving the ability to detect Epsilon waves. 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.

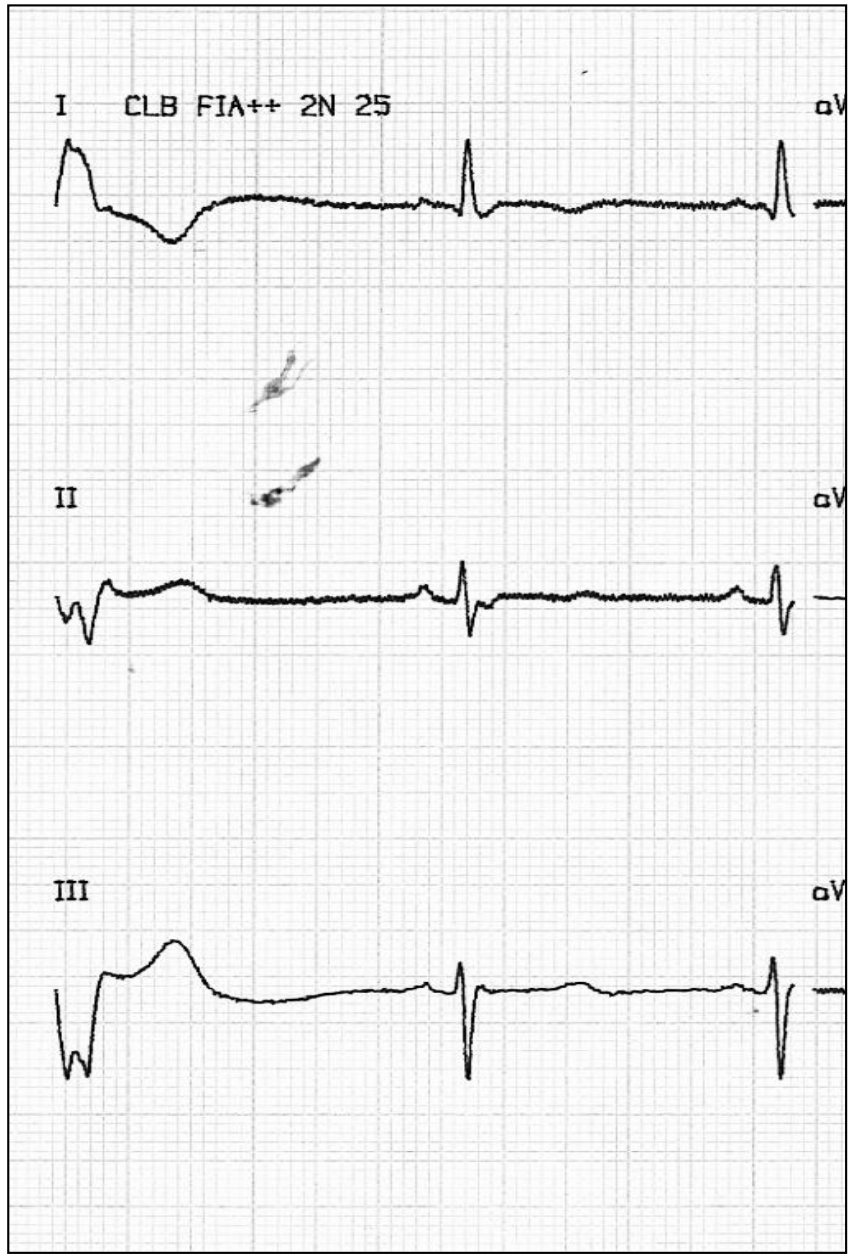
The figure in next slide shows electrodes location in R-ECG and F-ECG



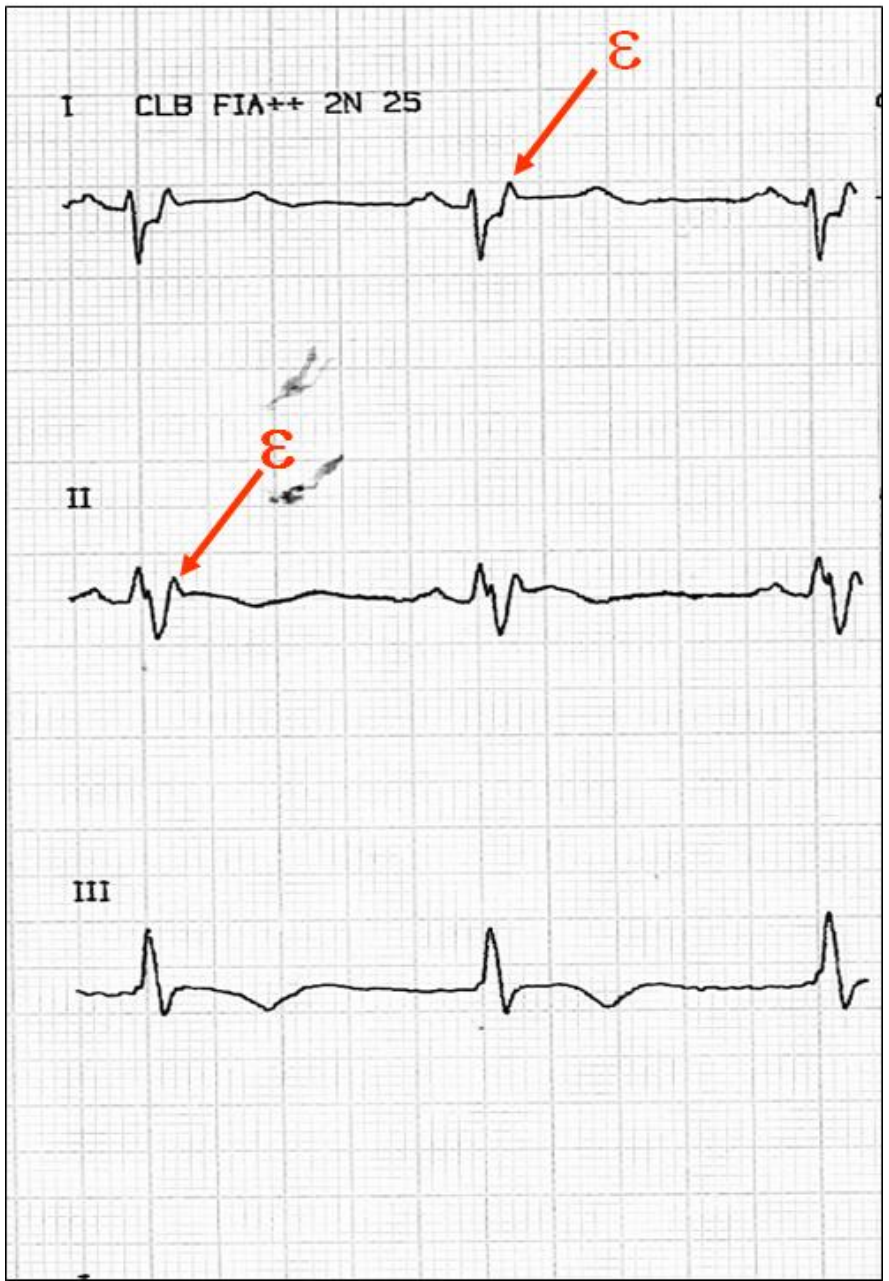
Right precordial leads **The Fontaine bipolar precordial leads**

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 V4 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 **ε** 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 " **ε**" was appropriate, because it occurs in the Greek alphabet after delta; thus, delta represents the pre-excitation and **ε** the post-excitation phenomenon (**Fontaine 1999**).

Conventional bipolar leads S-ECG



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



Pathognomonic character of ε waves: in spite of the characteristics in ARVC/D, they are not pathognomonic, since they have been described in other physiological and pathological scenarios associated with myocardial damage:

I. **Physiological ε waves ventricular hypertrophy in elite endurance athlete seniors:** ε wave, was found in 3 athletes seniors (1.57%) from 347 elite endurance athletes (seniors–190, juniors–157), mean age of 20; 200 subjects mean age of 21, belonging to the control group of 505 normal sedentary population (**Macarie 2009**). Bizarre QRS, ST-T patterns suggestive of abnormal impulse conduction in the right ventricle, including the right outflow tract, associated with prolonged QTc interval in some cases were observed in highly trained endurance athletes. The genetic analyses, negative in most athletes, identified surprising mutations in SCN5A and KCN genes in some cases (**Macarie 2009**).

II. **Pathological ε waves**

1. **Giant-cell myocarditis:** ε waves are a major diagnostic criterion for ARVC/D, but also other cardiac pathologies such as giant-cell myocarditis can cause severe RV conduction disturbances manifesting with ε waves and VT on surface ECG (**Vollmann 2014**).
2. **Sickle cell anemia** (**Hurst 1998**).
3. **Brugada syndrome:** it is believed that Brugada syndrome and ARVC/D are different clinical entities with respect to the clinical presentation and the genetic predisposition. The coexistence of these two relatively rare clinical entities was also reported (**Hoogendijk 2012**). In clinic practice, there may be cases where the dividing line is not so clear (**An 2008; Ozeke 2009**). ε waves appear to be rare in Brugada syndrome patients and were found in 2 of 47 patients by Letsas et al (**Letsas 2011**), and in 1 patient from a total of 12 unrelated index Brugada syndrome patients were included in the study by Yu et al (**Yu 2014**).

4. **Idiopathic ventricular fibrillation in the absence of Brugada syndrome phenotype** with loss-of-function mutation of the SCN3B-encoded sodium channel {beta}3 subunit (**Valdivia 2010**).

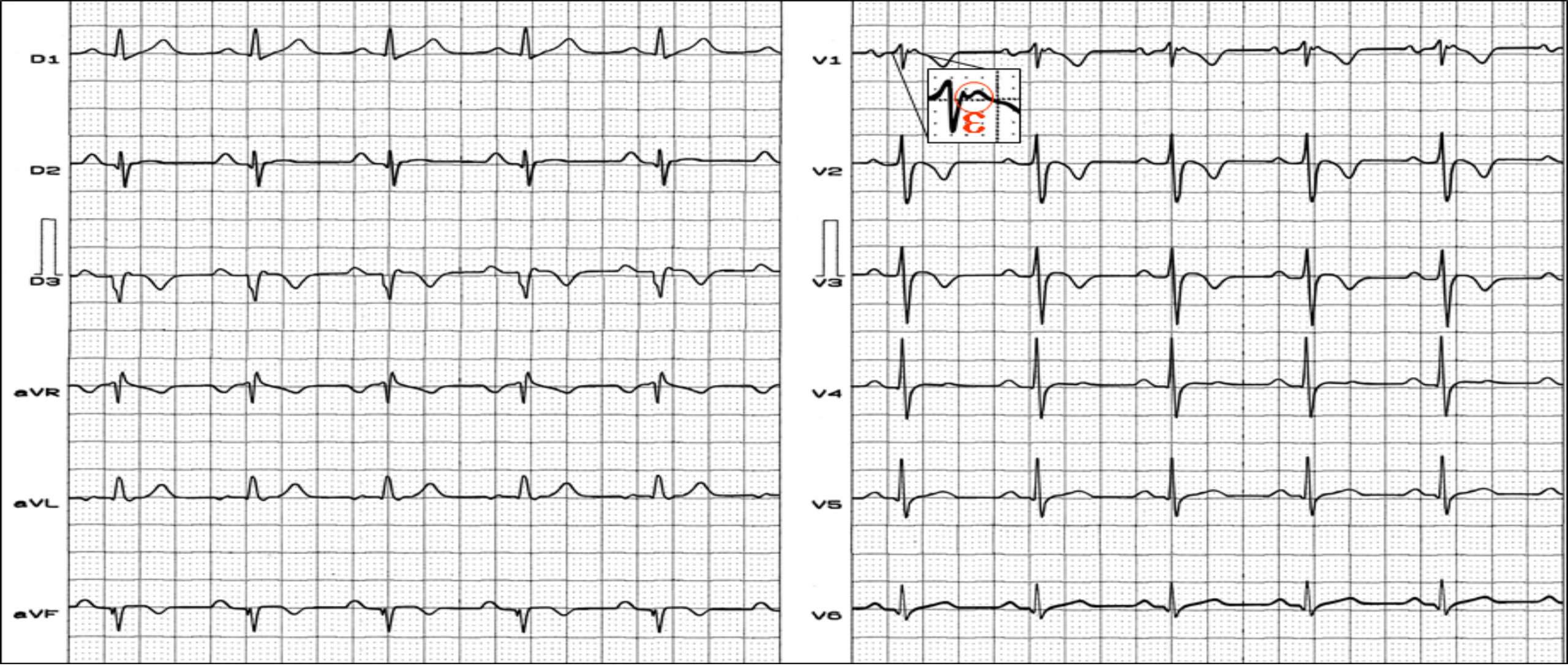
5. **During exercise stress testing or treadmill stress testing in asymptomatic gene carriers** Depolarization abnormalities during exercise testing in asymptomatic gene carriers were found to develop more frequently compared with healthy controls: **ε** waves appeared in 4 of 28 (14%) (**Perrin 2013**). Recently, Adler et al showed to uncover **ε** waves in asymptomatic patients carrying mutations in the PKP2 gene. This finding suggests that exercise testing may be valuable for the diagnosis of ARVC/D and that exercise-induced **ε** waves may be found in various genetic subtypes of this disease (**Adler 2015**).

6. **After repair Fallot's tetralogy** (**George 2011**).

7. **Right ventricular myocardial infarction** (**Zorio 2010**; **Andreou 2012**)

8. **Inferior or lateral (old dorsal) myocardial infarction** (**Zorio 2005**)

9. **Infiltrative diseases, such as cardiac sarcoidosis** (**Santuchi 2004**), increasing evidence suggests that cardiac sarcoidosis might produce the pathological substrate required for production of **ε** epsilon waves. Therefore, differentiating these two entities is of paramount clinical importance (**Khaji 2013**). The ECG in next slide shows a single **ε** wave in a patient with sarcoidosis.



Clinical diagnosis: cardiac sarcoidosis.

ECG diagnosis: QRS axis (SÂQRS) at - 60º, negative T-waves from V_1 to V_3, **ε** waves with two deflections in V_1.

Value of criterion: ε wave is considered to be a major depolarization criterion for diagnosis by the Task Force for ARVC/D diagnosis (**McKenna 1994; Fontaine 1999; Marcus 2010**).

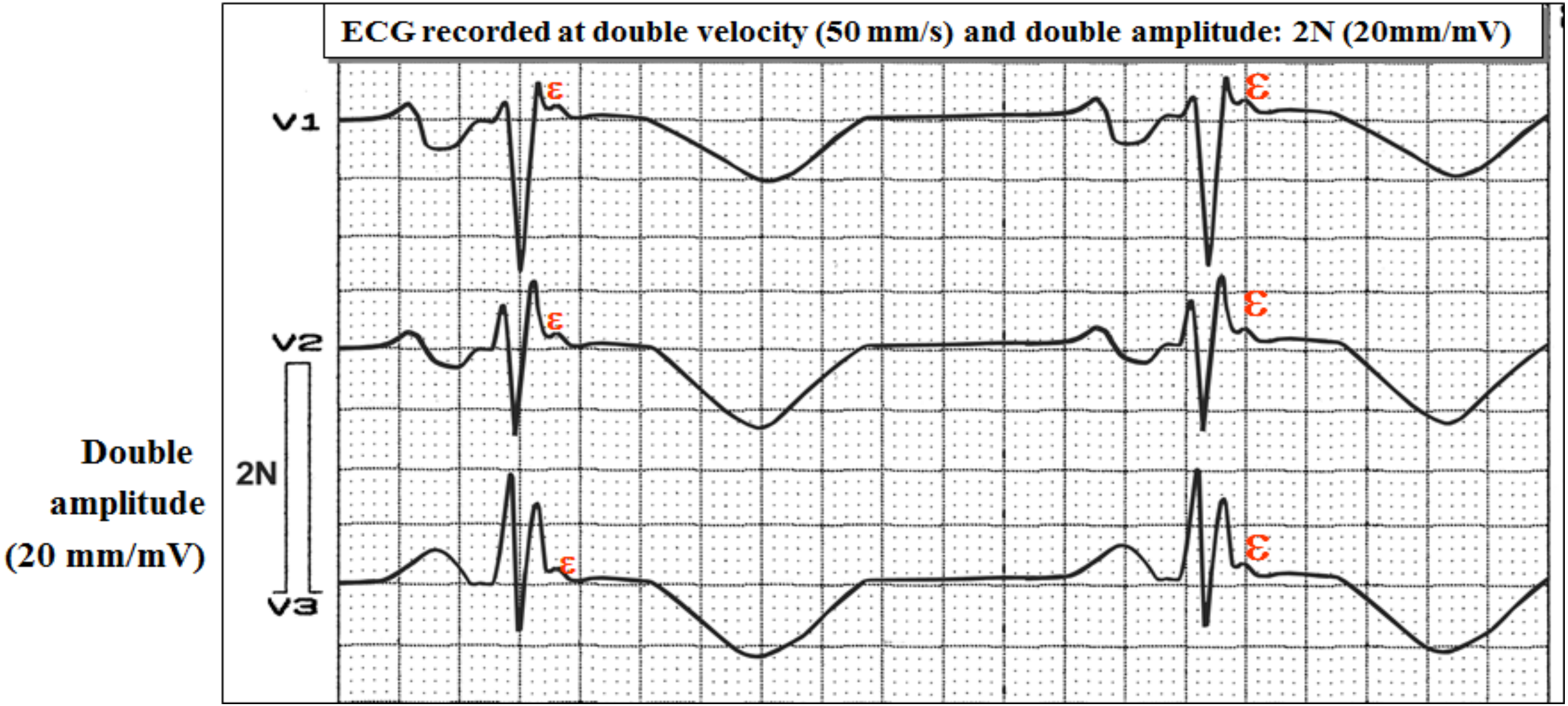
Progressive character of ε waves: ECG changes during long-term follow-up, in a large cohort of patients (111 patients from three tertiary care centers in Switzerland) with ARVC/D showed that ECG progression is significant for ε waves (baseline 14% vs. follow-up 31%, p = 0.01) (**Saguner 2015**).

