YOUNG ATHLETE WITH REPEATED EPISODES OF SYNCOPE
ATLETA JÓVEN CON EPISODIOS REPETIDOS DE SÍNCOPE
ATLETA JOVEM COM EPISÔDIOS REPETITIVOS DE SÍNCOPE

Andrés Ricardo Pérez-Riera MD. Ph.D.
Faculdade de Medicina do ABC - Fundação do ABC- Disciplina de Cardiologia Setor de Eletrovetorcardiografia Santo André, São Paulo, Brazil.
ABC Faculty of Medicine, Discipline of Cardiology, Foundation of ABC, Santo André, São Paulo, Brazil. riera@uol.com.br

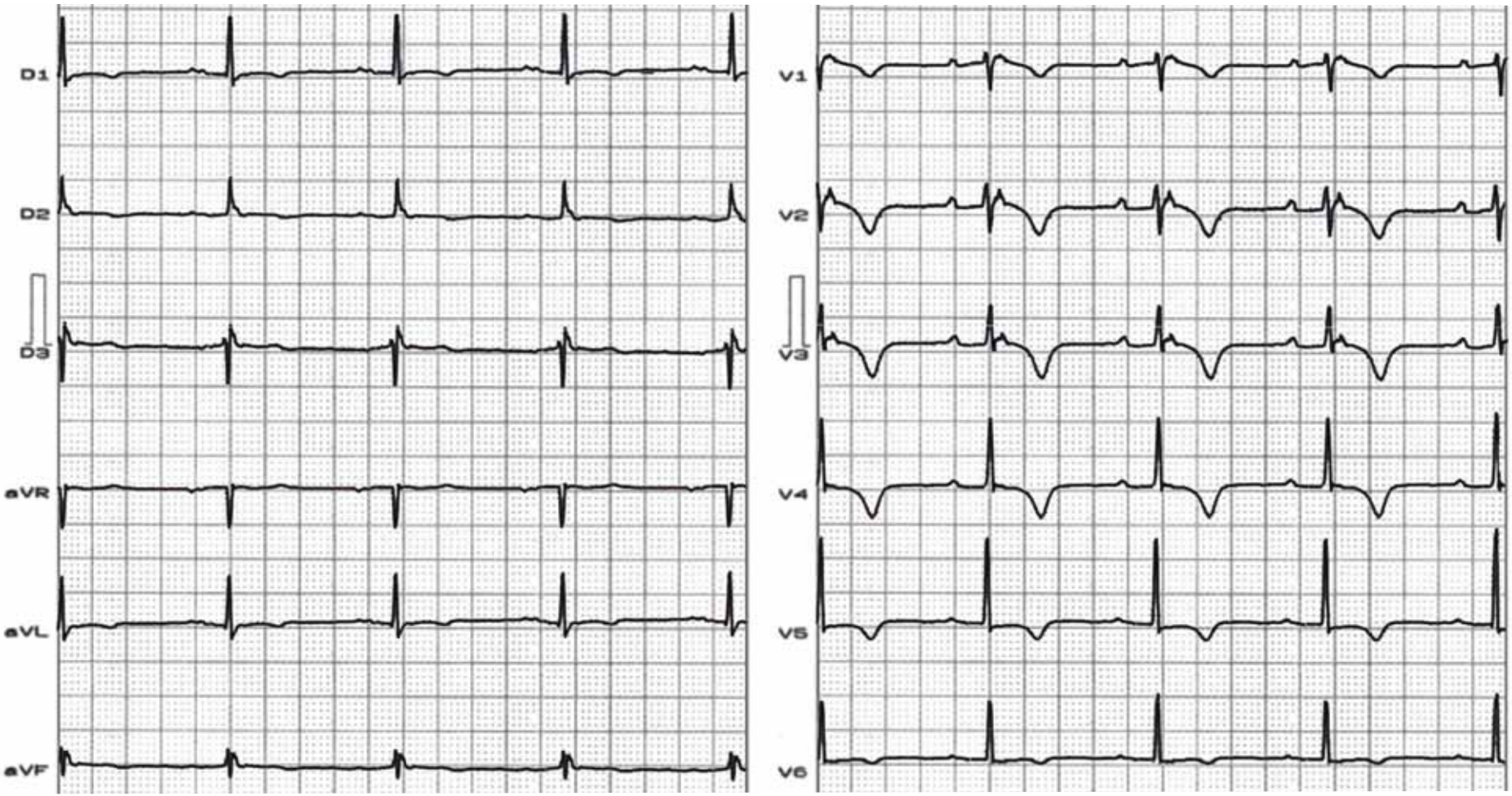
CASE REPORT

An 27-year-old masculine Caucasian Brazilian professional athlete of mixed martial arts (MMA). He was referred to our consultation for presenting three syncope episodes induced by efforts in the last two months. He had been practiced competitive exercise five days a week since the age of 17.
Interrogatory: Positive familial background of sudden death in first degree young relative (<40yo). His ancestral are immigrants from the north-eastern part of Italy (Belluno province)
Physical Examination: within normal limits.
The following electrocardiogram preformed at rest showed inverted T-waves across all precordial leads (from V_1 to V_6).
ECG preformed 3 years ago normal.

What is the ECG diagnosis?
Which is the appropriate approach?

Paciente masculino branco 27 anos atleta profissional Brasileiro de MMA foi encaminhado a nossa consulta por apresentar três episódios de sincopes induzidos por esforços nos últimos dois meses. Ele vem praticando exercícios competitivos cinco vezes por semana desde os 17 anos de idade.
Interrogatório: refere morte súbita em familiar de primeiro grau jovem(<40anos).
Seus ancestrais são imigrantes do nordeste da Itália da província de Belluno.
Exame físico: dentro dos limites da normalidade
O seguinte ECG realizado em repouso mostra ondas T invertidas em todas as precordiais de V_1 a V_6.
ECG realizado três anos antes normal.

Qual é o diagnóstico eletrocardiográfico?
Qual a conduta adequada?


D1
D2
D3
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

Colleagues Commentaries

Andres,

The ECG is very striking, particularly in leads V1-3. Combine this with the history, I would evaluate this young man for Arrhythmogenic Right Ventricular Dysplasia or cardiomyopathy. I believe the terminal components of the anterior precordial leads are Epsilon or Fontaine waves and while not absolutely pathognomonic for ARVD, with the clinical and family history, this is where I would look first. The syncopal episodes only started to occur recently. I would initiate long term Holter monitoring to assess his ambient level of arrhythmias. In addition, I would recommend that he discontinue his active participation in vigorous athletic activities, even on a personal level in addition to a competitive level until an diagnosis is made. It would be appropriate to begin to talk to him, with the family history, about the possible implantation of an ICD implant fully realizing that this might restrict vigorous athletic activities in the future.