Value of ECG in ARVC/D

ECG diagnosis of ARVC/D may be difficult in the initial stage of the disease, since a normal ECG is found in up to 40% of patients during the first year of follow-up. Jaoude et al (**Jaoude 1996**) found a strong correlation between QRS or T wave changes and the length of follow-up after the first symptom; mean time interval between first VT and ECG recording is significantly longer in patients with negative T waves in the right precordial leads, wide QRS, or left axis deviation, than in patients without such abnormalities. A normal ECG is found in 40% of patients during the first year of follow-up, 8% at 5 years, and never later than the 6th year. ARVC/D can be excluded if the ECG is found to be normal 6 years or later after a first VT event.

ECG association: Inversion of T wave in leads V1-V3 and/or ε wave found in 70% of patients with ARVC/D. Epicardical 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 (**Fontaine 1984**).

ε wave and relationship to VT: the simple presence of ε waves indicate slow and fragmented conduction, which favors reentry circuits, which in turn result in monomorphic VT runs with complete LBBB pattern by originating in the free wall of the RV (**Hurst 1998; McKenna 1994**).
The tracing should run at a double velocity (50 mm/s) and double voltage (20 mm/s) to compare the duration of QRS complexes (QRSd) in different leads, as well as to try to record ε waves.
The ECG in next slide shows more clearly the ε wave with double velocity and double voltage.



The rate of widespread T-wave inversion (exceeding V_3) was significantly higher in patients with ε waves than in those without

Signal-Averaged Electrocardiogram (SAECG): observed more frequently with this method.
In ARVC/D, SAECG frequently is associated to late potentials (LP).
The **ε** wave may be observed in surface ECG; however, it is seen much more frequently in SAECG (**Gregor 2003**).
SAECG is used to detect late potentials (LP) and ε waves in ARVC/D carriers.
Patients with positive SAECG (presence of LP) have statistically significant increase of S-VT and/or SCD in comparison to those with normal SAECG or bundle branch block.
SAECG with LP constitutes a marker of arrhythmic events in patients with non-ischemic dilated cardiomyopathies. On the contrary, patients with dilated cardiomyopathies with normal SAECG, display worsening only if they develop progressive CHF (**Mancini 1993**). Fibro-fatty substitution of the myocardium is the substrate of slow and fragmented activation, responsible for the presence of LP.
Abnormal SAECG seems to correlate with the severity of the disease.
SAECG does not seem a sensitive resource in the minor or concealed forms of the disease, since in these patients there is no proper information with this method (**Oselladore 1995**).
The combination of the analysis of time domain and frequency domain of SAECG may be useful for screening patients carriers of ARVC/D. This combination of both domains increases sensitivity without reducing specificity.
Use of filters with a range between 20 and 250 Hz (substituting the classical ranges between 40 and 250 Hz) (**Kinoshita 1995**).
The presence of LP in ARVC/D is found in 70% to 80% of cases. These LP may identify patients with a tendency to develop VT runs in little apparent or restricted forms, and it serves to differentiate them from benign RVOT idiopathic VT, with no underlying structural disease. In these cases, SAECG has LP in 0% to 5% of the cases as in normal patients.
When there is structural heart disease, LPs are found in 20% to 40% of cases. In doubtful cases, invasive studies are necessary to rule out a limited form of cardiomyopathy (**Fauchier 1996**).
In absence of bundle branch block, the presence of LP in SAECG is proportional to the size of the RV cavity, and thus is parallel to RV dysfunction (**Mehta 1996**).
In order to study the differences between benign repetitive MVT that originate in the RV and the VT from ARVC/D, ECG during the event and SAECG may be helpful.
ECG during VT and SAECG may be useful to differentiate both entities. In the case of ARVC/D, VT presents QS in V1 and QRSD related to the amount of fibrous tissue existing in the RV (**Kazmierczak 1998**).

There are significant differences for filtered and non-filtered QRS, low duration sign and square root. In absence of CLBBB, these differences become non-significant for filtered or non-filtered QRS (**Kazmierczak 1998**).

There is a narrow correlation between the result from SAECG and the extension of the disease, with the presence of VT.

SAECG is not a valuable resource in minor forms of the disease, but as this is a noninvasive method, it may be useful to assess the progression of the disease (**Nava 2000**).

In comparison to 12-lead ECG, SAECG detects abnormalities at higher rates in patients carriers of ARVC/D (57% vs. 86%). SAECG is more sensitive as screening test than 12-lead ECG to detect patients carriers of ARVC/D (**Sekiguchi 2001**).

The anatomopathological process of ARVC/D also considers late ventricular potentials, which when they are registered as LP in SAECG, indicate electrical stability worsening associated to rapid progression of SAECG, while clinical parameters remain unchanged. This fact suggests that progression parameters in SAECG are markers of electrical instability increase (**Bauce 2002**).

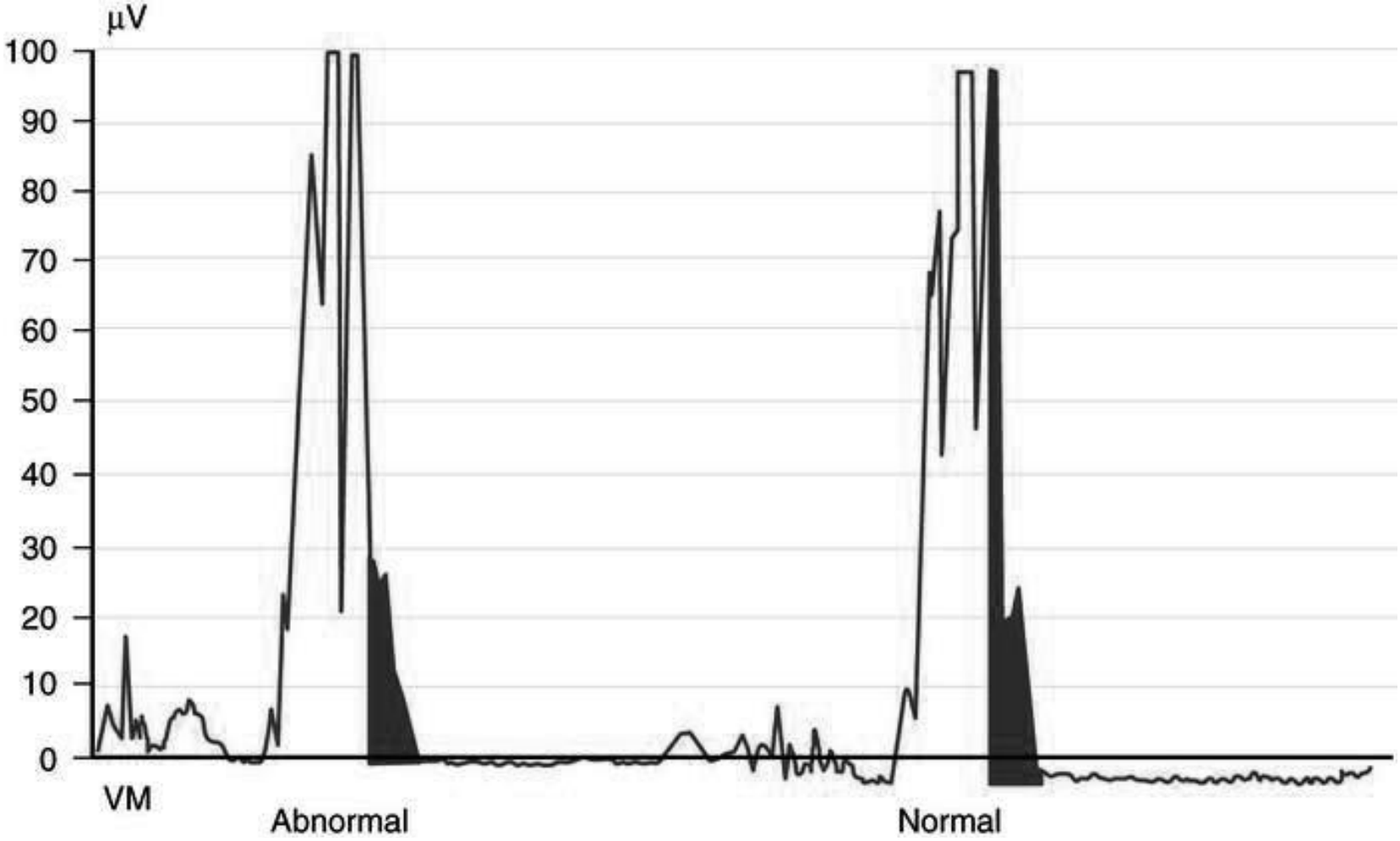
Sensitivity, specificity, predictive value and accuracy of the different criteria of SAECG were estimated in comparison to SMVT inducibility. Filtered QRS duration (fQRS) in SAECG is considered as predictive for the result of the electrophysiological study and ARVC/D evolution (**Nasir 2003**). The average of presence of late potentials in ARVC/D is between 70%-80%, with extreme values of 47-100%. The latter percentage is observed in severe forms and with documented spontaneous VT;

SAECG is a very useful resource to follow the evolution of the disease; In relatives of patients, SAECG presents a positivity of LP between 4-16%; Detecting posterior potentials improves by using 25 Hz filters and specificity is better observed in the orthogonal lead Z; SAECG should be considered a standard test in the study of patients with suspicion or carriers of ARVC/D;

Future research is necessary to confirm the value of SAECG as predictor of arrhythmic risk and determining factor of progression of the disease, as well as to study the prevalence of SAECG in relatives of patients, thus allowing early detection;

The majority of elite and amateur athletes participating in high dynamic and high static sports, reveal a prolongation of the filtered QRS duration (fQRS) on the SAECG, and according to the 2010 Task Force criteria for the diagnosis of ARVC/D, these athletes therefore demonstrate LPs. The extent of fQRS prolongation is positively correlated with RV dimensions. Therefore, SAECG findings should be interpreted with caution in endurance athletes (**Jongman 2015**). Multidisciplinary continuing studies on ARVC/D will help to answer some of these questions (**Nasir 2003**).

Interobserver variability in the assessment of **ε** waves is high; however, the impact of **ε** waves on ARVC/D diagnosis is negligibly low. The results urge to exercise caution in the assessment of **ε** waves, especially in patients who would not otherwise meet diagnostic criteria (**Platonov 2015**).



Positive SAECG demonstrating low-amplitude late potentials. VM, vector magnitude.

- 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 V1, V2, or V3, in the absence of complete right bundle-branch block (**Marcus 2010**).

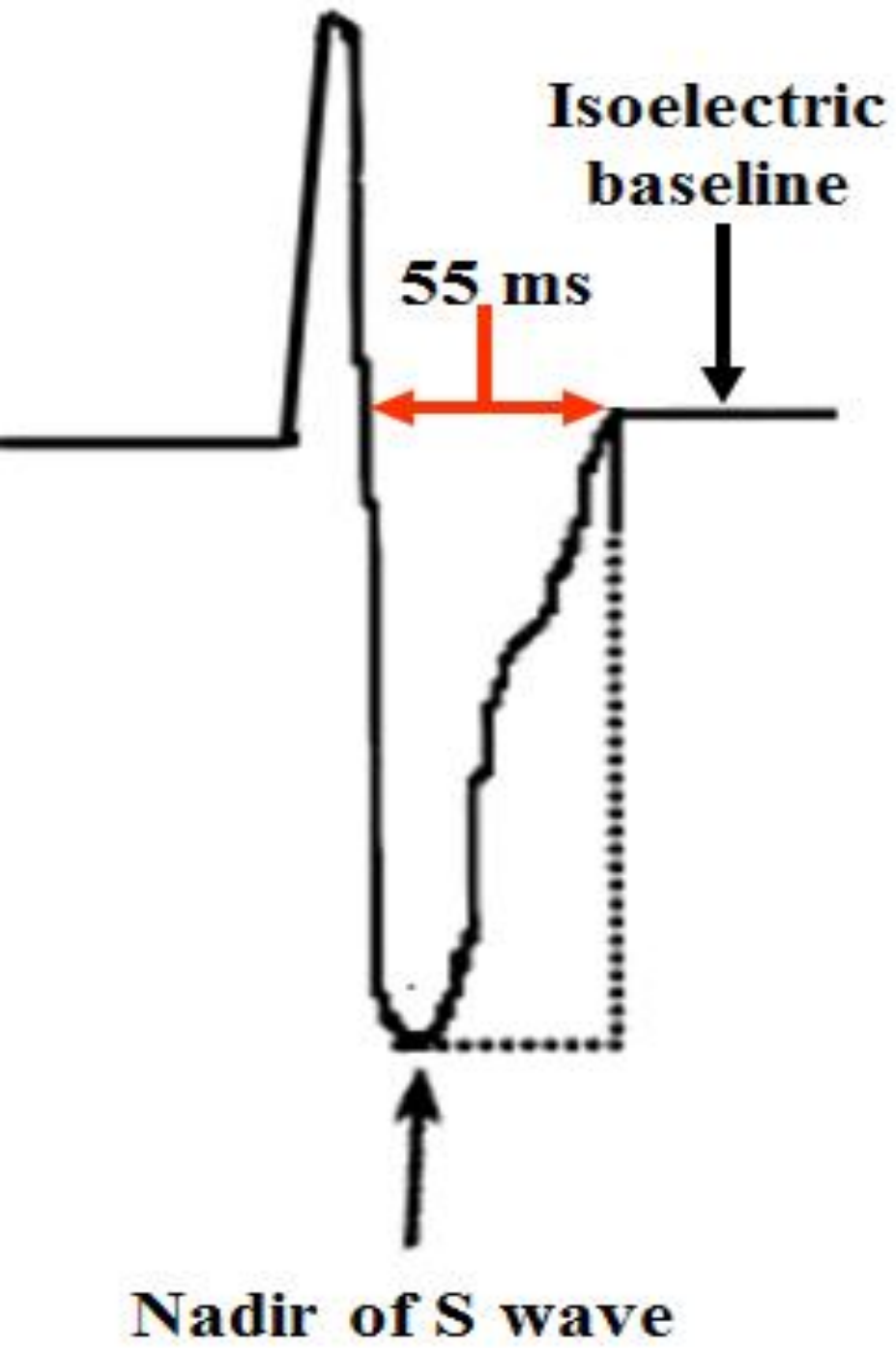
Others ECG features in ARVC/D

Approximately 90% of patients carriers of ARVC/D present ECG anomalies. ECG abnormalities were more frequent at 10 year and 5 year follow-up than on initial tracings. A normal ECG was found in 40% of patients during the first year of follow-up, 8% at 5 years, and never later than the 6th year. Consequently, ARVC/D diagnosis may be excluded if ECG is normal 6 years of follow-up (**Jaoude 1996**). In ARVD/C, a normal ECG is considered reassuring. However, some patients with ARVD/C experiencing ventricular arrhythmias have a normal ECG. Interpretation of ECG in young and older athletes requires in-depth knowledge in cardiology and sports medicine. The interpretation can only be carried out by considering medical history, clinical examination and ethnicity. Profound and long-term experience of athlete's ECG interpretation is required to protect athletes and to prevent cardiac emergencies (**Löllgen 2015**).