Paul

Paul A. Levine MD, FHRS, FACC, CCDS
25876 The Old Road #14
Stevenson Ranch, CA 91381
Cell: 661 565-5589
Fax: 661 253-2144
Email: paul91321@gmail.com

Andres,

O ECG é muito marcante, principalmente nas derivações V1-3. Combine isso com a história, gostaria de avaliar esse jovem para a displasia arritmogênica do ventrículo direito ou miocardiopatia. Acredito que os componentes do terminal leva anterior precordial são ondas Epsilon ou Fontaine e, embora não absolutamente patognomônicos de DAVD, com a história clínica e familiar, este é onde eu ficaria em primeiro lugar. Os episódios de síncope só começaram a ocorrer recentemente. Gostaria de iniciar Holter para avaliar seu nível de de arritmias. Além disso, eu recomendaria que se interrompa sua participação ativa em atividades atléticas vigorosas, mesmo em um nível pessoal, além de um nível competitivo até que um diagnóstico seja feito. Seria apropriado para começar a falar com ele, com a história da família, sobre a possível implantação de um implante de CDI plena consciência de que isso poderia restringir atividades atléticas vigorosas no futuro.

Dear Andres,

Thank you so much for sharing this case.With a positive family Hx of premature sudden death, personal Hx of being a competitive endurance training athlete for 10 years and ECG findings of 1) inverted T waves in V1-6, DI, DII and aVL; 2) epsilon waves in V2-3, my first suspicion is this 27 y.o. young man may suffers from ARVD (perhaps in the advanced stage with left ventricular involvement).

Since he has had three syncopal events he is a high risk patient. Besides good image tests to confirm the Dx and genetic testing to consider, EP study should be considered. If VTs (likely in LBBB morphology) are easily inducible, VT ablation and ICD will do help.

Please keep me posted for the outcome.

Li

Caro Andres: Muito obrigado por compartilhar este caso.
Com uma família positiva de morte súbita prematura, Historia pessoal de ser um atleta de treinamento competitivo de resistência para 10 anos e os resultados de ECG
1) ondas T invertidas em V1-6, DI, DII e aVL; ondas 2) epsilon em V2-3
minha primeira suspeita é que este jovem de 27 pode sofre de DAVD (talvez no estágio avançado com envolvimento ventricular esquerdo).
Desde que ele teve três síncope ele é um paciente de alto risco. Além de exames de imagem bons para confirmar o Dg e testes genéticos a considerar, estudo EP deve ser considerada. Se TVs (provavelmente na morfologia BRE) são facilmente induzível, VT ablação e ICD ajudará.
Por favor, mantenha-me informado pelo resultado.

Dear Andres,
the ECG findings are;
1) first degree AV block,
2) rSr' pattern in V1, but not RBBB (no S wave in V6),
3) epsilon wave in V1-2,
4) QRS duration in V1-3>V4-6,
5) T wave invertion in V1-6.
These are criteria for RV arrhythmogenic cardiomyopathy and due to the fact that his ancestrals come from Belluno province it seems that he has Naxos disease.
Thank you for the presentations.
I am waiting for your final comments which are very didactic.
Regards
Stavros N. Konstantinidis
Cardiologist
Florina-Greece

Prezado Andrés O ECG mostra: bloqueio AV de primeiro grau, padrão rSr´em V1 mas não BRD pela ausência de S em V6, onda epsilon en V1-V2, duração do QRS de V1 a V3 > que de V4 a V6, onda T invertida de V1 a V6.
Há critérios de DAVD devido ao fato que seus ancestrais são procedentes da provincia de Belluno o que sugere que ele tem a doença de Naxos
Obrigado pelas suas apresentações
Espero por seus comentários finais sempre muito didáticos.
Cumprimentos
Stavros N. Konstantinidis
Cardiologist
Florina-Grécia

Potro
MIre como se hace:Joven con sincope, con familiar directo con muerte subita, provenienetes de la region Italiana mencionada: hasta que se demuestre lo contrario es una Displasia Arritmogenica del Ventriculo Derecho. Si ademas Ud le suma:

1. Voltajes bajos
2. Bloqueo completo o incompleto de rama derecha
3. Desviacion del eje a la izquierda
4. Inversion de onda T de V1 a V4
5. Onda Epsilon
Se cumpliria el axioma de: si tiene 4 patas y ladra: es perro.
Pues aqui Ud tiene un buen perro de buena raza
Diagnostico: ARVD
Confirmar con: RNM
Puede hacerse EEF e intentar ver caracteristicas de las arritmias, pero dada la condicion evolutiva de esta enfermedad y lo impredecible del comportamiento de la arritmia: debe implantarse un CDI.
Desde la agitada isla de Antigua, reporto AB, para el increible mundo del Foro de Arritmias en Internet!
AB

Dr Andrés, miocardiopatia/displasia arritmogenica do VD.Estou de acordo com Dr Adrian
Raimundo

Perdonen nunca intervengo pero ustedes me hace estudiar:
Tiene ecocardiografía? Esta recibiendo alguna medicación?
Por lo que he leido podria ser miocardiopatía arritmogénica del ventrículo derecho, es una causa frecuente de muerte súbita en deportistas. Es una enfermedad de causa genética. Es una enfermedad más difícil de diagnosticar
que la miocardiopatía hipertrófica. Los afectados por esta enfermedad no deben realizar ejercicio físico. La enfermedad progresa más rápidamente en los deportistas. Esta enfermedad es la primera causa de muerte súbita en jóvenes y deportistas italianos.Ud dirán si estoy muy equivocada gracias

Saludos Rita Rufo de Uruguay

Estimado Maestro Perez Riera:
Comparto el diagnostico presuntivo de DAVD, como bien han referido. y los criterios diagnosticos para esta.
Ademas bajos voltajes en las derivaciones de los miembros, y precordiales izquierdas con trastornos de la repolarizacion en cara lateral y lateral alta. Y el patron rSr' en DIII y AVF, presenta los criterios de DAVD, y afectacion del VI, en diferentes mutaciones se puede observar ademas de la infiltracion grasa del VD, compromiso del VI con infiltracion grasa del mismo.
Conducta?
RMN cardiaca
Con el resultado de estos si confirma el diagnostico presuntivo. CDI.
ECG a familiares del paciente.
Interesante caso para un estudio genetico.
Saludos
Martin Ibarrola

ECG: Ritmo: sinusal , FC: 60 x', Eje QRS: 0º, PQ: 0,22 a 0,24, QRS: 0,10, QT: 0,32", Bloqueo AV 1er G, BIRD, alteraciones repolariz ventricular (sobrecarga ventricular).La prevalencia e incidencia de la DAVD en la población general es desconocida. En el norte de Italia y Francia hay una alta frecuencia de casos detectados, lo que sugiere o bien la participación de factores genéticos y ambientales o bien una mejor precisión diagnóstica debido a una búsqueda sistemática de la enfermedad. La edad media en el momento del diagnóstico se sitúa en los 30 años, que coincide con la edad de inicio de los síntomas. Se observa una prevalencia mayor en el sexo masculino y se pueden encontrar antecedentes familiares en aproximadamente un 30% de los pacientes . La presentación clínica más habitual consiste en la presencia de crisis de TV MS que pueden provocar síncope o incluso FV. Sin embargo, en la mayoría de pacientes son bien toleradas puesto que la función ventricular izquierda se halla preservada. Típicamente en el ECG durante la TV se observa un patrón de BCRI, puesto que ésta se origina en el VD. Ocasionalmente, si el origen se halla situado en el septum intraventricular, se puede presentar un patrón de BRD. Se han descrito casos de pacientes asintomáticos en quienes la primera manifestación de la enfermedad es en forma de muerte súbita. Igualmente, la enfermedad se puede manifestar en algunos casos en forma de insuficiencia ventricular derecha lentamente progresiva sin la presencia de taquicardia ventricular . Un dato a tener en cuenta es la alta prevalencia del diagnóstico de displasia en atletas y deportistas. No sabemos si este alto índice de diagnósticos en deportistas se debe a que las taquicardias son a menudo inducidas por el esfuerzo, lo que lleva a un diagnóstico más habitual en atletas o si es el mismo ejercicio el que modifica las características del VD facilitando la aparición de anomalías estructurales. Estudios complementarios ECG, ECG de señal promediada, Rx de torax, técnicas por imagen no invasiva, ecocardiograma, ventriculografía isotópica, resonancia nuclear magnética, tomografía axial computarizada, angiografía del VD, biopsia endomiocárdica, estudio electrofisiológico Referencias:)Rev Esp de Cardiología. 1997; 50: 541-7.-Vol.50 Displasia arritmogénica del ventriculo derecho. Josep Brugada. Lluis Monti y Ramón Brugada. Unidad de Arritmias. Instituto Cardiovascular. Hospital Clinic i Provincial. Universidad de Barcelona. Eduardo Quiñones.

No por vieja es menos cierta. El ECG es el primer estudio que debemos realizar ante la sospecha de una arritmia, luego podría continuar con un Holter (24, 48, implantable) para documentar la arritmia (si tenemos suerte). El ecocardiograma no da resultados definitivos. Pasariamos a la resonancia magnética o a la ventriculografía isotópica, el estudio electrofisiologico, y como ultimo recurso (aunque a veces hay que acertar el lugar de la zona arritmogenica) a la biopsia.
Los sintomas clínicos y los antecedentes (personales y familiares) nunca se descartan a pesar de las nuevas tecnologías, y eso es lo mas viejo.
Con afecto Eduardo Quiñones.

Querido Dr Quinones
Gracias por su resumida clase. Y Ud que piensa?
Que le haria Ud de todos los estudios que menciona en la lista? Todos? Algunos? Ha dedicado seis lineas de su email a describir como es la TV en DAVD, pero este paciente NO tiene TV documentada.
Creo que es importante recordar los datos que Ud da, pero debe Ud procesarlos de alguna manera, para que se ajusten a la disucsion del caso (como hace el Maestro Riera, por ejemplo). Me llamo la atencion que ni siqueira Ud mencione criterios mayores y menores de la enfermedad...). Yo le pregunto: le haria una biopsia a este paciente? A que paciente le haria Ud una biopsia con el fin de descartar DAVD?
Algun estudiante de los muchos que tenemos en el foro podria, de acuerdo a su clase, pensar que a este paciente Ud le indicaria una biopsia (como dice el anteultimo estudio). Pero no es asi...o si? Ud le haria una biosia?
Gracias por aclarar mis dudas, (la referencia es buena, pero NO es considerada referencia "madre" y ademas es un poco anticuada, dado los avances que se han hecho en los ultimos 5 anios...)
AB

Hola como les va? en este caso el episodio de síncope se relaciona con la inversión de la onda T en DI, V1,V2,V3,V4,V5 y V6, y presenta criterios de bloqueo de rama bisfacicular.
Que estudios previos tenía cuando llego a este nivel de lesión que afecto el corazón con esta cardiopatía restrictiva dando como resultado lo visto anteriormente? es evidentete en DII,III y aVF el patrón de QRS no se distinguen bien las ondas P y T y resalta el bloqueo bifascicular. Tenía antecedentes de hipertensión pulmonar? QRS en VI, V2,V3 tiene la morfología de bloqueo bifascicular como quedó posterior al evento sincopal y si decidieron aplicarle un marcapasos.

Gregorio Malsivar

El tema es,...y despues que? Nosotros lo hemos hecho unas 4-5 veces. Si el pte se presenta con TV, uno siempre puede mapear la TV. Pero si el paciente NO se presenta con TV (como este caso) o si la TV es NO mapeable por compromiso hemodinamico, el tema es mas complejo. Porque? porque la DAVD es progresiva, entonces si te hago el estudio hoy, quemaria en las zonas adyacentes al tejido graso-fibroso, donde encuentre potenciales diastolicos, zonas fragmentadas, etc. Pero dentro de 1-2 anos esas zonas varian porque NO son lesiones fijas sino progresivas.Como uno NUNCA puede estar seguro de remover el sustrato anatomico-electrico en una patologia progresiva, debe recomendar una estrategia "back-up", en este caso un CDI.Entonces la pregunta es: CDI + ablacion?nNo. Porque? Porque puedo esperar. Si el paciente tiene su CDI y nunca la utilizo, porque cuernos voy a quemarle lo poco que le quede de VD sano. Diferente, insisto, si el apciente se presenta con TV. Ahi si, CDI + mapa de voltaje y ablacion. Poruqe? P{Orque Ud de esa manera, si bien no remueve el sustrato (porque es progresivo) por lo menos reduce las descargas del CDI, que son dolorosas y deterioran la calidad de vida de pacientes jovenes.
AB

Adrian:Tu explicación es muy clara, una enfermedad progresiva no puede "aislarse" porque se saltará la barrera que le coloquemos. Lo que Corrado proponía es el mapeo pero sin quemar nada, colocándolo como una prueba anatomica-funcional a la altura de la RNM -que en manos no entrenadas tiene una alta tasa de falsos positivos- o el Eco -que a no ser que tenga una enfermedad muy florida no permite una detección clara-

Entiendo tu punto de vista como el del electrofisiólogo, una vez mapeado querrás hacer algo más.. (En hemodinamia lo llaman el reflejo oculoestenótico, en electrofisio no lo sé, oculotaquicárdico)En este caso puntual más allá de las disquisiciones que se puedan hacer para abarcar con más claridad, el joven deportista tiene altas posibilidades que sea una DAVD. Siguiendo una conducta práctica lo primero que le haría sería un Holter, luego en la consulta un eco y si no veo nada le pediría una RNM.Pienso que si está sintomático tenemos más posibilidades de documentar algun tipo de TV aunque sea no sostenida.

Una vez diagnosticado, te pediría que le coloques un CDI. No tenemos documentada la TV- tal vez el holter- pero los síncopes están ahi .

Diego Fdez

Diego Es un disparate. 1. Cambiar tecnica no invasiva por no invasiva (y NO terapeutica)2. Costos por el cielo, solo el parche de navex 600 y el cateter 25003. Sensibilidad de esta tecnica? (no lei el paper de Corrado, pero el no es invasivo) Todo depende de la mano del operador, el contacto cateter tejido y como uno setea el equipo para determinar que es cicatriz y que es corazon sano. Si yo te digo: maquina, por debajo de 0.5 MV todo es escara, la mitad del corazon aparece gris (escara) pero si le digo: maquina por debajo de 0.25 es escara solo hay un parche gris, y ojo que aun dependo de meter el cateter en el lugar justo.