Main ECG features in ARVC/D classification:

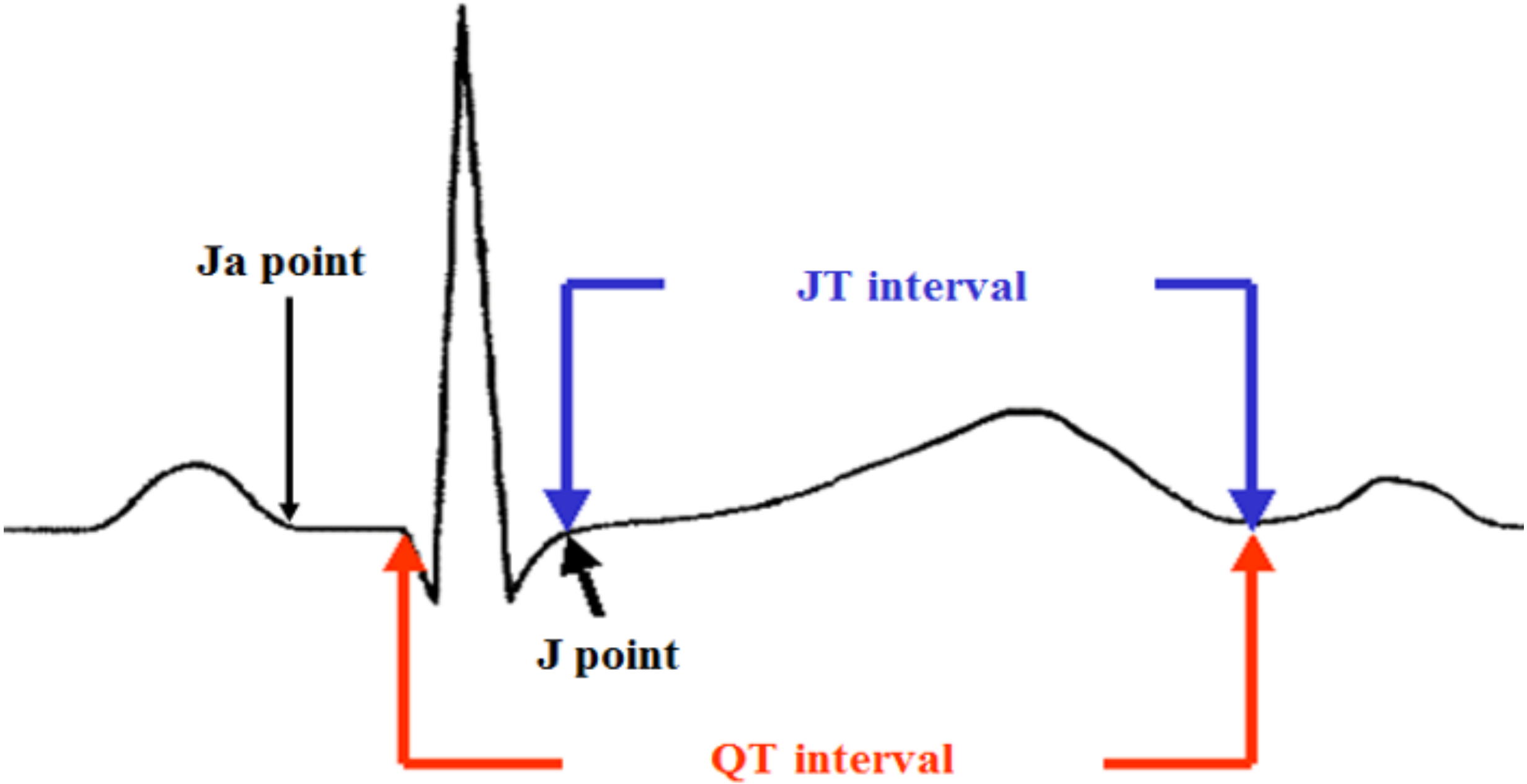
I) Depolarization criteria

- **Right ventricular parietal block** (**Fontaine 1984**): Prolonged S-wave duration due to slow depolarization of the terminal part of the QRS because the RV is the last part of the heart to undergo depolarization, a prolonged S-wave upstroke in V1 through V3 (≥ 55ms) is the most frequent ECG finding in ARVD/C and should be considered as a diagnostic ECG marker. Among those without RBBB, a prolonged S-wave upstroke in V1 through V3 ≥ 55 ms was the most prevalent ECG feature (95%) and correlated with disease severity and induction of VT on EPS (see figure next slide).



This feature also best distinguished ARVD/C (diffuse and localized) from RVOT. The sensitivity of this criterion is not known in other entities and it speaks in favor of slow RV conduction. A study shows that the sign is not specific, since it is found in Brugada syndrome (**Pitzalis 2003**) with QT interval prolongation only from V1 to V3. If QT interval prolongation occurs only from V1 to V3, it is clear that this is due to depolarization time prolongation. If we admit that in Brugada syndrome there is some degree of RBBB, this QT interval prolongation may be partially due to this fact. QT interval constitutes a classical measurement for ventricular repolarization; however, it includes depolarization (QRS), which represents the so-called "electrical systole", which includes ventricular depolarization and repolarization. In these cases of branch block and WPW, it is better to measure the JT interval and not QT (See next slide)

The JT interval value and its limits



QT interval is used to measure ventricular repolarization; nevertheless, this parameter includes ventricular depolarization (QRS) and represents the so-called electrical systole, which is the addition of ventricular depolarization (QRS) and repolarization (ST/T = JT interval).
If bundle branch block or WPW type ventricular pre-excitation occurs, the QTc interval does not express ventricular repolarization correctly. In these cases, JT interval measurement is more reliable (JT = QT - QRSd) than QT interval, because the parameter excludes depolarization that is prolonged, as a consequence of sequential activation of biventricular chamber (normally this activation is simultaneous).
Localized QRSD prolongation on right precordial leads > 110ms (depolarization/conduction abnormality).
$QRSd_{V1+V2+V3}/QRSd_{V4+V5+V6} > 1.2$ in approximately 65% of cases. QRS prolongation located in right precordial leads has 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVC/D (**Nasir 2003; 2004**).
The terminal S wave length and area in the right precordial leads are diagnostically useful and suitable for automatic analysis in ARVC/D. The bipolar chest leads (CF leads) are diagnostically superior to the unipolar precordial leads. Among members of ARVC families, those with mutations had shorter QRS length in V2 and V3 and smaller QRS area in lead V2 compared with those without mutations. In ARVC patients, the CF leads were diagnostically superior to the standard unipolar precordial leads. Terminal S wave duration in V1 ≥ 48 ms and T wave negativity in CF leads separated ARVC/D patients from matched controls with 90% sensitivity and 86% specificity (**Batchvarov 2015**).
Observation: The bipolar chest leads (CF leads) is a lead that resembles V1 (modified CL1 lead) The positive electrode is placed at V1 and the negative electrode is placed close to the left shoulder. It is frequently used for detecting arrhythmias during continuous monitoring of the patients admitted to the coronary care unit.
ε waves, epsilon potentials, ventricular post-excitation waves (**Maia 1991**), **post-excitation (ε) waves** (**Okano 1995**) **or Fontaine waves** due to slow conduction in the RV. The extent of ECG abnormalities correlate with the degree of structural change in the RV (**Marcus 2009**).
QRS fragmentation(fQRS): QRS fragmentation in the S wave of right precordial leads identifies patients with recurrent VT, primary VF, and recurrent ICD discharges; fQRS ≥3 leads characterized patients who died from SCD (**Peters 2012**).
Reduced QRS amplitude: Q waves or precordial QRS amplitudes <1.8 mV;
Poor R Wave Progression (PRWP) on precordial leads: The most likely cause of PRWP is clockwise rotation caused by RV enlargement (**Fontaine 1984**).
Complete or incomplete RBBB based on the findings from epicardical mapping and histological data, is likely attributable not only to the impaired septal pre-divisional right bundle branch but also to distal block on RV free wall due to the irregular and delayed propagation of activation in the zones of dysplasia.

Repolarization criteria

Inverted T-wave in the right precordial leads V1-3 or anterior T wave inversion (TWI) above 12 years with no RBB (repolarization criteria): T-wave inversion on a 12-lead ECG is usually dismissed in young people as normal persistence of the juvenile pattern of repolarization. However, T-wave inversion is a common ECG abnormality of cardiomyopathies such as hypertrophic cardiomyopathy and ARVC which are leading causes of SCD in athletes. In absence of CRBBB in patients >12 years of age, T wave inversion(TWI) \from V1 to V3 is a sign with great value for the diagnosis. The juvenile pattern of T wave inversion in V_1-V_3 or beyond is a normal variant in children under 12 years of age. This variant is present in 1%-3% of the healthy population aged 19 to 45 years and 87% of patients with ARVC (**CapulzinI 2010**). In normal, young patients, there is usually positive T polarity in V1; however, it may flatten and nearly always has a positive polarity in V2. In symptomatic patient's carriers of ARVC/D, the ECG generally shows T wave inversion in V1 and V2, which may reach up to V6 (**Fontaine 1994**). Physiological cardiac adaptation to regular exercise, including biventricular dilation and T-wave inversion (TWI), may create diagnostic overlap with ARVC/D. There are no electrical, structural, or functional cardiac differences between athletes exhibiting TWI and athletes without TWI. When athletes are compared with ARVC/D patients, markers of physiological remodeling included early repolarization, biphasic TWI, voltage criteria for RVH or LVH, and symmetrical cardiac enlargement. Indicators of RV pathology included the following: syncope; Q waves or precordial QRS amplitudes <1.8 mV; 3 abnormal SAECG parameters; delayed gadolinium enhancement, RV ejection fraction ≤45%, or wall motion abnormalities at CMRI; >1,000 premature ventricular contractions (or >500 non-RV outflow tract) per 24 h; and symptoms, ventricular tachyarrhythmias, or attenuated blood pressure response during exercise (**Zaidi 2015**).

Nonspecific parameters included the following: prolonged QRS terminal activation; ≤ 2 abnormal SAECG parameters; RV dilation without wall motion abnormalities; RV outflow tract ectopy; and exercise-induced T-wave pseudonormalization. In ARVC/D TWI is due to scarring of the free wall of the RV and regional conduction delay on free wall RV (**Marcus 1982, Peters 2003, Steriotis 2009**), is one of the most common ECG abnormalities in ARVC/D. To day is considered a major taskforce diagnostic criterion (**Marcus 2010; Sen-Chowdhry 2007**) may be the causes of T wave inversion in V1-3 or beyond. It is a secondary rather than a primary repolarization abnormality. T wave inversion beyond V3 is more common in ARVC/D patients in the advanced stage of the disease with severe RV dilatation and LV involvement. Thus it has been considered a risk factor and perhaps an indication of a poor prognosis. T wave inversion in the right precordial leads can also be seen in many other conditions such as acute pulmonary embolism, athlete heart, Brugada syndrome, long QT syndrome caused by *KCNH2* mutations or compound mutations, and occasionally in normal adult female. Exercise-induced T-wave pseudonormalization.

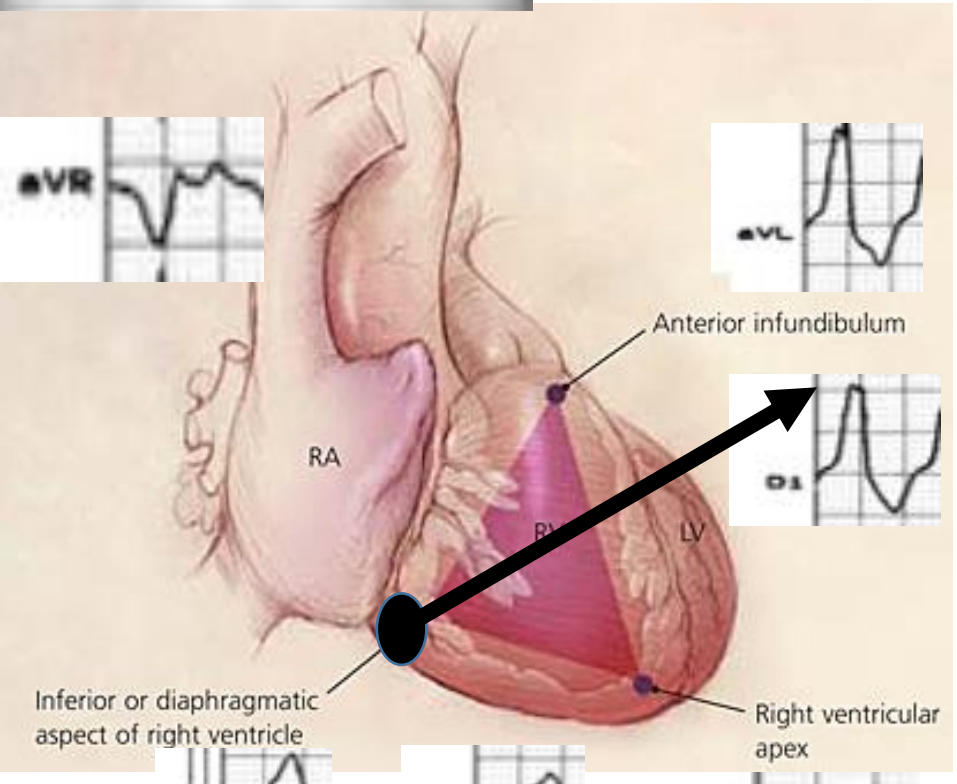
ST segment elevation: The combination of J-point elevation and TWI confined to lead V1-V4 offers the potential for an accurate differentiation between 'physiologic' and 'cardiomyopathic' anterior TWI, among athletes of both white/Caucasian or black/Afro Caribbean descent (**Calore 2015**). Conversely, ST-segment elevation without J-point elevation preceding anterior TWI may reflect cardiomyopathy. is not uncommon in ARVC/D (**Peters 1999**). In a cohort study, 37% of ARVC/D patients had a ST elevation. Among these, 42% showed a small notch in the first half of the ST segment and such findings are more frequently seen in patients in the presence of **ε** waves.

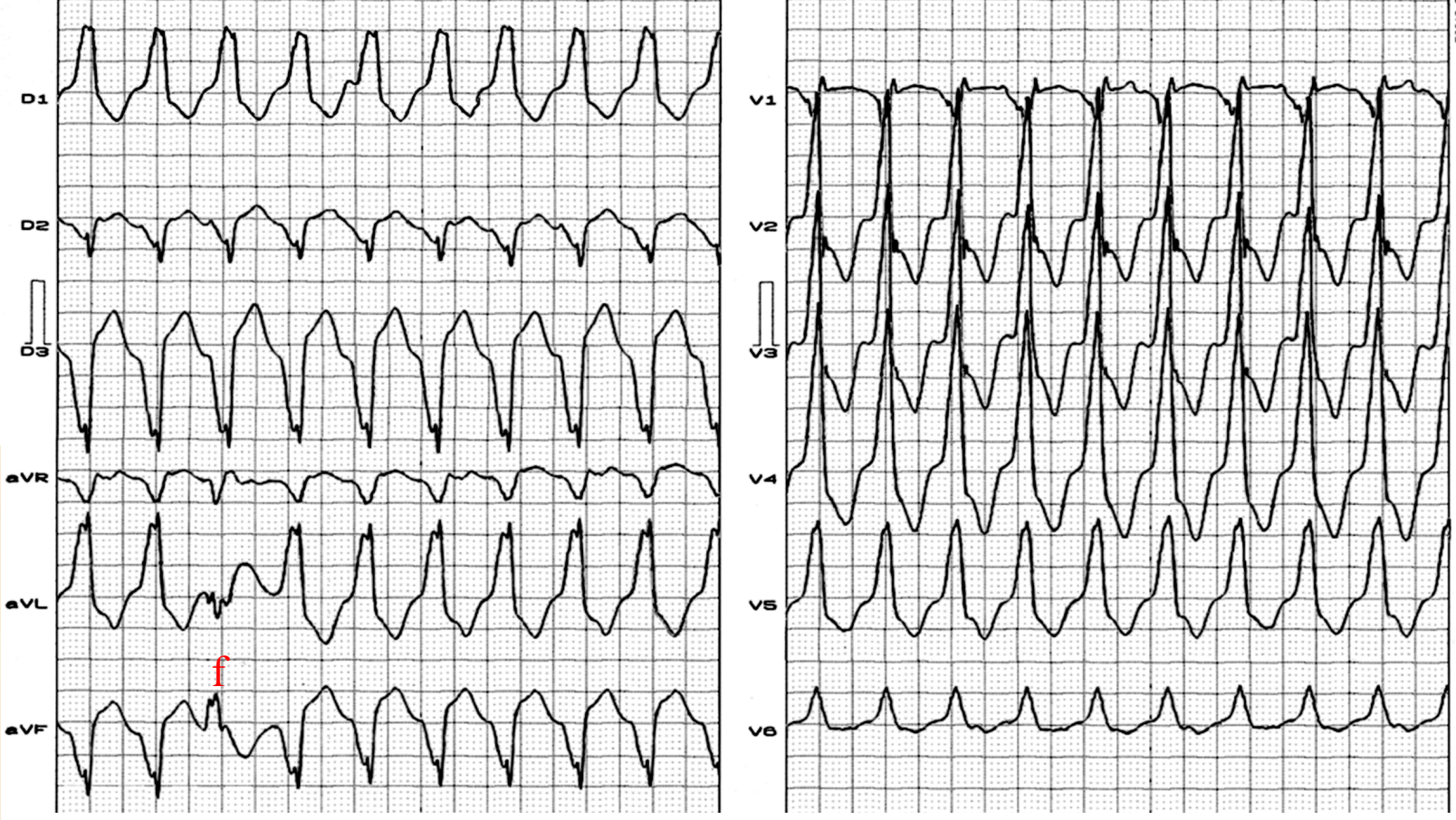
Ventricular arrhythmias

Non-sustained or sustained ventricular tachycardia in the morphology of left bundle branch block with superior axis: Predominant negative or indeterminate in inferior leads and positive in aVL is considered a major criterion following 2010 revised Task Force Criteria for the Diagnosis of ARVC/D. VT with LBBB morphology and an inferior axis commonly originates from the Right Ventricular Outflow Tract (RVOT). In contrast to ARVC/D, RVOT VT occurs in structurally normal hearts (occasionally the RVOT is dilated and RV regional wall motion abnormalities are seen on CMR) and is readily treatable with verapamil and β-blockers or radiofrequency ablation. The ECG in sinus rhythm in RVOT VT is normal as is the SAECG. In contrast to ARVC, there are no family screening implications with RVOT VT. Other differentials to consider include idiopathic dilated cardiomyopathy (IDCM) and Uhl's anomaly. Patients with IDCM usually have a progressive decline in left ventricular function, in contrast to ARVC/D where the right heart is primarily affected. In Uhl's anomaly the RV myocardium is paper thin and devoid of myocardium. There is no replacement of muscle by fatty tissue. It usually presents in childhood.

1,000 ventricular extra systoles (or >500 non-RV outflow tract) per 24 h.

The event of the present case analysis





LBBB/superior axis VT from a patient with ARVC/D. In this case the focus is in right ventricular inflow tract (RVIT) in inferior or diaphragmatic aspect of the RV. Presence of fusion beats (**f**). ARVC/D patients have a greater frequency of the site of origin of the right ventricular free-wall, more remote from the normal His–Purkinje conduction tissue than in those patients with RVOT-VT. Multiple VT forms, wider QRS duration (lead I ≥ 120 ms), QRS notching, earliest onset QRS in lead V_1 later, and precordial transition (>V5) all increase the odds of ARVC/D.

Differential diagnosis of ARVC/D

- Idiopathic Monomorphic Right Ventricular Tachycardia arising from Right Ventricular Outflow Tract;
- Sarcoidosis;
- Uhl's Anomaly, Uhl's disease, myocardial dysplasia of the right ventricle or "Parchment Right Ventricle";
- Fatty Replacement of the Right Ventricular Myocardium;
- Brugada Syndrome (with Minor or Concealed Forms);
- Carvajal Syndrome (with Naxos Disease).
- Idiopathic Dilated Cardiomyopathy (IDC);

Differential diagnosis with Idiopathic Monomorphic Right Ventricular Tachycardia arising from Right Ventricular Outflow Tract (IMVT-RVOT)

	IMVT-RVOT	ARVC/D
Family history of arrhythmia or SCD	Has not family history antecedents.	Present in 30% to 50% of cases. Genetic heterogeneity (**Basso 1997**)
Age	Most patients are initially diagnosed between the ages of 30 and 50 years. In Lermans series there ranged between 6 and 77 years (**Lerman 2000**)	Manifest between the 15 and 30 years old. Adolescence and early adulthood (**Nava 2000**). The illness is cause of SCD in < 35 years old. At least 80% of cases being diagnosed before the age of 40.
Sex	Adenosine-sensitive RVOT segregates equally between both sexes (**Lerman 2000**).	Male predominance 3:1 or equal.
Pattern of inheritance	Non-familial arrhythmic condition.	Sporadic (65%) or familial (35%) autosomal-dominant. An autosomal-recessive pattern has also been reported which affects the long arm of chromosome 17 (17q21) associated to non-epidermolytic palmoplantar keratoderma with woolly hair. ("Naxos disease") (**Portonotarios 2001**).
Prevalence	More frequently that ARVC/D.	It is estimated as 1/5000 (**Czarnowska 2003**). The prevalence is estimated at 0.4% depending on geographic circumstances (**Hagenah 2004**)
Endemic areas of the world	No preference in some endemic areas.	Endemic in Veneto region (Italy), Nova Scotia and Naxus Greek island (recessive form).
Prognosis	Excellent. Rare SD	The incidence of SCD is ≈2.5% a year.
PR interval	Normal.	Eventual prolongation (**Wisten 2004**).

	IMVT-RVOT	ARVC/D
Symptoms	In 80% palpitations; 50% dizziness; 10% syncope during VT, in 80% class I and II symptoms; in 20% class III: pre-syncope or syncope. Triggered by stress or exercises, gestation, extreme consumption of alcohol, coffee or tobacco.	Palpitations are the most common complaint (**Maia 1991**). Syncope, dizziness or SCD, frequently triggered by stress or exercise.
P wave and sinus function	Normal.	Rarely giant P wave associated with a QRS of a very low amplitude (**Martini 1990**) in advanced forms. Standard ECG with right atrial enlargement and an increased mean precordial QRS dispersion of 47.1+/-18.9 ms is observed in cases of right heart failure. Biatrial enlargement and a reduced precordial QRS dispersion are observed in cases of biventricular heart failure (**Peters 1999**). Rarely, sick sinus syndrome during evolution (**Balderramo 2004**).
Incomplete or complete RBBB pattern	Present in 10% of cases (**Buxton 1983**).	Incomplete RBBB ≈18% of the cases and CRBBB in 15% (**Niwa 2004**). The mechanism of the right conduction defects is distal block in the RV wall. This hypothesis is supported by the histological appearances of the dysplastic zones (**Fontaine 1984**). Patients with RBBB and right precordial ST-segment elevation may experience SCD in the setting of either ARVC/D or a functional electrical disorder such as BrS (**Corrado 2001**).
Parietal block	Absent. QRSD <110 ms in V1, V2 or V3.	Very frequent in right precordial leads.
ε wave	Absent	S-ECG: 15-30%; R-ECG and F-ECG increased sensitivity.
VT	LBBB with inferior axis only one pattern	LBBB with superior axis (mayor criteria) with exercise, frequent with several morphologies.

	IMVT-RVOT	ARVC/D
T-wave polarity	Always T wave upright from V2- V5.	Negative T waves of V1 to V2 or V3 are very characteristic when present in children over 12 years old in the absence of RBBB (**Metzger 1993**). T-wave inversions in V1 through V3 were observed in 85% of ARVC/D patients in the absence of RBBB compared with none in RVOT and normal controls, respectively (**Nasir 2004; Toh 2004**). 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 intraparietal RV conduction defects. In 24 cases T wave was negative only on V1 in 37%; from V1 to V2 in 25%; from V1 to V3 in 8%; from V1 to V4 in 4% and from V1 to V5 in 8% (**Nava 1998**).
VT mechanisms	I. Trigged activity (Adenosine-Sensitive): 70% of cases. cAMP-mediated triggered activity. II. Delayed triggered activity, dependent on post-depolarization in phase 4, associated to increase of cyclic AMP and mediated by catecholamines: adrenergic-dependent. III. Intrafascicular Reentry (Verapamil sensitive); 10% of cases. IV. Enhanced Automaticy (Propranolol-sensitive); V. Reentry; VI. Undifferentiated (**Lerman 1996**).	I. VT around an anatomical obstacle (**Bauce 2002**). II. VT as a result of increased automaticity during exercise; III. Vortex-like reentrant VT, which may explain SCD during sleep; IV. Combination of the previous ones.

	IMVT-RVOT	ARVC/D
Atrial arrhythmias	Absent	Late and secondary
VCG	Normal	Evidence of peripheral RBBB: IRBBB or CRBBB topography occurs in the divisional portion of the right bundle branch, i.e. in the free wall of the RV after the trunk of the branch splits in the base of the papillary muscle of the tricuspid valve, and its mechanism seems to respond to dysplastic involvement of the free wall, whether in the RVOT, the RVIT, or in the apical region (dysphasia triangle) where the dysplastic area is found (**Fontaine 1984**). Nava et al. showed modifications on T loop in the HP of VCG. The authors observed three T-loops patterns: I. CCW rotation with a mean axis range of + 150° to –100°; II. A figure-eight pattern with mean range of +10° to – 40°; III. CW rotation with mean axis range of –40° to –110° (**Nava 1998**)
SA-ECG	Normal	Frequently abnormal. Filtering in the range of 20 to 250 Hz is more sensitive for identification of asymptomatic cases than the usual band pass of 40 to 250 Hz. Abnormal in 94.4% of patients with the extensive form, in 77.7% of patients with the moderate form and in 31.8% of patients with the minor form, demonstrating good correlation with the extent of the disease (**Oselladore 2000**).
Microvolt T-wave Alternans (TWA)	Negative in > 90% of cases.	Positive in 87% of cases (**Kinoshita 2003**).

	IMVT-RVOT	ARVC/D
Exercise Stress Testing	In 50% of cases adrenergic-dependent effort induced VT and induced by exercise VT. Tree variants are exercise induced: I. Adenosine-Sensitive (Triggered Activity); II. Propanolol-Sensitive III. Undifferentiated.	Should be performed with particular attention paid to evaluating ST segment changes in RV precordial leads. Occurrence of PVCs during increasing exercise followed by a prolonged observation during the recovery phase. A crescendo of PVCs.
Holter monitoring 24h	Detection of frequent or in bursts monomorphic PVCs that occur predominantly during the day. Record M-VT with LBBB pattern with inferior SÂQRS: between +30° and +120° indicative of RVOT origin.	Proper evaluation requires a 12-lead Holter system; Record MVT with typical LBBB pattern.
Echo	Normal in 90% of cases. Rarely, slight enlargement of RV.	Increased RV size and/or wall motion abnormalities. Dilatation of the RVOT and hypocontractility It is difficult in patients with minimal RV abnormalities. Aneurysm of the basal RV free wall below tricuspid valve is related
RV Ventriculogram	Usually Normal.	Usually abnormal. It is difficult to evaluate in patients with minimal RV abnormalities.
Cardiac Magnetic Resonance Imaging or Nuclear Magnetic Resonance (CMRI, MRI or NMR)	Usually normal.	Increased signal intensity of RV free wall; wall motion abnormalities with CINE MRI has emerged as clinical tools for evaluation of myocardial pathology. The device providing morphologic and functional information, has the ability to demonstrate intramyocardial fat, which is the pathological hallmark in ARVC/D.

	IMVT-RVOT	ARVC/D
Response to Programmed Electrical Stimulation (PES) (Induction)	Inducibility of VT by PES with ventricular extra stimuli: 3%; More than one pattern during VT: 0%; Fragmented diastolic potentials during ventricular arrhythmia: 0%.	Inducibility of VT by PES with ventricular extrastimuli: 93%, Presence of more than one ECG morphology during tachycardia: 73%, Fragmented diastolic potentials during ventricular arrhythmia: 93% (**Takagi 2003**).
Entrainment	Negative. Insensitive / not present.	Positive. Sensitive / present.
Response to Catecholamines Agents	Facilitates in cAMP-Triggered Activity (Adenosine-Sensitive) and Propanolol-Sensitive (Automatic). Facilitates/no effect in reentry in Verapamil-Sensitive, in undifferentiated, atriofascicular and Bundle Brach reentry variants.	Catecholamines Facilitation. The induction of the VT generally is dependent of the infusion of isoproterenol. Catecholamines increase the ST segment elevation.
Response to Ajmaline challenge	No tested.	Could be positive: coved ST segment elevation of at least 2 mm in at least two right precordial leads (**Shimizu 2001**).
Response to Class II Antiarrhythmic Agents: β-blocker	Adenosine-Sensitive: Present/ sensitive; Verapamil-Sensitive: Present/ sensitive or not present/insensitive; Propanolol-Sensitive: Terminates/transient suppression; Undifferentiated: not p3resent/insensitive.	β-blocker agents by themselves do not offer a fail-safe protection in adult with ARVC/D. 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 LV function in some patients with ARVC/D. Carvedilol may be a first-line drug for some patients with ARVC/D (**Hiroi 2004**).
Plasma levels of Brain Natriuretic Peptide (BNP)	They are not increased. Mean value: 8.3+/-5. 5 pg/mL	Increased. Mean value: 61.4+/-59.6 pg/mL (**Matsuo 1998**).

	IMVT-RVOT	ARVC/D
Endomyocardial Biopsy (EMB)	Usually negative: without clear structural heart disease. EMB has shown abnormalities in ≈65% of cases, which increases to more than 80% when the material is product of an autopsy. Thus, the following were described (**Markowitz 1997**). Indicatives of structural heart disease: ➢ Hamartoma of Purkinje fibers was described (**Garson 1987**); ➢ Mild form of ARVC/D; ➢ Microangiopathy associated to subendocardial fibrosis; ➢ Sub-clinical myocarditis; ➢ Focal cardiomyopathy; ➢ Atherosclerotic ischemic cardiomyopathy; ➢ Non-atherosclerotic ischemic cardiomyopathy; ➢ Hypertrophic cardiomyopathy; ➢ Mitral valve prolapse.	It has the potential for in vivo demonstration of typical fibrofatty replacement of the RV myocardium. However, sensitivity of this test is low because, for reasons of safety, samples are usually taken from the septum, a region uncommonly involved by the disease. Fibrofatty replacement of the myocardium, the hallmark pathologic feature, may be a response to injury caused by myocyte detachment. Apoptosis is present in EMB of patients with ARVC/D, especially in the early symptomatic phase of disease (**Valente 1998**).
Response to therapy	Therapy only mandatory if presyncope or syncope present. Beta-blockers are effective in 35% of cases; Calcium channels blockers: are effective in 30% of cases; Association Class IA and IC is effective in 35% of cases; Class III drugs are effective in 50% of cases. Acute termination: Vagal maneuver; adenosine, intravenous verapamil and lidocaine.	1) Empirical drug therapy: Sotalol; amiodarone +/- ; beta blockers, carvedilol (alpha and β-blocker). 2) Anticoagulant therapy. In patients in whom ARVC/C has progressed to severe RV or biventricular systolic dysfunction with risk of thromboembolic complications (**Corrado 2001**). 3) Radiofrequency catheter ablation. 4) Implantable Cardioverter-Defibrillators (ICDs)

An electrocardiographic scoring system for distinguishing idiopathic ventricular tachycardia from arrhythmogenic right ventricular cardiomyopathy/dysplasia

Ventricular arrhythmias in patients with ARVC/D and idiopathic ventricular VT can share a LBBB pattern with inferior QRS axis Hoffmayer et al created a simples score with high sensitivity, specificity, positive and negative predictive value for differential diagnosis of both entities.