Un disparate total: esta es una enfermedad MUY rara y atractiva. No compliquemos las cosas: la cine MRI o angio MRI como dijo Banina es el gold standard, la biopsia a pesar de Quinones casi NO se usa mas, y el resto es historia. La ablacion ayuda pero si hubo TV o sincope, se impone el CDI.Tendremos que aprender mas sobre todo esto, pero la incidencia es tan baja que levara años Abrazo AB

Prof. Riera:

Minha atitude é de contribuição/lembrança de como aprendi análise de ECG:

1. LAUDO DO ECG:

Ritmo Sinusal

FC = 52 bpm

Duração de Ondas:

P = 0,08s PR = 0,22s QRS = 0,08s QTC = 0,40s

Eixos:

SÂP = 15º SÂQRS = 10º SÂT = 120º

Alterações Morfológicas: - Ondas P com entalhes e de baixa voltagem no plano frontal

- Entalhes na rampa descendente de r´ em D3, aVF, V1, V2 e V(Ondas ε)

- Ondas T invertidas nas precordiais(V1 a V6)

Laudo: 1. Possível onda Épsilon(ε)nas precordiais direitas (Sugere Displasia Arritmogênica de Ventrículo Direito).

Alteração difusa da repolarização ventricular.

2. CONDUTA:

a) Investigar arritmia como possível causa das síncopes e identificando tratá-la como indicada.

b) Identifiicar e avaliar miocardiopatia e função miocárdica.

Obs: Na investigação e avaliação, claro, os exames se sobrepõem e se completam. A patologia sob suspeita, seu conhecimento pelo médico e o bom senso o levará a decidir quais. (Para mim: Holter e registros mais prolongados e detalhados de ritmo, Ecocardiograma, Ergometria e RNM).

Adail – Bahia - Brasil

Adrián: Entiendo perfectamente lo que has explicado y por eso me queda claro que no se puede utilizar como primera prueba de screening. He adjuntado el artículo* -se descarga gratis, no creo que haya problemas de copy rights- que si bien lo firman los Brugada la parte en cuestión es sobre una cita de Corrado, y lo citan en el texto.Este es el artículo que repasa un poco el diagnostico de arritmias que tienen que ver con el VD y en la pagina 969 está el tema del mapeo, le ponen un corte de 1,5 mv. Todo esto me ha hecho leerlo otra vez y señalan que es util para diferenciar un estadío muy temprano de DAVD de la TV originada en el TSVD, dado que en las etapas precoces los pacientes con un VD aparentemente normal en las pruebas por imagen, si en el mapeo observamos que tienen varias areas de bajo voltage se puede identificar a un subgrupo que tiene alta posibilidad de dearrollar MS. Y cuidado! que me da más certeza tu comentario que es realista y sensato que esta cita que parece un poco más puntual, para algunos casos.**

Probablemente nuestro deportista no requiera para nada de un mapeo, pero la pregunta apunta a si a la gente que realmente lleva a cabo la técnica, le parecería util o si tendría sentido en algún caso puntual agarrarse de esto.

Reformulo la pregunta: Otro caso, un paciente con TV del TSVD, en principio una patología benigna o cuyo tto definitivo pasa seguramente por ablacionarla, presenta varias areas de bajo voltaje. En un laboratorio de EEF:¿ ese dato te hace pensar en DAVD¿Perdón por ser un pesado, pero este tema me interesa y me parece una ventaja poder contrastarla con vuestra experiencia.

Un saludo (no me peguen que soy Giordano)

Diego Fdez

Querido Diego Giordano: El tema que tocas es apasionante. Como diferenciar una TV de TSVD de una TV por DAVD. Pero convengamos, para no marear a nadie, que esto NO tiene nada que ver con el paciente, que se presento con sincope y sin TV documentada, OK? Bien, hay hermosos papers que te ayudan a encontrar diferencias electrocardiograficas entre una TV y la otra (seguro el potro tiene una tabla comparativa) pero la realidad es que durante taquicardia, es muy dificil.Si bien el ECG en RS te ayuda un monton (mientras que en TV de TSVD el ECG basicamente normal; en DAVD el ECG muestra lo que se discutio en este caso: bajo voltaje, epsilon, T negativas etc etc). Obviamente, la HClinica ayuda mucho, zona de origen MS familiar (muy rara en TSVD) etc.Pero finalmente, como te das cuenta, si voy a ofrecer una ablacion, quiero estar seguro. Porque? Por lo que discutimos antes, porque TSVD, si la agarras, la ablacion es CURATIVA, pero en DAVD no, por su caracter progresivo. Mientras que TSVD raramente ocasiona la muerte, la TV asociada a DAVD si. Por eso, a nuestros pacientes conTV originada en TSVD (a todos) les hacemos un RNM. Porque? porque si bien los datos clinicos-ECG estan ausentes pueden encontrarse elementos incipientes de la enfermedad.Es necesario hacer TODAS las TSVD con mapeo endocardico: NO (lo digo para que quienes no tienen acceso directo a esta modalidad se alegren). Pero la realidad es que en mi servisio TODAS se hacen con mapeo, justamente para hacer lo que vos propones. Mapeo endocardico a 0.5 (1.5 es casi como no hacer nada). Si no hay cicatriz, pues es TSVD y si la hay, debe ponerse en contexto clinico pues bien puede ser forma incipiente de DAVD. Por ultimo: no toda cicatriz inesperada en el VD indica DAVD...pero eso es otra historia. Y asi fue, Diego, sin servilleta, pero con la misma pasion.

Salud
AB

Dear friends, After my commentary on ARVC, I went on holidays for a few days and I have just read all the messages that followed it. In Uruguay, at least for the time being, there is no electroanatomic mapping equipment, so we have no experience on this at all. I think the commentaries about Adrian's experience about the use of mapping both in ARVD and VT of the RVOT were very practical and interesting. I would like to pose a topic: would you perform EPS on this patient with syncope by strain and ARVD? Or would you implant at once the ICD and wait for a spontaneous event? I would like to make a brief commentary on ICD implantation: it is necessary to place active fixation electrodes and fix it in the septum and not in the apex, because RV tip may be affected by ARVD, while the septum is rarely affected. This as long as it is not a biventricular dysplasia, in which case we have to choose and hope to be right about the sector of the septum chosen to place it. One question, do you have experience with strokes associated to ARVC? The last patient we saw with ARVC suffered an ischemic stroke with hemorrhagic conversion that was lethal. We still have a doubt about whether there was some relationship (the patient did not present AF) that was not known currently.
Regards,

Daniel Banina

Estimados,Luego de mi comentario sobre la ARVC me fui de vacaciones unos días y acabo de leer todos los mail que siguieron. En Uruguay, por lo menos por el momento no hay equipos de mapeo electroanatómicos, por lo cual no tenemos ninguna experiencia. Me parecieron muy prácticos e interesantes los comentarios de la experiencia de Adrián sobre el uso del mapeo tanto en ARVC como TV del TSVD. Quisiera plantear un tema: le realizarían EEF a este paciente con síncope de esfuerzo y ARVC? O directamente le implantarían el CDI y esperarían que tuviera un evento espontáneo?

Quisiera hacer un breve comentario respecto al implante del CDI: es necesario colocar electrodos de fijación activa y fijarlo en el septum y no en el ápex, porque la punta del VD puede verse afectada por la ARVD,mientras que el septum es raro que se vea afectado. Esto siempre y cuando no sea una displasia biventricular, en los cuales hay que elegir y tener suerte con el sector del septum elegido para colocarlo.

Una consulta, tiene experiencia de stroke asociados a ARVC? El último paciente que vimos con ARVC sufrió un stroke isquémico con conversión hemorrágica que fue mortal. Nos quedó la duda de si hubiera alguna relación(no tenía FA) que no fuera conocida al momento actual.

Saludos,
Daniel Banina

Final conclusions

Repetitive syncope episodes induced by efforts.
Ancestral immigrants from the north-eastern part of Italy (Belluno province). This is in Veneto province below to Veneto region Italy. This an endemic area of ARVC/D.

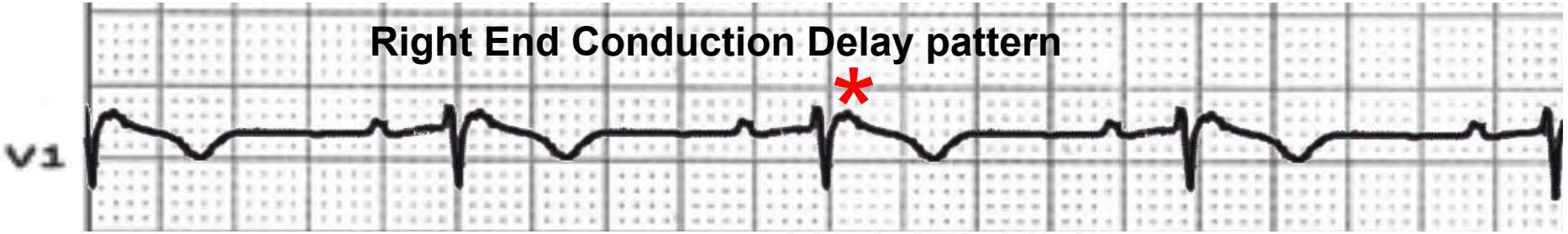
The estimated prevalence of ARVC/D ranges from 6 per 10,000 in the general population to 4.4 per 1,000 in some areas with higher prevalence. For example the Veneto region of northern Italy seems to present an unusually high prevalence of the disease; in this country several large kindred have been identified and allowed to established linkage to several loci.

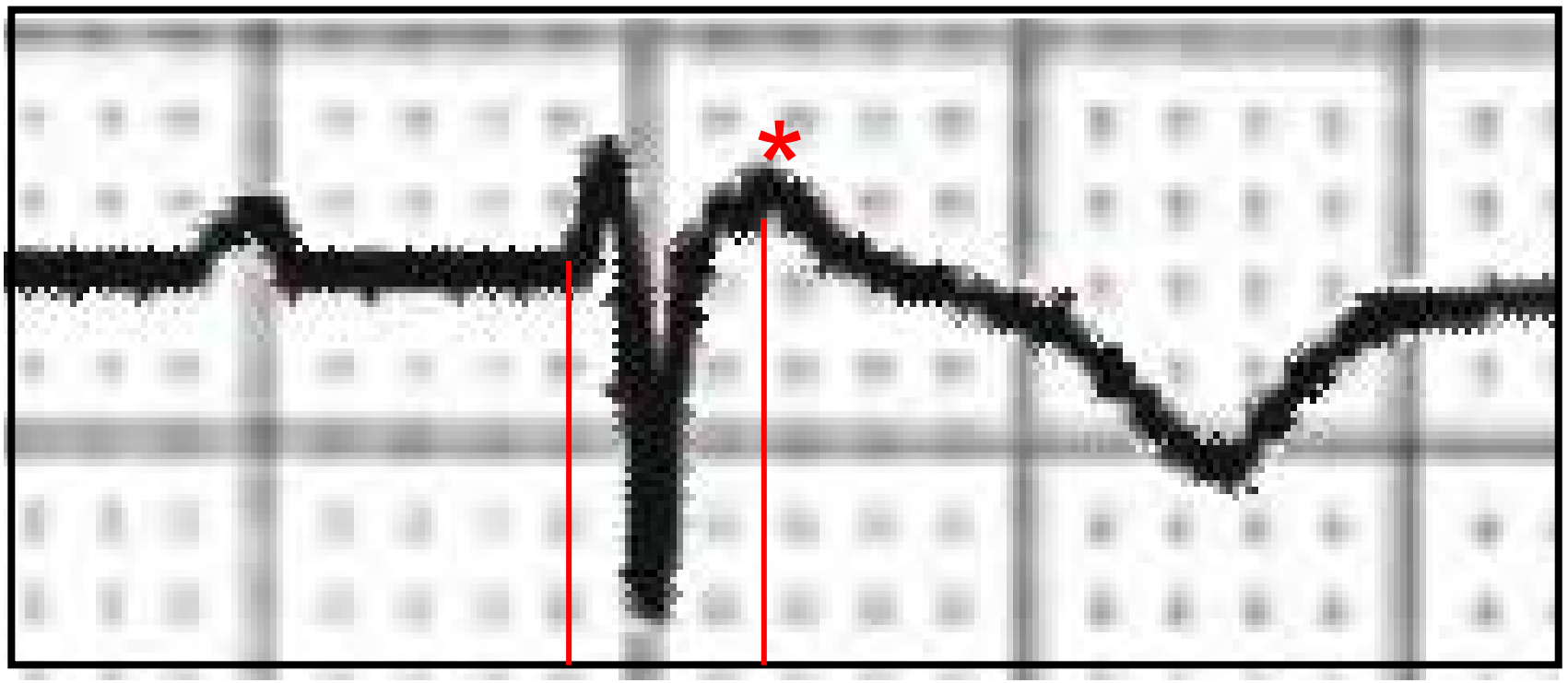
Normal pervious ECG

ECG diagnosis

1. **Right End Conduction Delay pattern on free wall of right ventricle:** This may be due to delayed activation on the free wall of right ventricle, rather than any intrinsic abnormality in the right bundle branch.
2. **Prolonged QRS duration (≥110ms) on right precordial leads (V1-V3): Mayor criteria**
3. **Presence of epsilon waves or Fontaine wave: Major criteria.**
4. **Negative T waves across all precordial leads from V1 to V6: Minor criteria.**

1. **Corrado D, Basso C, Buja G, et al. Right bundle branch block, right precordial st-segment elevation, and sudden death in young people.Circulation. 2001 Feb 6;103:710-717.**





Prolonged QRS duration(≥110ms) on right precordial leads (V1-V3) Mayor criteria

Epsilon wave Major Mayor criteria

1. ***McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 1994; 71:215-218.***

The diagnosis is based on **a combination of major and minor criteria.** To make a diagnosis of ARVC/D requires either 2 major criteria *or* 1 major and 2 minor criteria *or* 4 minor criteria.