ECG Characteristic	Points
Anterior T-wave inversion (V1-V3) in sinus rhythm	**3**
Lead I QRS duration ≥ 120ms	**2**
QRS notching in multiple leads	**2**
Late precordial transition (V5)	**2**
Maximum total	**8**

A score of ≥ 5 distinguishes ARVC/D form idiopathic VT 93% of the time (sensitivity of 84%, specificity of 100%, positive predictive value of 100% and negative predictive value of 91% **Hoffmayer 2013**).

Differential Diagnosis With Cardiac Sarcoidosis

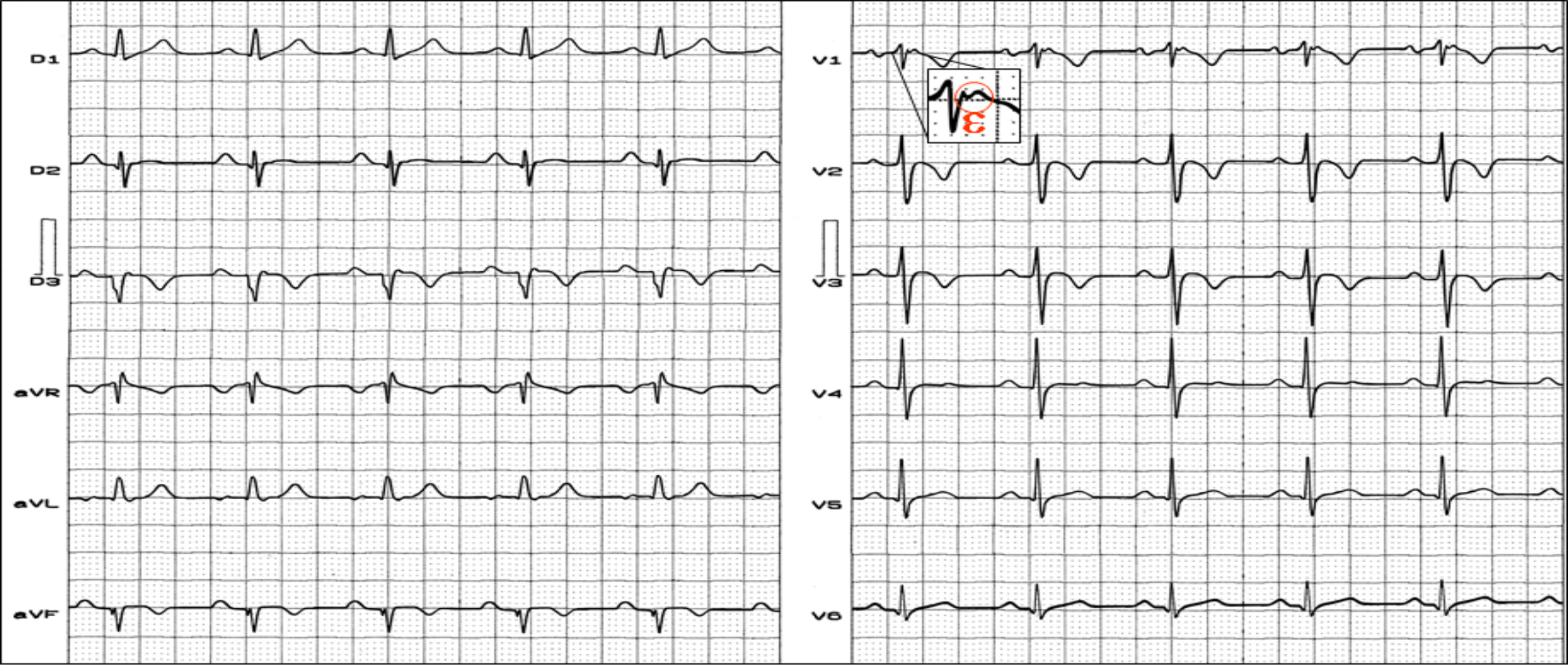
Patients with cardiac sarcoidosis may present with clinical and morphological features similar to ARVC/D or cardiomyopathy (**Ott 2003**)**.** Sarcoidosis is an inflammatory granulomatosis entity of unknowns cause, characterized by multisystemic involvement. Practically no organ is immune to sarcoidosis; most commonly, in up to 90% of patients, it affects the lungs (**Hoitsma 2004**). The most commonly involved organ in sarcoid related death has been reported to be the lung in western countries, while it was the heart in the Japanese autopsy series (**Iwai**). The diagnosis of myocardial sarcoidosis is difficult and frustrating. Its clinical manifestations depend on the location and extent of granulomatous inflammation, and the symptoms and signs range among benign arrhythmias, heart block, intractable CHF, intense chest pain, to fatal VF (**Sharma 2003**). The ECG finding may be normal or may reflect every degree of block of the atrioventricular junction and bundle branch blocks and every type of arrhythmia along with nonspecific ST-T-wave changes (**Flemming 1994**). Cardiac sarcoidosis should be considered in all young patients with unexplained conduction disorders (**Kollermann 2001**), CHF or in cases of SCD (**Lip 1996**). In extensive forms are frequently pseudo myocardial infarction patterns with pathological Q waves on ECG (**Shindo**). MRI abnormalities, consisting of cardiac signal intensity and thickness, with the following three patterns:

1. Nodular;
2. Focal increase in signal on gadolinium diethylenetriamine Penta acetic acid-enhanced, T1-weighted images;
3. Focal increased signal on T2-weighted images without gadolinium uptake.

The improvement or stability of the MRI findings is correlated with clinical features. With corticosterotherapy, the MRI images improved either partially or completely. The cardiac MRI may find its usefulness as a guide to obtaining EMB specimens and to monitoring the response of the disease to treatment. The study is small and lacks a correlation of myocardial histology with MRI features. However, the study clearly calls for a large multicenter trial. The most significant drawback of MRI is that the patient with a pacemaker and/or automatic ICD will not be able to take advantage of it. In such patients, ^{201}Tl scanning remains the test for assessing myocardial damage. Cardiac PET using F-FDG under fasting conditions (fasting F-FDG PET) is a promising technique for identification of cardiac sarcoidosis and assessment of disease activity. The methodology can detect the early stage, in which fewer perfusion abnormalities and high inflammatory activity are noted, before advanced myocardial impairment. The sensitivity and accuracy of fasting F-FDG PET in detecting cardiac sarcoidosis was 100%, significantly higher than that of (99m)Tc-MIBI SPECT (63.6%) or Ga scintigraphy (36.3%) (**Okumura 2004**). An endomyocardial biopsy (EMB) is preferable, but the procedure has low sensitivity (20%) (**Uemura 1999**). Other authors referred sensitivity approximately of 50% thus, the search for a safe, reliable, and easily available diagnostic test for cardiac sarcoidosis continues. The pathological feature is the presence of non-caseating granulomas that eventually form fibrotic scars. The following table shows the main differences between both entities (**Riera 2006**):

	Cardiac Sarcoidosis	ARVC/D
Family history	Absent	Present in 30% to 50% of cases. When the disease is identified genetic screening should be performed among patient's family members.
Gender (M/F)	1 to 1	2.9 to 1
Age at presentation	Young or middle-aged adults	Adolescents and young adults, perhaps there are rare references in childhood
Multisystemic involvement	Yes	No
Chest pain	Intense chest pain is refered.	No
Clinical myocardial restrictive features	Possible	No
Mitral regurgitation	Common	Only in late stage with involvement of LV.
Pseudo MI patterns on ECG	Fequent in extensive forms.	No
Chest roentgenogram	Bilateral hiliar linphoadenopathy.	Eventually RV cardiomegaly.
Lungs affectation	In up to 90% of patients. Cor pulmonale is frequent.	No
Pathological features	Noncaseating granulomas that eventually form fibrotic scars.	Typical fibro-fatty replacement of the RV myocardium on dysplasia triangle.
More common cardiac sites involved	LV free wall and interventricular septum.	RVOT, RVIT, and apex of RV.
Pericardial effusion	Not uncommon.	Absent
Pseudo MI patterns on ECG	Frequent in extensive forms.	No

	Cardiac Sarcoidosis	ARVC/D
Improved MRI images with corticosteroid therapy	Yes	No
Biventricular angiography with measurement of O_2 saturation and pressure curves in different position coronary angiography	Ventricular aneurysm are sometimes present. Free wall of the RV thin, dyskinesia and possible dilatation.	With the exception of full-thickness histological examination of the RV free wall, contrast ventriculography remains the most definitive gold standard for a positive diagnosis (**Fontaine 1999**). but must be performed with appropriate views and with care to avoid PVCs (**Marcus 1995**). Findings consistent with ARVC/D are an akinetic or dyskinetic bulging localized to the infundibular, apical, and subtricuspid regions of the RV. The specificity is 90%; however, the test is observer dependent. 68% of ARVC/D patients had normal RVEF and RV volumes, and 80% of ARVC/D patients had normal LVEF. Decreased Tricuspid Annulus Plane Systolic Excursion (TAPSE) <12 mm and a diffuse RVOT aneurysm were sensitive and specific indicators of RVEF <35% and LVEF <40%, respectively (**Hebert2004**). Angiography as well as the MRI eventually demonstrates not only reduced RV function but also regional abnormalities of contraction in the inferior and diaphragm regions and typical "outpouchings" and "bulging's" (**Wellemeyer 2003**.).
Theraphy with corticosterroids, hydroxychloroquine, methotextate or cyclosphosphamide	Sometimes are indicated immunosuppressive and anticytokine treatments can be effective in severe systemic sarcoidosis and should be considered in sight-treating disease.	Empirical drug therapy, anticoagulant therapy. RFCA, Implantable Cardioverter-Defibrillators, Heart transplantation or Orthotopic Heart Transplantation (OHT).



Clinical diagnosis: cardiac sarcoidosis.

ECG diagnosis: QRS axis (SÂQRS) -60º, negative T wave from V_1 to V_3, **ε** waves (ε) with two deflections in V_1.

Differential diagnosis between Focal Fatty Replacement of the Right Ventricular Myocardium (adpositas cordis) and ARVC/D

The relationship between ARVC/D and pure fat replacement of the RV is unclear. ARVC/D is a familial arrhythmogenic disease characterized by fibrofatty replacement of myocytes with scattered foci of inflammation. Fat infiltration per se is probably a different process that should not be considered synonymous with ARVC/C. Intramyocardial fat was frequently seen in normal hearts (**Burke 1998**).

Focal fatty replacement in the RV is present in cardiac MRI showed focal fatty replacement and other abnormalities of the RV in most of patients with frequent monomorphic RV extrasystoles. In A long-term follow-up study, no patient died of SCD nor developed ARVC/D; two-thirds of the patients were asymptomatic, and, in half of the patients, ectopy had disappeared (**Gaita 2001**).

Some radiologists erroneously consider fatty substitution as the main sign of ARVC/D, even though an evaluation of fat substitution alone may be a source of error for two reasons (**di Cesare 2003**):

1. Because isolated areas of fatty replacement are not synonymous with ARVC/D since small non-transmural focal fatty areas of fat are also present in the normal patients;
2. Because the MRI detection of fat may be overestimated due to partial-volume artefacts with normal subepicardial fat.

Fatty infiltration of the RV has to be considered "per se" a sufficient morphologic hallmark of ARVC/D is a source of controversy; ARVC/D should be kept distinct from both fatty infiltration of the RV and adipositas cordis. In fact, it is well known that a certain amount of intramyocardial fat is present in the RV anterolateral and apical regions even in the normal heart and that the epicardical fat increases with increasing body weight. However, both the fibro-fatty and fatty variants of ARVC/D show, besides fatty replacement of the RV myocardium, degenerative changes of the myocytes and interstitial fibrosis, with or without extensive replacement-type fibrosis.

The need to adopt strict diagnostic criteria is warranted not only in the clinical setting but also in the forensic and general pathology arena. When dealing with a case of SD, in which the only morphologic finding consists of an increased amount of epicardial or intramyocardial fat, a more convincing arrhythmogenic source such as myocardial inflammatory infiltrates, fibrosis, anomalous pathways, and ion channel disease should always be searched for, in order to avoid an over-diagnosis of ARVC/D cases (**Basso 2005**).

The following table shows the main differences between both entities:

	Fatty Replacement of the Right Ventricular myocardium without fibrosis (FaRV)	ARVC/D
Anatomopatological aspect	Show normal or increased myocardial thickness, a diffuse increase in intramyocardial and epicardium fat, little inflammation, and an absence of myocardial atrophy. Intramyocardial fat was frequently seen in normal hearts, especially in the anteroapical region, but was less extensive than in fibrofatty ARVC/D.	Characterized by RV myocardial thinning, fat infiltration of the anterobasal and posterolateral apical RV, subepicardial LV fibrofatty replacements (64%), myocyte atrophy (96%), and lymphocytic myocarditis (80%).
Family history of premature SCD	Negative: 0%	Positive (56%)
History of arrhythmias	Negative	Frequently positive
SCD tendency	Negative*	Frequently
ECG clues	Absent	Very important and frequently
MVT with LBBB pattern	Negative	Characteristic

* It is important to differentiate the entity called "**adipositas cordis sudden death**". It is an entity clinically characterized by SD as the first symptom near 80% of the cases. ≈1/5 of the cases complain of dyspnea or chest distress. At autopsy, the subjects' heart weight was mild or moderately increased, and a large amount of fatty tissues but not fibrous or fibro fatty was accumulated underneath the epicardium and infiltrated toward the RV walls, and even infiltrated to all layers of the cardiac walls. Regional epidemiological data showed that about 80% of cases were living north and only 20% were living south of the Yangtze River, China, but not any familial heredity. Adipositas cordis SD is a very severe disease, it occurs mostly in youth and middle-aged and SD is often (80%) the first symptom. There is a significant regional difference, but not any genetic correlation. We do not know the pathogenesis of adipositas cordis SD (**Liang 2015**).

	Ulh Anomaly, Uhl's disease or "Parchment RV"	ARVC/D
Cardiothoracic index	Over 0.60 is more common (**Fontaine 1982**)	Normal or only slight cardiomegaly
Exercise induced deaths	Rare	Frequent
Pathology	Uhl's anomaly of the right ventricle is an unusual cardiac disorder with almost complete absence of right ventricular myocardium, normal tricuspid valve, and preserved septal and left ventricular myocardium (**Ulh 1952**). Whole heart in diffuse forms (parchment heart). Absence of myocardium in the juxta-septal anterior wall of the RV (**Tabib 1992**). Partial aplasia of the myocardium of the anterior wall of the RV (**Luders 1988**) or RV myocardial hypoplasia (**Iakovtsova 1989**). The RV wall is very thin and hypocontractile. The endocardium essentially connects directly to the epicardium without the muscle layer in between. The tricuspid valve hinges normally, is not dysplastic, and serves to exclude Ebstein's anomaly of the tricuspid valve as the cause of a dilated and thin-walled RV. The right atrium is dilated and hypertrophied as a consequence of the RV restrictive cardiomyopathy and dependence on atrial contraction to augment pulmonary artery forward flow.	**1) Fatty** (40%): adipose infiltration of the RV was either isolated (20%) or associated with fibrosis (74.5%) and lymphocytes (5.5%). **2)Fibro-fatty** (60%) associated to RV wall thinning as a consequence of apoptosis and secondary repair by fibro-fatty tissue mediated by patchy myocarditis. The association with focal lymphocytic myocarditis is high, as well as with LV and septum involvement; and appearance of RV aneurysms and inflammation is almost exclusive to the fibro-fatty variety. Whether inflammation is a primary phenomenon or a spontaneous reaction to apoptosis, still remains to be solved (**Basso 1996**).
Macroscopic appearances	Severe dilatation of the ventricle and almost complete absence of muscle fibers only leaves a few zones with surviving, partially degenerated myocardial fibers. The parietal wall was paper thin with complete absence of musculature and apposition of the endocardial and epicardium layers (**Gerlis 1993**). Heart with a parchment-like appearance to its walls (**Sutter 1996**). There is an absence of fibrofatty infiltration of the right ventricular free wall (**Tumbarello 1998**).	Seems to be a slowly progressive condition with one or more localizations in the RV where the myocardium is replaced by adipose or fibro-adipose tissue with progression of lesions from the epicardium towards the endocardium. These fibers may be the site of slowing of activation and the anatomical basis of intraventricular reentry phenomena.

Differential diagnosis between Brugada Syndrome with Minor or Concealed Forms of ARVC/D

Sometime is very difficult or impossible the differential diagnosis between BrS and canceled forms of ARVC/D. The principal differences and similitude between both entities are explained as follow:

Family history of arrhythmia or SCD and gene defects mapped ARVC/D: Positive family history is present in 30% to 50% of cases. In the setting of positive family history, even minor ECG abnormalities are diagnostic. Several gene defects were mapped, thus providing evidence for genetic heterogeneity. Until the present moment if they know the following 12 Types ARVC/D type 3: chromosome 14 Loci 3p21.3.3p23; In the BrS the cardiac sodium channel isoform encodes hH1 and has been mapped to the short arm of chromosome 3 p21-24. ARVC/D occurs in an estimated 1 in 1,000 to 1 in 1,250 people. ARVC can result from mutations in at least 10 genes. Many of these genes are involved in the function of desmosomes, which are structures that attach heart muscle cells to one another. Desmosomes provide strength to the myocardium and play a role in signaling between neighboring cells. Without normal desmosomes, cells of the myocardium detach from one another and die, particularly when the heart muscle is placed under stress (such as during vigorous exercise). These changes primarily affect the myocardium surrounding the right ventricle, one of the two lower chambers of the heart. The damaged myocardium is gradually replaced by fat and scar tissue. As this abnormal tissue builds up, the walls of the right ventricle become stretched out, preventing the heart from pumping blood effectively. These changes also disrupt the electrical signals that control the heartbeat, which can lead to arrhythmia. Gene mutations have been found in 30 to 40% of patients. Mutations in a gene called *PKP2* are most common. In people without an identified mutation, the cause of the disorder is unknown. Researchers are looking for additional genetic factors, particularly those involved in the function of desmosomes, that may play a role in causing ARVC/D.

ARVC/D genetic variants

Type	OMIM	Gene	Locus
ARVD1lpl	107970	*TGFB3*	14q23-q24
ARVD2	600996	*RYR2*	1q42-q43
ARVD3	602086	?	14q12-q22
ARVD4	602087	?	2q32.1-q32.3
ARVD5	604400	*TMEM43*	3p23
ARVD6	604401	?	10p14-p12
ARVD7	609160	*DES*	10q22.3
ARVD8	607450	*DSP*	6p24
ARVD9	609040	*PKP2*	12p11
ARVD10	610193	*DSG2*	18q12.1-q12
ARVD11	610476	*DSC2*	18q12.1
ARVD12	611528	*JUP*	17q21

Brugada Syndrome (http://www.ncbi.nlm.nih.gov/books/NBK1517/): Diagnosis is based on clinical findings. Pathogenic variants in 16 genes have been associated with Brugada syndrome: SCN5A, SCN1B, SCN2B, SCN3B, GPD1L, CACNA1C, CACNB2, CACNA2D1, KCND3, KCNE3, KCNE1L (KCNE5), KCNJ8, HCN4, RANGRF, SLMAP, and TRPM4. Other phenotypes have been associated with other pathogenic variants in the following genes:

- ***SCN5A*** pathogenic variants have been associated with long QT syndrome (**Bezzina 1999, Priori 2000b,Veldkamp 2000, Grant 2002**), Progressive conduction system disease (PCCD, Lenegre disease, isolatedcardiac conduction disease) (**Schott 1999, Tan 2001, Wang 2002**), Atrial fibrillation (**Olson 2005**), Dilated cardiomyopathy (**McNair 2004**), Sick sinus syndrome 1 (**Benson 2003**), Familial paroxysmal ventricular fibrillation 1 (**Watanabe 2011**).
- ***SCN1B*** pathogenic variants have been associated with Temporal lobe epilepsy and generalized epilepsy with febrile seizures plus type 1 (GEFS+1) (**Scheffer 2007**) and AF (**Watanabe 2009**).
- ***SCN2B*** pathogenic variants have been associated with epilepsy (**Haug 2000**).
- ***SCN3B*** pathogenic variants have been associated with AF (**Wang 2010**).
- ***CACNA1C*** pathogenic variants have been associated with LQTS (**Splawski 2004**).
- ***CACNB2*** pathogenic variants have been associated with Lambert-Eaton myasthenic syndrome (**Taviaux 1997**), LQTS (**Burashnikov 2010**).
- ***CACNA2D1*** pathogenic variants have been associated with malignant hyperthermia susceptibility (**Robinson 2000**), SQTS (**Templin 2011**), early repolarization syndrome (**Burashnikov 2010**).
- ***KCND3*** pathogenic variants have been associated with spinocerebellar ataxia (**Bible 2012**), and some polymorphism with susceptibility to long QT syndrome (**Raudenská 2008**).
- ***KCNE3*** pathogenic variants have been associated with hyperkalemic periodic paralysis (**Sternberg 2003**).
- ***KCNE1L*** *(KCNE5)* pathogenic variants have been associated with AF (**Ravn 2008**) and LQTS (**Palmer 2012**).
- ***KCNJ8*** pathogenic variants have been associated with idiopathic VF (**Pérez-Riera 2012**).
- ***SLMAP*** pathogenic variants have been associated with muscular dystrophy (**Bönnemann & Finkel 2002**).
- ***TRPM4*** pathogenic variants have been associated with progressive familial heart block type 1B (**Kruse 2009**).

Age of clinical manifestation

ARVC/D: Manifest between the 15 and 30 years old. Adolescence and early adulthood (**Nava 2000**). The illness is cause of SCD in < 35 years old.

BrS: During adulthood with a mean age of SCD of 41±15 years. The youngest patient clinically diagnosed with the syndrome is 2 days of age, and the oldest is 84 years old.

Sex predominance

ARVC/D: Male predominance or equal: 1.3 to 1:1.

BrS: Male predominance: 8:1 or 10:1. These differences may be related to a larger transient outward current (Ito)-mediated right ventricular epicardium action potential (AP) notch in males versus females, resulting in a higher incidence of all-or-none repolarization at the end of phase 1 and phase 2 re-entry (P2R) when challenged with voltage-gated Na+ and Ca^{2+} channel block (**Fish 2003**).

Pattern of inheritance

ARVC/D: Sporadic (65%) or familial (35%) (**Wlodarska 2004**). Autosomal-dominant, although an autosomal-recessive pattern has also been reported which affects the long arm of chromosome 17 (17q21) associated to non-epidermolytic palmoplantar keratoderma with woolly hair. ("Naxos disease") (**Protonotarios 2001**).

BrS: From 44 unrelated index patients and family members, Schulze-Bahr et al (**Schulze-Bahr 2003**) performed a complete genetic analysis of SCN5A in BrS. The authors concluded that:

The sporadic cases are predominant: 63% against 37% of familiar cases. Disease penetrance (disease absence in some individuals with disease gene), is complete in the SCN5A+ adult patients, but incomplete in SCN5A+ children (17%).Genetic testing of SCN5A is especially useful in familial disease to identify individuals at cardiac risk. In sporadic cases, a genetic basis and the value of mutation screening has to be further determined genetic heterogeneity of the disorder.

Prevalence

ARVC/D: It is estimated as 1/5000 (**Czarnowska 2003**). The prevalence is estimated at 0.4% depending on geographic circumstances (**Hagenah 2004**).

BrS: 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 structurally normal hearts (**Juang 2004**).

	ARVC/D	Brugada syndrome
Age	25-25	35-40
Sex (male/female)	3:1	8:1
Distribution word wide	Endemic in Veneto region (Italy), Nova Scotia and Naxus Greek island.	Endemic in Southeast Asia Thailand, Philippines and Japan.
Inheritance	AD or rarely AR or sporadic	AD or sporadic
Gens mutations	TGFB3, RYR2, TMEM43, DES, DSP, PKP2, DSG2, DSC2, JUP	*SCN5A*, *SCN1B*, *SCN2B*, *SCN3B*, *GPD1L*, *CACNA1C*, *CACNB2*, *CACNA2D1*, *KCND3*,*KCNE3*, *KCNE1L(KCNE5)*, *KCNJ8*, *HCN4*, *RANGRF*, *SLMAP*, and *TRPM4*.
Symptoms	Palpitations, syncope and cardiac arrest	Syncope and cardiac arrest
Circumstances	Effort	At rest
Imaging	Morpho-functional RV and LV abnormalities	Normal
Pathology	Fibrofatty replacement	Normal with exceptions
ECG repolarization	Inverted T-wave in right precordial leads in absence of RBBB and > 12 yo. The fQRS complex on standard 12-lead ECG predicts fatal and nonfatal arrhythmic events in patients with ARVC/D. Therefore, large scale and prospective studies are needed to confirm those findings.	**Type 1:** ST-segment elevation ≥ 2mm (in >1 right precordial lead V_1-V_3 followed by negative symmetrical T wave. **Type 2:** J point and ST segment elevation with saddleback appearance, followed by positive or biphasic T wave. Frequent early depolarization.
ECG depolarization	**ε** wave, parietal block in right precordial leads, late potentials(LPs). fQRS complex on ECG predicts fatal and nonfatal arrhythmic events (**Campolat 20013**).	Right end conduction delay, left axis deviation, LPs. Exceptional **ε** waves. Rare fragmentation of QRS..

	ARVC/D	Brugada syndrome
AV conduction	Developed AV block and SA block 3 degrees (18%) (**Peters 2008**)	PR prolongation HV prolongation or Split His
Ajmaline challenge	Coved-type ST-segment elevation in right precordial leads in 16% (**Peters 2008**)	Always positive
Atrial arrhythmias	Late secondary	Early primary 10-25%
ECG changes	Fixed (mostly)	Dynamic
Ventricular arrhythmias	VT with LBBB and superior axis	Polymorphic VT/VF with very high HR
Monomorphic VT	Is the rule	Possible but unusual
Main mechanism of arrhythmias	Scar-related reentry	Phase 2 reentry
Natural history	Sudden death and heart failure	Syncope and cardiac arrest

Mutations in genes associated with ARVC/D could cause electrophysiological changes that facilitate the pathophysiological mechanism of the BrS. The adhering junctions, cardiac Na^+ channels and gap-junctions, responsible for the electrical coupling between cardiomyocytes, located at desmosomes. Mechanical stability of the intercalated disk is thought to be important for the function of cardiac Na^+ channels and gap-junctions (**Delmar 2010**). In cultured neonatal rat ventricular myocytes a reduction in the expression of plakophilin-2 is associated with a reduction in the I_{Na} (**Sato 2009**) and electrical coupling (**Oxford 2007**). However, no indications of altered I_{Na} characteristics could be found recently in a murine model of heterozygous desmoplakin knockout (**Gomes 2012**). Reversely, loss-of-function in *SCN5A* associated with BrS may predispose patients to develop structural myocardial derangements as observed in ARVC/D.

Differential diagnosis between Carvajal syndrome and recessive form of ARVC/D (Naxos disease)

The following table shows the main differences between Carvajal syndrome and recessive form of ARVC/D.

	Carvajal syndrome	ARVC/D (Naxos disease)
Inheritance pattern	Autosomal recessive. Genetic heterogeneity.	Autosomal recessive
Affected chromosome	6 short arm. (6p24). Caused by a 7901delG mutation in exon 24 of desmoplakin mutations (DSP) and plakoglobin genes (**Nehme 2012**).	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.	It affects predominantly RV.
Manifestations	Woolly hair, palmoplantar keratosis, missing teeth and dilated cardiomyopathy with CHF, first degree AV block, complete LBBB, non-compaction of the apex of the LV.	Unique form of RV cardiomyopathy. It presents a high prevalence of malignant ventricular arrhythmias, including SCD. CHF.
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. Recently was described by the triad oligodontia, hypoacusis, recurrent infections, and noncompaction (**Stöllberger 2016**).	Progressive replacement of myocardial cells by fat and fibrous tissue on RV. Deletion in plakoglobin in ARVC/D 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 (**McKoy 2000**).
Geographic distributions	Spain. Ecuador. Others?	It appears in families descending from the Hellenic island of Naxos and Milos (**Narin 2003**).
Treatment:	Conventional for CHF.	ICD associated to drugs (**Gatzoulis 2000**).

Differential diagnosis with Dilated Cardiomyopathy (DCM)

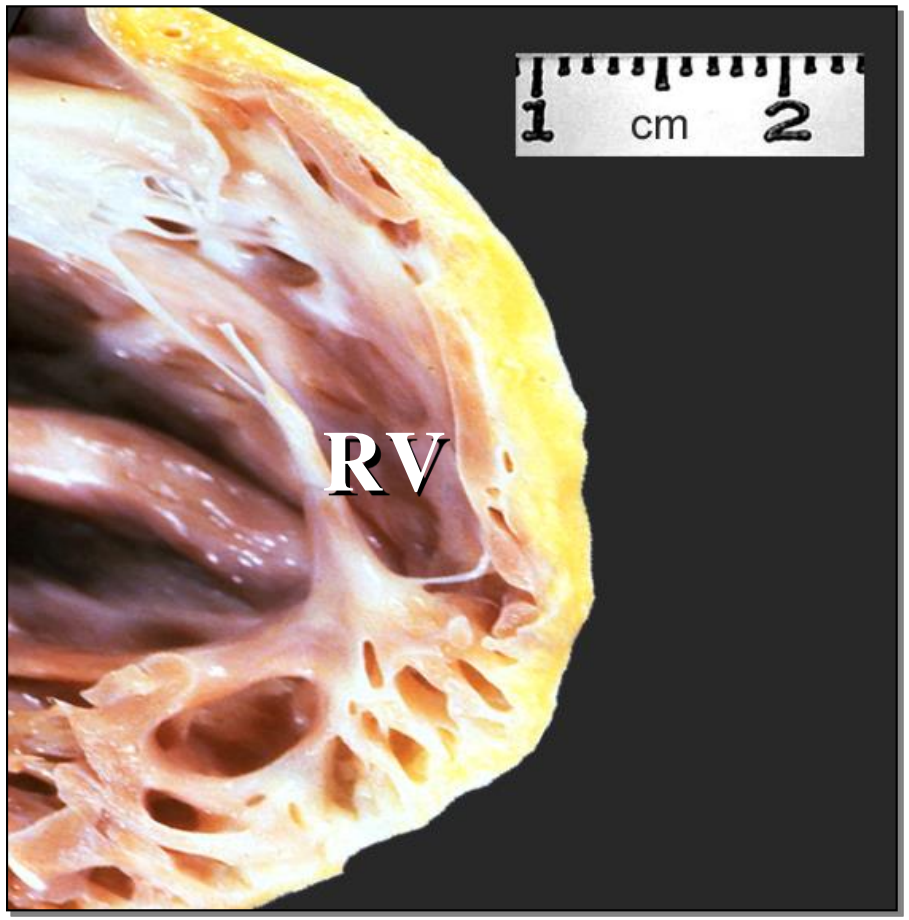
Concept: entity of poorly defined etiology (primary), which surely comprises a heterogeneous, multifactorial group, with a significant immunological component, viral or genetic-familial, isolated or associated, which is characterized by left, right or global chamber dilatation (cardiomegaly) with alteration of contractile function of LV, RV or both. This is translated by systolic dysfunction syndrome, significant decrease of ejection fraction, significant increase of LV end of diastole or both, secondary non-significant ostial mitral or mitro-tricuspid insufficiency, and significant alterations in electrical and autonomous behavior, with a high index of potentially fatal arrhythmic events and frequently accompanied by reactive myocardial hypertrophy.