Major Criteria

Right ventricular dysfunction

- Severe dilatation and reduction of RV ejection fraction with little or no LV impairment
- Localized RV aneurysms
- Severe segmental dilatation of the RV

Tissue characterization

- Fibrofatty replacement of myocardium on endomyocardial biopsy

Conduction abnormalities

- **Epsilon waves in V1 - V3.**
- **Localized prolongation (>110 ms) of QRS in V1 - V3**

Family history

- Familial disease confirmed on autopsy or surgery

Minor Criteria

Right ventricular dysfunction

- Mild global RV dilatation and/or reduced ejection fraction with normal LV.
- Mild segmental dilatation of the RV
- Regional RV hypokinesis

Tissue characterization

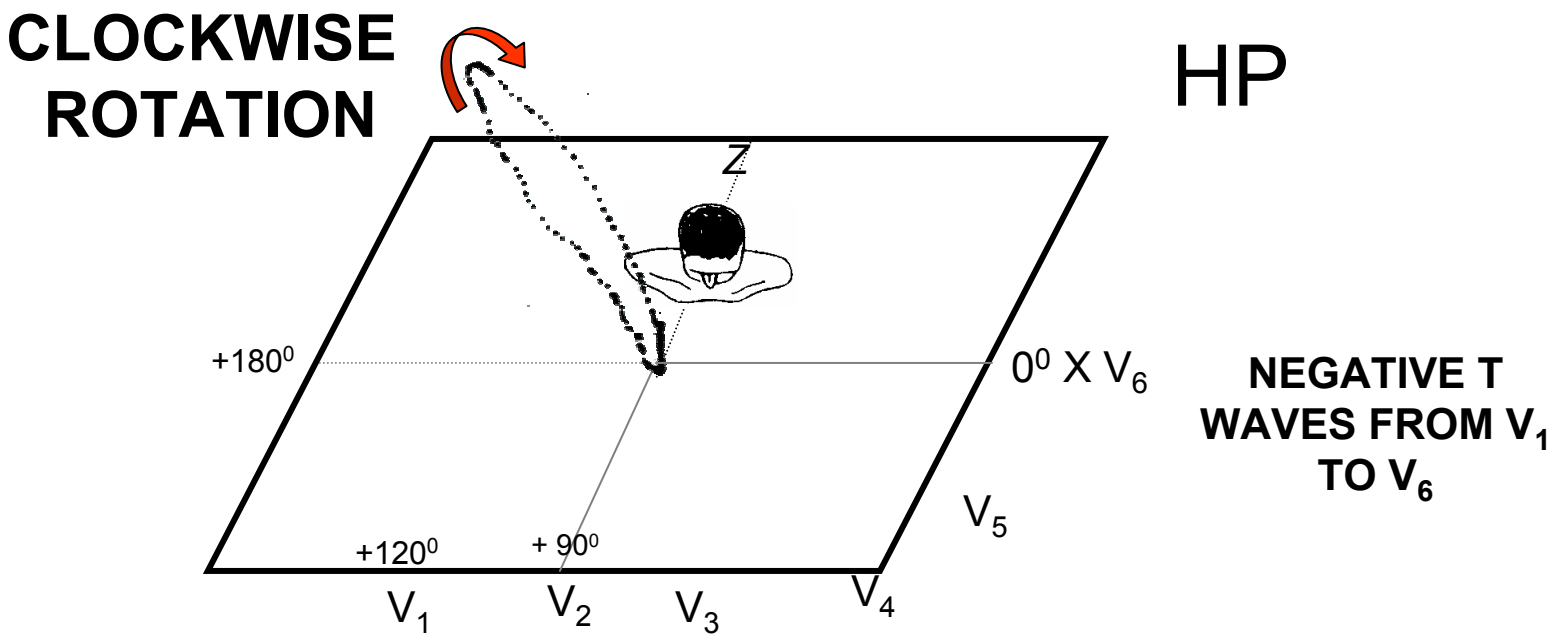
Conduction abnormalities

- **Inverted T waves in V2 and V3** in an individual over 12 years old, in the absence of a RBBB
- Late potentials on signal averaged ECG.
- VT with a LBBB morphology
- Frequent PVCs (> 1000 PVCs / 24 hours)

Family history of sudden cardiac death before age 35 Family history of ARVC/D

1. ***McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 1994; 71:215-218.***

T LOOP BEHAVIOR IN ARVC/D AND ITS RELATIONSHIP WITH RV END DIASTOLIC VOLUME



When the RV end diastolic volume is large (in average 320 ml/m^2), the T loop displays clockwise rotation in the HP and is located in the right posterior quadrant, which justifies the negative T wave in all precordial leads.

Note: the presence of T loop of clockwise rotation, indicates the presence of underlying heart disease.

1. **Nava A, Canciani B, Buja G, et al. Electrovectorcardiographic study of negative T waves on precordial leads in arrhythmogenic right ventricular dysplasia: relationship with right ventricular volumes. J Electrocardiol. 1988 Aug;21:239-245.**

Main ECG features in *Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia*

1. **Prolonged QRS duration(≥110ms) on right precordial leads (V1-V3): parietal block**
2. **Prolongation of the terminal QRS activation duration ≥ 55 ms measured from the nadir of the S wave to the end of the QRS complex in V1:parietal block**
3. **Epsilon or Fontaine wave**
4. **T wave inversion in right precordial leads, V1, V2 and V3 in individuals over the age of 14 years in absence of RBBB and T wave inversion in V1 – V4 ECG on proband**
5. **Low QRS voltage: indicates a widespread myocardial process**
6. **Poor r wave progression in the right precordial leads,**
7. **Incomplete Right Bundle Branch Block (IRBBB). This may be due to delayed activation of the free wall of right ventricle, rather than any intrinsic abnormality in the right bundle branch.**
8. **Complete Right Bundle Branch Block (CRBBB)**
9. **Frequent Ventricular Premature Contractions (PVCs) with LBBB pattern (more than >200 PVCs in 24 hours. / Holter ECG 24h or Long-Term Electrocardiographic Recording.)**
10. **Non-sustained (NS-VT) or Sustained Monomorphic Ventricular Tachycardia (S-VT) with LBBB pattern. Observation: NS-VT: Non-Sustained Ventricular Tachycardia. It is defined as a run of tachycardia of less than 30 seconds duration; a longer duration is considered S-VT. Or during exercise testing**
11. **The origin of the PVCs is usually from one of the three regions of fatty degeneration (the "triangle of dysplasia"): the RVOT, the RVIT, or the RV apex.**
12. **Late potentials by signal-averaged ECG (SAECG) or high-resolution electrocardiography.**

ECG IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA (ARVC/D)

Approximately 90% of patients carriers of ARVC/D present ECG anomalies.
ARVC/D diagnosis may be excluded if ECG is normal 6 years after the VT episode.(1)

I) Rhythm: sinus rhythm; however, there is a report of the case of a male patient, 60 years old, carrier of ARVC/D, who developed sick sinus (SA node with recovery time of 6113 ms). The authors explained the cause of atrial arrhythmia by gradual reposition of right atrial myocytes by fatty tissue.(2)

1. **Jaoude SA, Leclercq JF, Coumel P. Progressive ECG changes in arrhythmogenic right ventricular disease. Evidence for an evolving disease.Eur Heart J. 1996 Nov;17:1717-22.**
2. **Balderramo DC, Caeiro AA. Arrhythmogenic right ventricular dysplasia and sick sinus syndrome. Medicina (B Aires). 2004;64:439-441.**

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

ECG IN ARVC/D

P wave: there is a description of giant P wave associated to QRS complex of low amplitude, in patients carriers of ARVC/D.(1)

Rest ECG with right ventricular enlargement (RVE) and significant increase of QRS complex dispersion of 47.1+/-18.9 ms is observed in cases of heart failure.
Biatrial enlargement and reduction of QRS dispersion of 33.0+/-23.1 ms are observed in cases of biventricular heart failure.(2)

PR interval: PR interval prolongation has been described.(3). Prolonged PR interval is a predictor of adverse results in patients with ARVC/D.