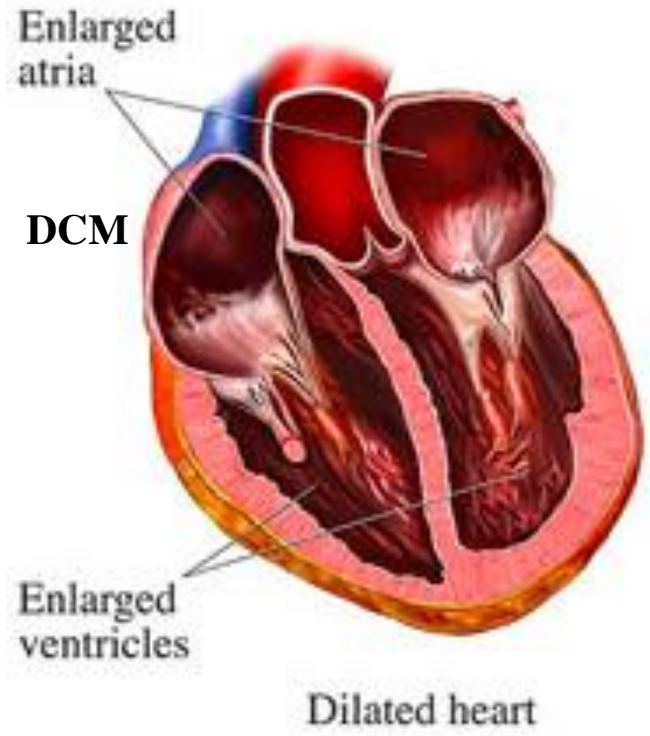
DCM are primary disorders of cardiac muscle associated with abnormalities of cardiac wall thickness, chamber size, contraction, relaxation, conduction, and rhythm. They are a major cause of morbidity and mortality at all ages and, like acquired forms of cardiovascular disease, often result in heart failure. Over the past two decades, molecular genetic studies of humans and analyses of model organisms have made remarkable progress in defining the pathogenesis of cardiomyopathies. Hypertrophic cardiomyopathy can result from mutations in 11 genes that encode sarcomere proteins, and DCM is caused by mutations at 25 chromosome loci where genes encoding contractile, cytoskeletal, and calcium regulatory proteins have been identified. Causes of cardiomyopathies associated with clinically important cardiac arrhythmias have also been discovered: Mutations in cardiac metabolic genes cause hypertrophy in association with ventricular pre-excitation and mutations causing ARVC/D were recently discovered in protein constituents of desmosomes. This considerable genetic heterogeneity suggests that there are multiple pathways that lead to changes in heart structure and function. Defects in myocyte force generation, force transmission, and calcium homeostasis have emerged as particularly critical signals driving these pathologies. Delineation of the cell and molecular events triggered by cardiomyopathy gene mutations provide new fundamental knowledge about myocyte biology and organ physiology that accounts for cardiac remodeling and defines mechanistic pathways that lead to heart failure. DCM are characterized by ventricular chamber enlargement and systolic dysfunction with normal or thin LV wall thickness; usually diagnosis is made with 2-dimensional echocardiography. DCM leads to progressive HF and a decline in LV contractile function, ventricular and supraventricular arrhythmias, conduction system disturbances, thromboembolism, and/or SD / HF related death. Indeed, DCM is a common and largely irreversible form of heart muscle disease with an estimated prevalence of 1:2500. It is the third most common cause of HF and the most frequent cause of heart transplantation. DCM may manifest clinically at a wide range of ages (most commonly in the third or fourth decade but also in young children) and usually is identified when associated with severe limiting symptoms and disability.

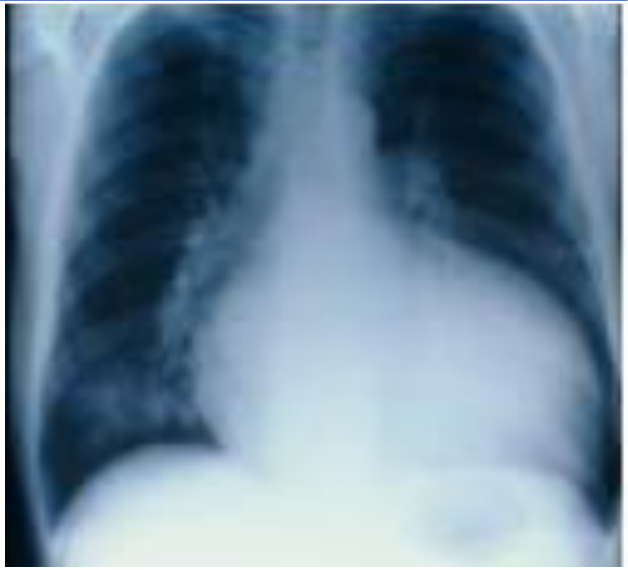
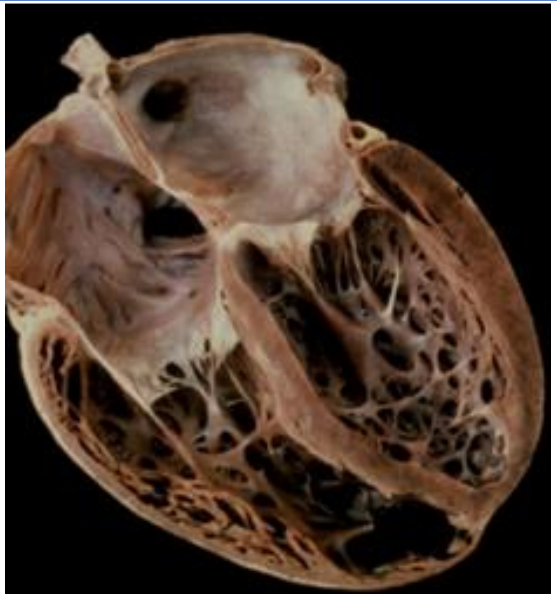
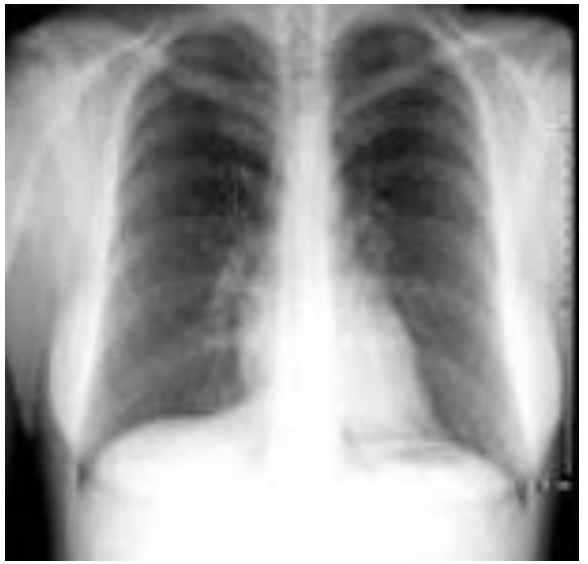
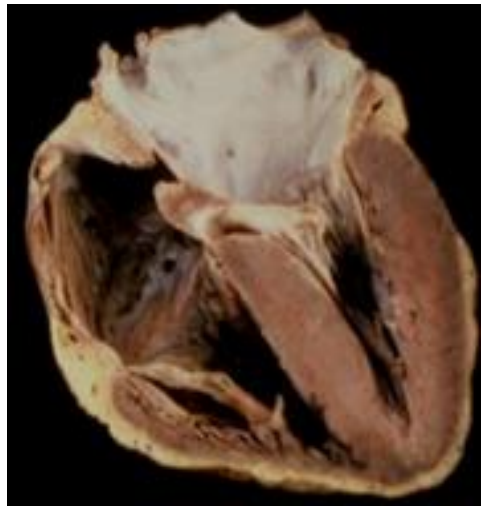
In family screening studies with echocardiography, asymptomatic or mildly symptomatic relatives may be identified.

The DCM phenotype with sporadic occurrence may derive from a particularly broad range of primary (and secondary) causes, including: infectious agents, particularly viruses, often producing myocarditis (coxsackie virus, adenovirus, parvovirus, HIV); bacterial; fungal; rickettsial; myobacterial; and parasitic (eg, Chagas disease endemic in Latin America resulting from Trypanosoma cruzi infection). Other causes include toxins; chronic excessive consumption of alcohol; chemotherapeutic agents (anthracyclines such as doxorubicin and daunorubicin); metals and other compounds (cobalt, lead, mercury, and arsenic); (tafazzin), a mitochondrial protein of unknown function, causes Barth syndrome, which is an X-linked cardioskeletal myopathy in infants. Autoimmune and systemic disorders (including collagen vascular disorders); pheochromocytoma; neuromuscular disorders such as Duchenne/Becker and Emery-Dreifuss muscular dystrophies; and mitochondrial, metabolic, endocrine, and nutritional disorders (eg, carnitine, selenium deficiencies). About 20% to 35% of DCM cases have been reported as familial, although with incomplete and age-dependent penetrance, and linked to a diverse group of 20 loci and genes. Although genetically heterogeneous, the predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance less frequent. Several of the mutant genes linked to autosomal dominant DCM encode the same contractile sarcomeric proteins that are responsible for HCM, including -cardiac actin; -tropomyosin; cardiac troponin T, I, and C; beta- and -myosin heavy chain; and myosin binding protein C. Z-disc protein-encoding genes, including muscle LIM protein, -actinin-2, ZASP, and titin, also have been identified. DCM is also caused by a number of mutations in other genes encoding cytoskeletal/sarcolemmal, nuclear envelope, sarcomere, and transcriptional coactivator proteins. The most common of these probably is the lamin A/C gene, also associated with conduction system disease, which encodes a nuclear envelope intermediate filament protein. Mutations in this gene also cause Emery-Dreifuss muscular dystrophy. The X-linked gene responsible for Emery-Dreifuss muscular dystrophy, emerin (another nuclear lamin protein), also causes similar clinical features. Other DCM genes of this type include desmin, caveolin, and β-sarcoglycan, as well as the mitochondrial respiratory chain gene. X-linked DCM is caused by the Duchenne muscular dystrophy (dystrophin) gene. The clinical and pathologic differential diagnosis of DCM is meant to exclude secondary causes of HF. Pathologically, the histologic features are nonspecific. Grossly, enlarged, dilated hearts can be seen in long-standing hypertensive heart disease, valve disease and severe CAD should be excluded. At endomyocardium biopsy, amyloid, iron deposition, and significant inflammation should be excluded by routine staining supplemented by special stains. In addition, the clinical history that excludes other causes of HF should be elicited before a specific diagnosis of DCM is made.

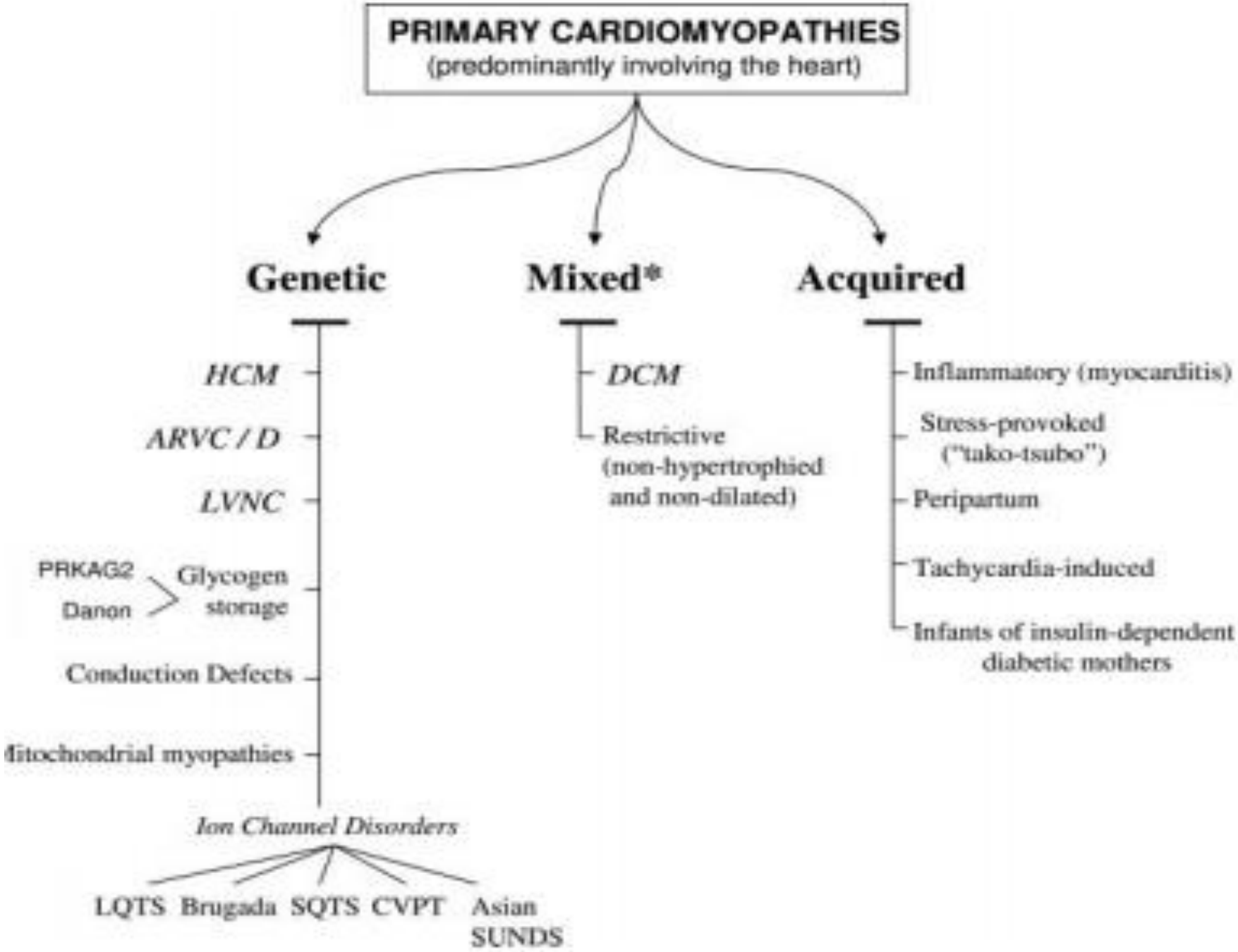
Finally, the biventricular subtype of ARVC/D defined by early and parallel involvement of the RV and LV (**Sen-Chowdhry 2010**) or in the advanced stage of ARVC/D characterized by biventricular dilation and systolic impairment is another differential diagnosis. The clinical picture is generally characterized by a composite of right-dominant or left-dominant features. Ventricular arrhythmias of both RBBB and LBBB patterns may occur, and at least 15% of cases RBBB and LBBB patterns may occur, and at least 15% of cases show both morphologies of PVCs. The ratio of RV to LV volume remains close to 1 throughout the disease course. During the progression of the disease an initial right or left-dominant pattern can evolve into a biventricular dysfunction (**Pinamonti 1995; Corrado 1997**). Biventricular arrhythmogenic cardiomyopathy can mimic clinically and at imaging examinations a DCM and be diagnosed only by pathologic examination at necropsy or of the explanted heart (**Nemec 1999**).





DCM		Normal heart	
Chest X-Ray posteroanterior view	**Macroscopic pathological features**	**Chest X-Ray posteroanterior view**	**Normal heart specimen**
			

DCM is a progressive disease of heart muscle that is characterized by ventricular chamber enlargement and contractile dysfunction with normal or thin left ventricular (LV) wall thickness. The right ventricle may also be dilated and dysfunctional. DCM is the third most common cause of HF and the most frequent reason for heart transplantation.


PRIMARY CARDIOMYOPATHIES
(predominantly involving the heart)
Genetic
Mixed*
Acquired
HCM
ARVC / D
LVNC
PRKAG2
Danon
Glycogen storage
Conduction Defects
fitochondrial myopathies
Ion Channel Disorders
LQTS
Brugada
SQTS
CVPT
Asian SUNDS
DCM
Restrictive (non-hypertrophied and non-dilated)
Inflammatory (myocarditis)
Stress-provoked ("tako-tsubo")
Peripartum
Tachycardia-induced
Infants of insulin-dependent diabetic mothers

Conclusions: Answer to the questions:

1. Which is the diagnosis of the event? Sustained monomorphic VT with LBBB pattern and superior QRS axis (major criteria), fusion beats. Additionally, clinical evidence of AV dissociation: Canon waves and variation in first sound intensity.
2. Which is the ECG diagnosis after the event? Biatrial enlargement, bizarre very broad complete RBBB, probable LVH in association with severe RVH (biventricular hypertrophy). Septal fibrosis? VCG RBBB type Cabrera with bizarre appearance because of LVH in association and **ε** wave with multiple oscillations inside the QRS complex, observed in right precordial leads, inferior leads and aVR ("pre-, top-, and postsilons")*.
3. Which is the most probable clinical diagnosis? ARVC/D with biventricular involvement, confirmed by echo, magnetic resonance imaging, SA-ECG (positive late potentials), and family genetic screening. Mutation in PKP2 (plakophilin 2) in several members, confirmed desmosomepathy** (see next slide), Cytogenetic Location: 12p11. The biventricular subtype of ARVC/D is defined by early and parallel involvement of the RV and LV (**Sen-Chowdhry 2010**). Advanced disease is characterized by biventricular dilation and systolic impairment. The clinical picture is generally characterized by a composite of right-dominant or left-dominant features. Ventricular arrhythmias of both RBBB and LBBB patterns may occur, and at least 15% of cases show both morphologies of PVCs. The ratio of RV to LV volume remains close to 1 throughout the disease course. During the progression of the disease an initial right or left-dominant pattern can evolve into a biventricular dysfunction (**Pinamonti 1995; Corrado 1997**). Biventricular arrhythmogenic cardiomyopathy can mimic clinically and at imaging examinations a dilated cardiomyopathy and be diagnosed only by pathologic examination at necropsy or of the explanted heart (**Nemec 1999**).

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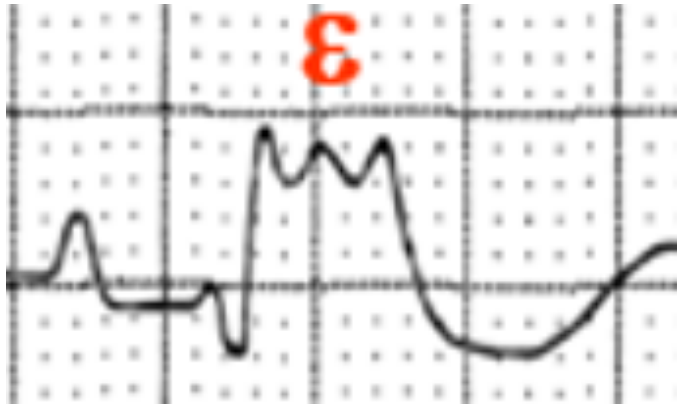

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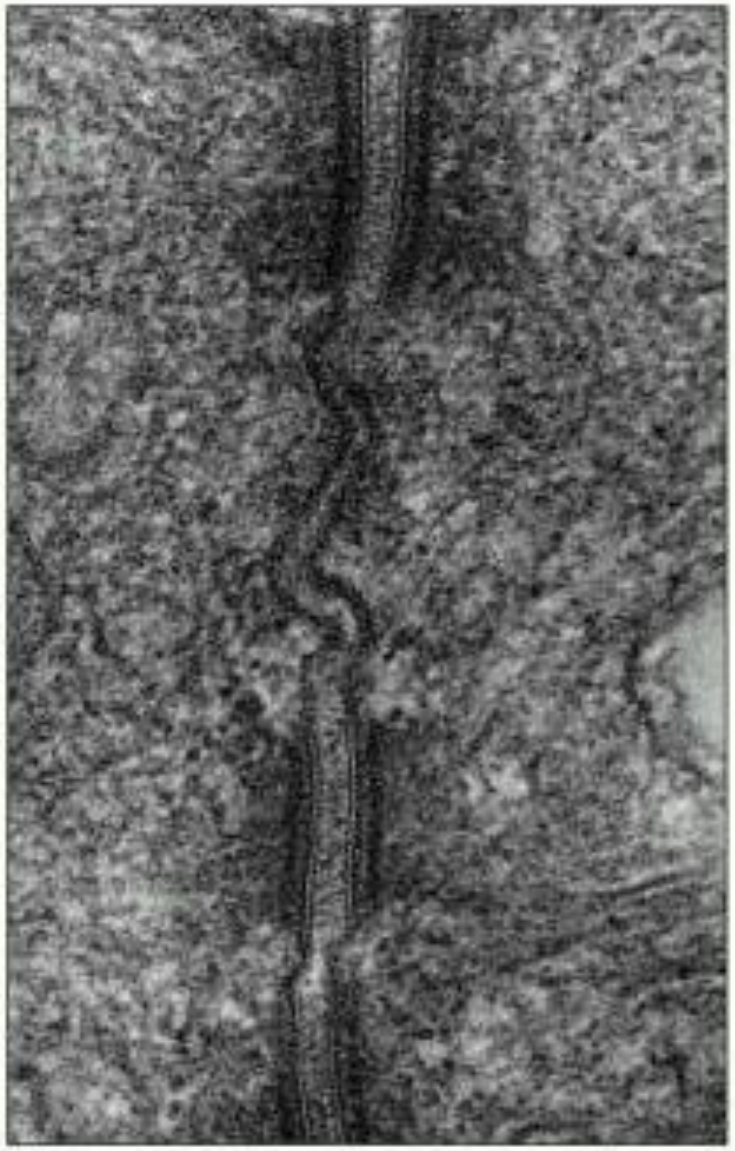
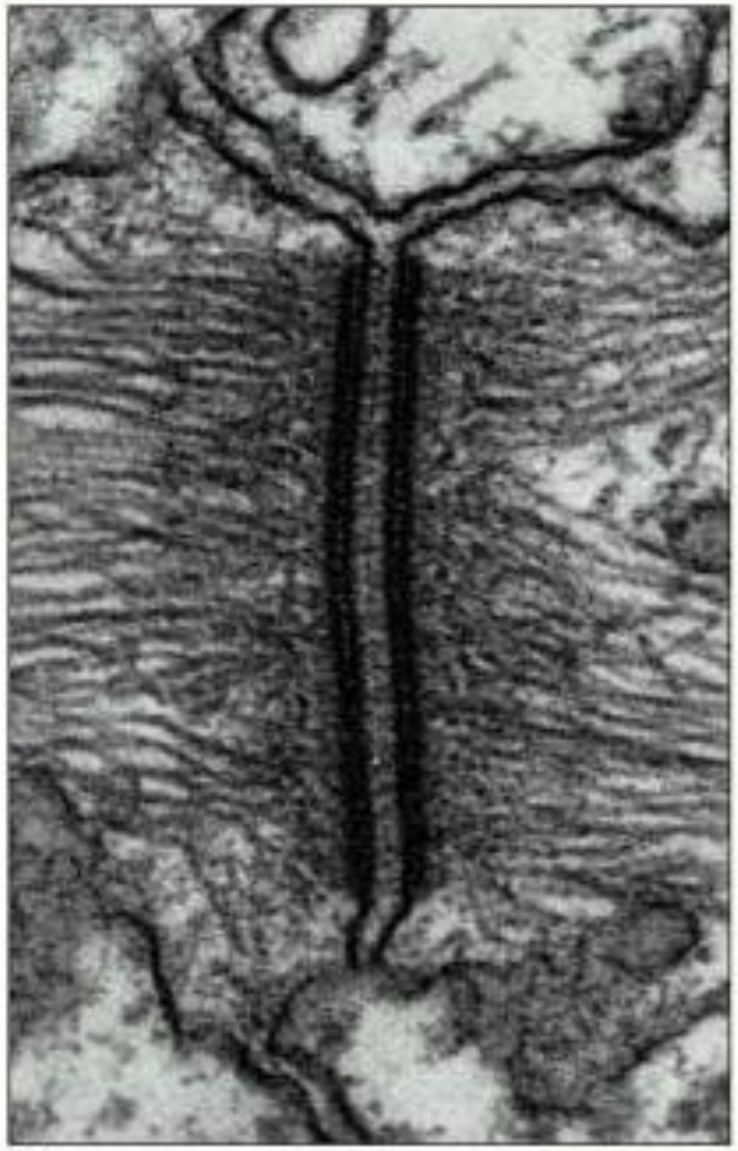
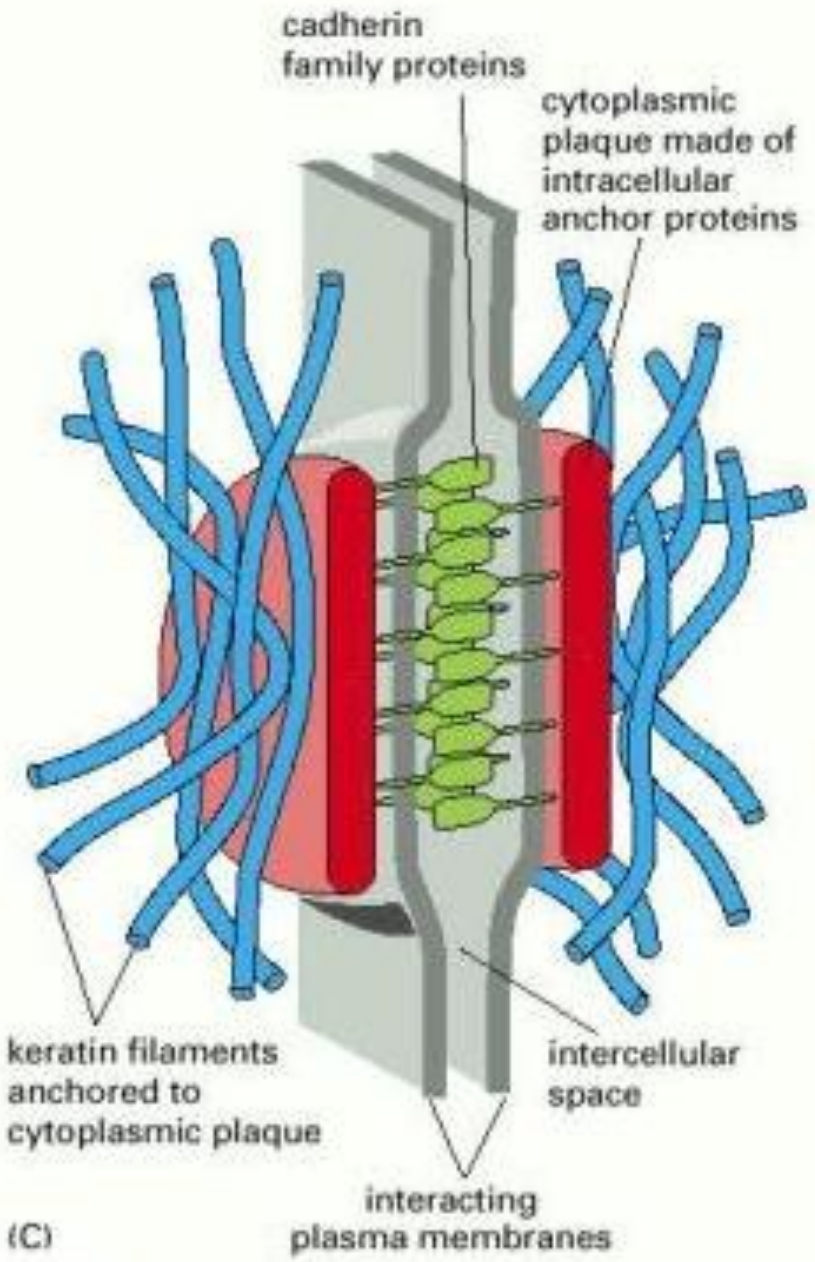
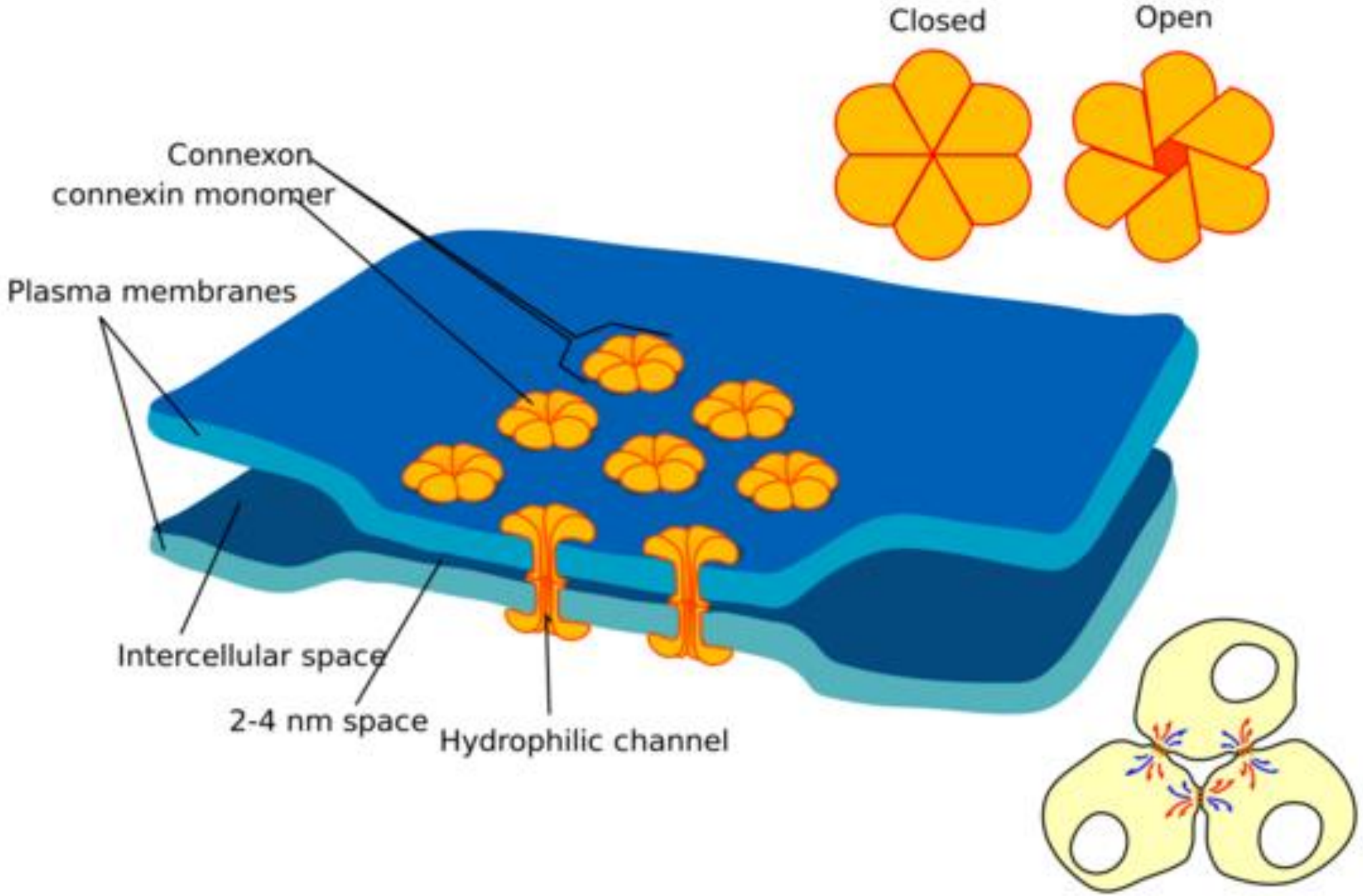
Desmosome structure







Desmosome structure



4. Which is the appropriate approach?

a) Eligibility for exercise in specific recreational or competitive sports activities are strongly discouraged. It corresponds to the present case.

b) Pharmacological treatment of heart failure and empirical drug therapy: sotalol; amiodarone +/- ; β-blockers, carvedilol (α and β-blocker). Treatment of biventricular heart failure (carvedilol + furosemide + spironolactone).

c) Anticoagulation: In patients in whom ARVC/D has progressed to severe RV or biventricular systolic dysfunction with risk of thromboembolic complications.

d) RFCA: Seldom curative; it may modify substrate to permit AA drugs to be effective.

- Arrhythmias of different morphology tend to recur.
- In general the procedure does not have success for the gradual nature of the illness and the multiple morphologies of VT.
- Defining the abnormal electrophysiological anatomical VT substrates mapping for guiding ablation of ARVC/D-VTs using a non-contact mapping system linear ablation across a critical isthmus or between the early activation and the exit point can effectively cure these arrhythmias. Useful for electrical storm (**Zou 2004**).

e) Prophylactic CDI in this case, because documented unequivocal syncopal episode

- Patients with documented cardiac arrest or unequivocal syncopal episode that cannot be induced in PES;
- Patients who have non-coronary ST segment elevation in the right precordial leads. They may have inducible PVT/VF at rest or sleep;
- SCD in a close family member;
- Patients that do not want to take antiarrhythmic drugs for the rest of theirs lives;
- Patients in who drugs are producing unacceptable side effects;
- Patients who do not respond to drug therapy by PES or because of clinical recurrence.

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