1. **Martini B, Nava A, Buja GF, et al. Giant P wave in a patient with right ventricular cardiomyopathy.Clin Cardiol. 1990 Feb;13:143-145.**
2. **Peters S, Peters H, Thierfelder L.Heart failure in arrhythmogenic right ventricular dysplasia-cardiomyopathy. Int J Cardiol. 1999 Dec 1;71:251-256.**
3. **Wisten A, Andersson S, Forsberg H, et al. Sudden cardiac death in the young in Sweden: electrocardiogram in relation to forensic diagnosis. J Intern Med. 2004 Feb; 255 :213-220.**

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

ECG IN (ARVC/D)

Abnormalities in depolarization and repolarization in ECG are common in cases of ARVC/D.

Abnormalities in depolarization/conduction in ECG

Prolongation of QRS complex (≥110 ms) located in right precordial leads (V1-V3) in adult patients in absence of CRBBB (prolonged S wave upstroke) from V1 to V3, ≥55 ms is the most prevalent characteristic of ECG (95% of cases) and are correlated with the severity of the disease and induction of VT in programmed ventricular stimulation.

Prolongation in S wave duration in anteroseptal wall of ECG (V1-V3) is a significant marker for ARVC/D diagnosis. Automated medition in S wave duration in the surface of ECG leads V1-V3, was conducted in 141 healthy children between 5 and 15 years old and they were compared to 27 pediatric patients carriers of ARVC/D. Available ECGs were assessed in the initial and final phase in patients carriers of ARVC/D, obtained respectively at ages 11.6 ± 3.9 and 14.3 ± 3.4 years old. ARVC/D was diagnosed in children with VT and CLBBB morphology, using diagnostic criteria already published for adult patients, carriers of ARVC/D or who had typical findings in biopsy.

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

ECG IN (ARVC/D)

The result from the addition of QRS complexes duration from V1 + V2 + V3 when divided by the addition of the duration of QRS complexes from V4 through V6 (V4 + V5 + V6). When this equation results in a value ≥ than 1.2, it constitutes a sign of high sensitivity for ARVC/D diagnosis, since it is present in 98% of patients carriers of this cardiomyopathy(1).

Pitzalis et al showed that the sign is not specific of ARVC/D because it has been observed also in Brugada syndrome. This longer duration of QRS complexes at the right in precordial leads is due to the so-called right parietal block characteristic of ARVC/D. In accordance with the electrophysiological background, the typical ECG pattern of Brugada syndrome is also characterized by a considerable prolongation of the QT interval in right precordial leads. (2)

Possibly QRS complexes may be of low voltage, which is observed when the disease is diffuse or there is participation with the conduction system.

1. **Peters S, Trümmel M. Diagnosis of arrhythmogenic right ventricular dysplasia-cardiomyopathy: value of standard ECG revisited. Ann Noninvasive Electrocardiol. 2003 Jul;8:238-245.**
2. **Pitzalis MV, Anaclerio M, Iacoviello M, et al. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003 Nov 5;42:1632-1637.**

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

ECG IN (ARVC/D)

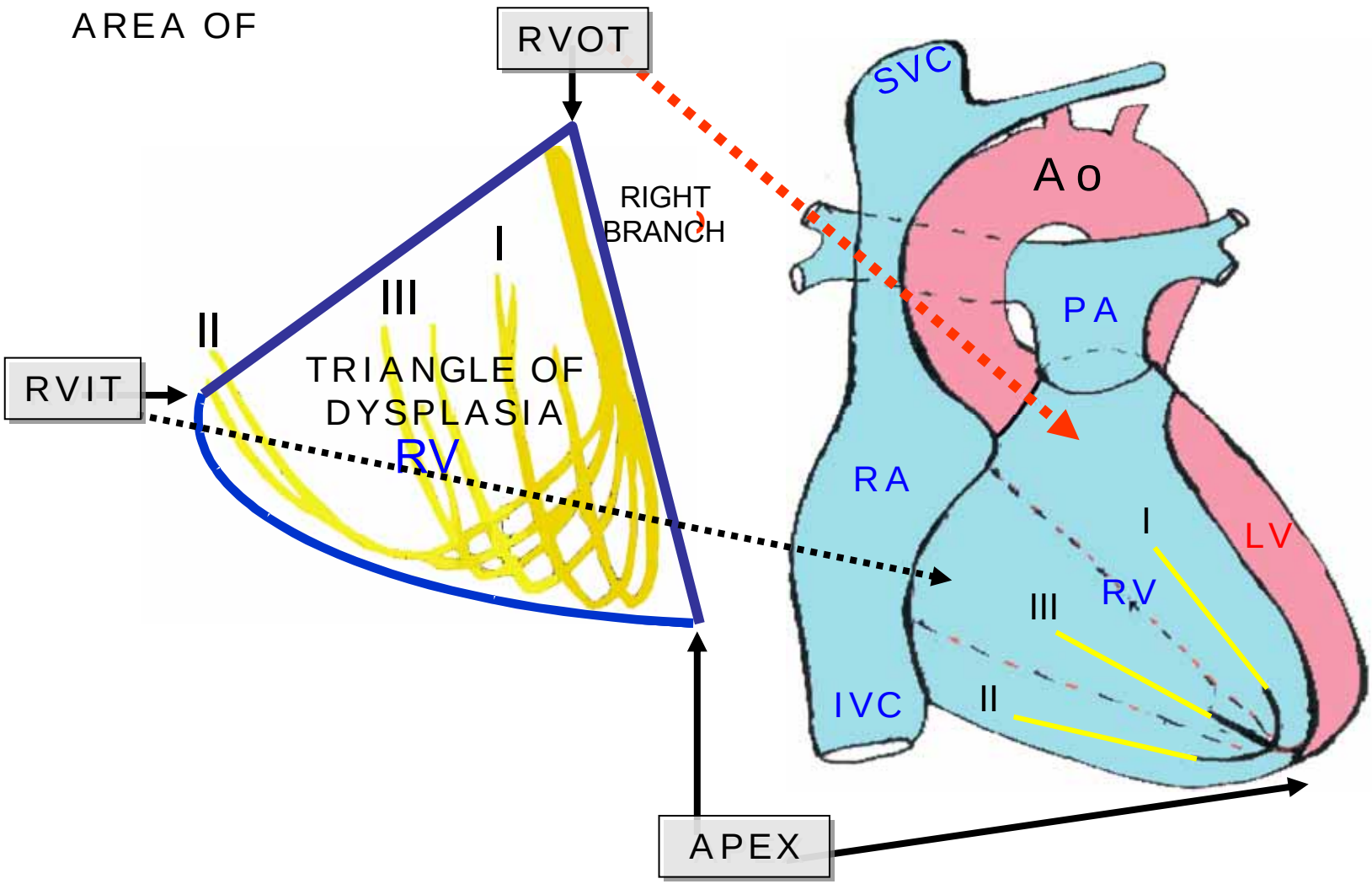
In ARVC/D there is evidence of peripheral right branch blocks (Right End Conduction Delay), as the Professor Guy Fontaine proved some time ago: topographic IRBBB or Complete RBBB occurs in the fascicular portion of the right branch and/or in the right ventricle free wall after the trunk of the branch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

The mechanism of the conduction defects is not disease of the bundle branch itself but a distal block probably situated in the right ventricular free wall. This hypothesis is supported by the histological appearances of the dysplastic zones. Pattern of Complete RBBB is observed in15% of cases, and IRBBB or ECD in 18% of cases.(2;3)

1. **Fontaine G, Frank R, Guiraudon G, et al. Significance of intraventricular conduction disorders observed in arrhythmogenic right ventricular dysplasia.Arch Mal Coeur Vaiss. 1984 Aug;77:872-879.**
2. **McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J. 1994 Mar;71:215-218**
3. **Fontaine G, Fontaliran F, Hébert JL, Arrhythmogenic right ventricular dysplasia. Annu Rev Med. 1999;50:17-35.**

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

RIGHT BUNDLE BRANCH ON FREE WALL OF RV INSIDE TRIANGLE OF DISPLASIA



ECG IN (ARVC/D)

- Alterations of depolarization and conduction

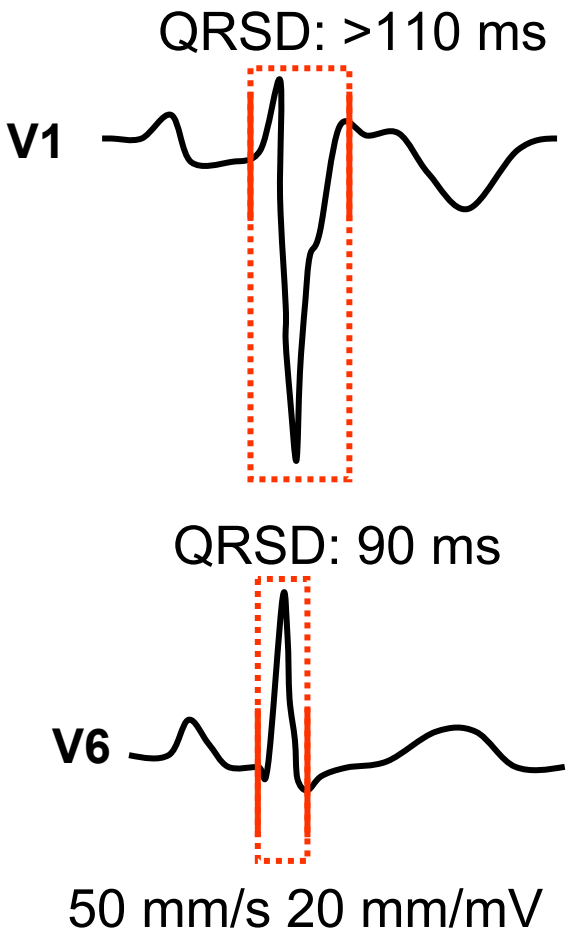
1. Epsilon waves (ε): (30%) are abnormal deflection resulting from delayed RV activation at the end of QRS complex. They are, late potentials with low amplitude and short duration oscillations near the J point (before or immediately after): major criterion: if the addition of QRS complexes duration in V1+ V2+ V3 / V4+ V6+ V6 is ≥ than 1.2;
2. Increase in QRS complex duration (>110º) in V1, V2 and V3, in absence of CRBBB: parietal block. Major criterion: if the addition of QRS complexes duration in V1+ V2+ V3 / V4+ V6+ V6 is ≥ than 1.2;
3. Prolongation in the ascending ramp of S wave from V1 to V3, in absence of CRBBB (prolonged S wave upstroke): distance from the nadir of S wave up to the isoelectric line ≥55 ms.(1)
4. Late potentials in high resolution ECG.
5. Low voltage QRS complexes in cases where the disease is more diffuse or with involvement of conduction system.

- Alterations of repolarization

1. ST segment elevation with different morphologies present in 25% of cases.
2. Inverted T wave in right precordial leads (V1 and V2) >12 years old, in absence of CRBBB.

1. **Steriotis AK, Bauce B, Daliento L, et al. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 2009 May 1;103:1302-1308.**

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



QRSD of $^{V1+V2+V3}$ / $_{V4+V5+V6}$ ≥ 1.2 in approximately 65% of cases. QRS prolongation located in right precordial leads.(1)

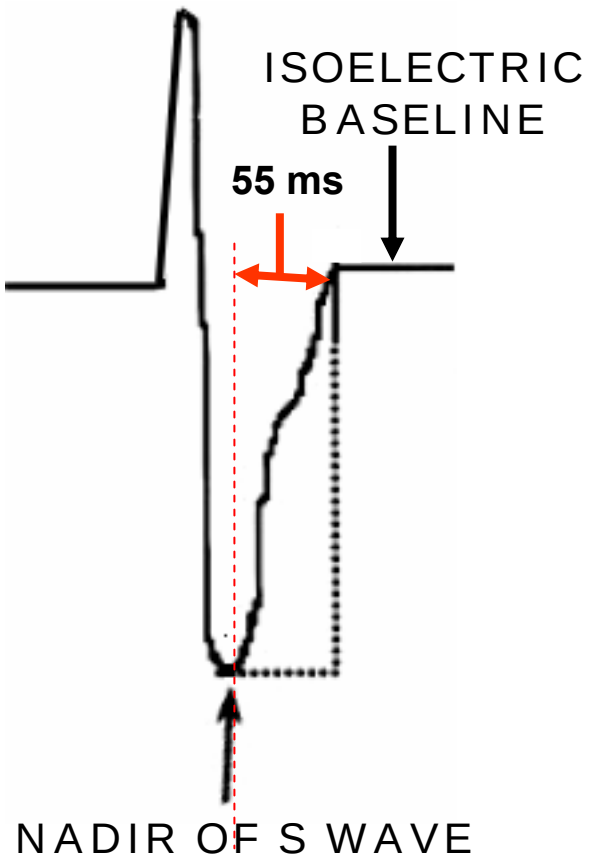
QRSD ≥110 ms from V1 to V3: 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVC/D.

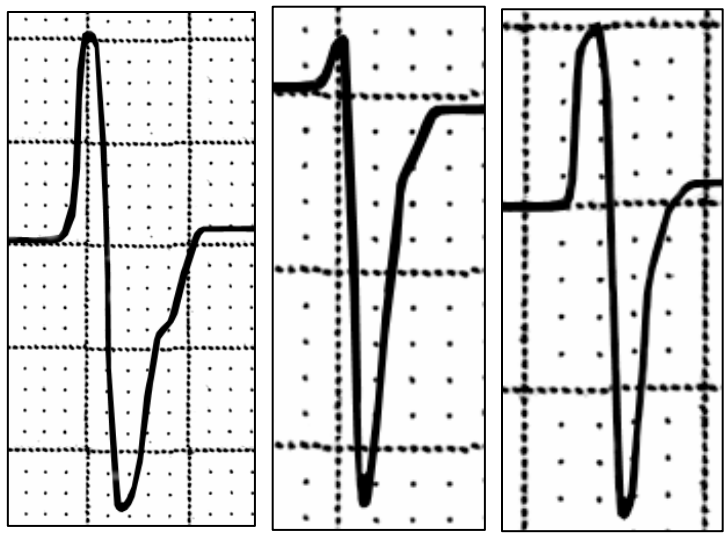
Brugada syndrome may display prolongation in QT interval duration from V1 to V3 and subsequently prolongation of QTc interval in right precordial leads.(2)

1. **Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004 Sep 21;110:1527-1534.**
2. **Pitzalis MV, Anaclerio M, Iacoviello M, et al. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003 Nov 5;42:1632-1637.**

PARIETAL BLOCK IN ARVC/D

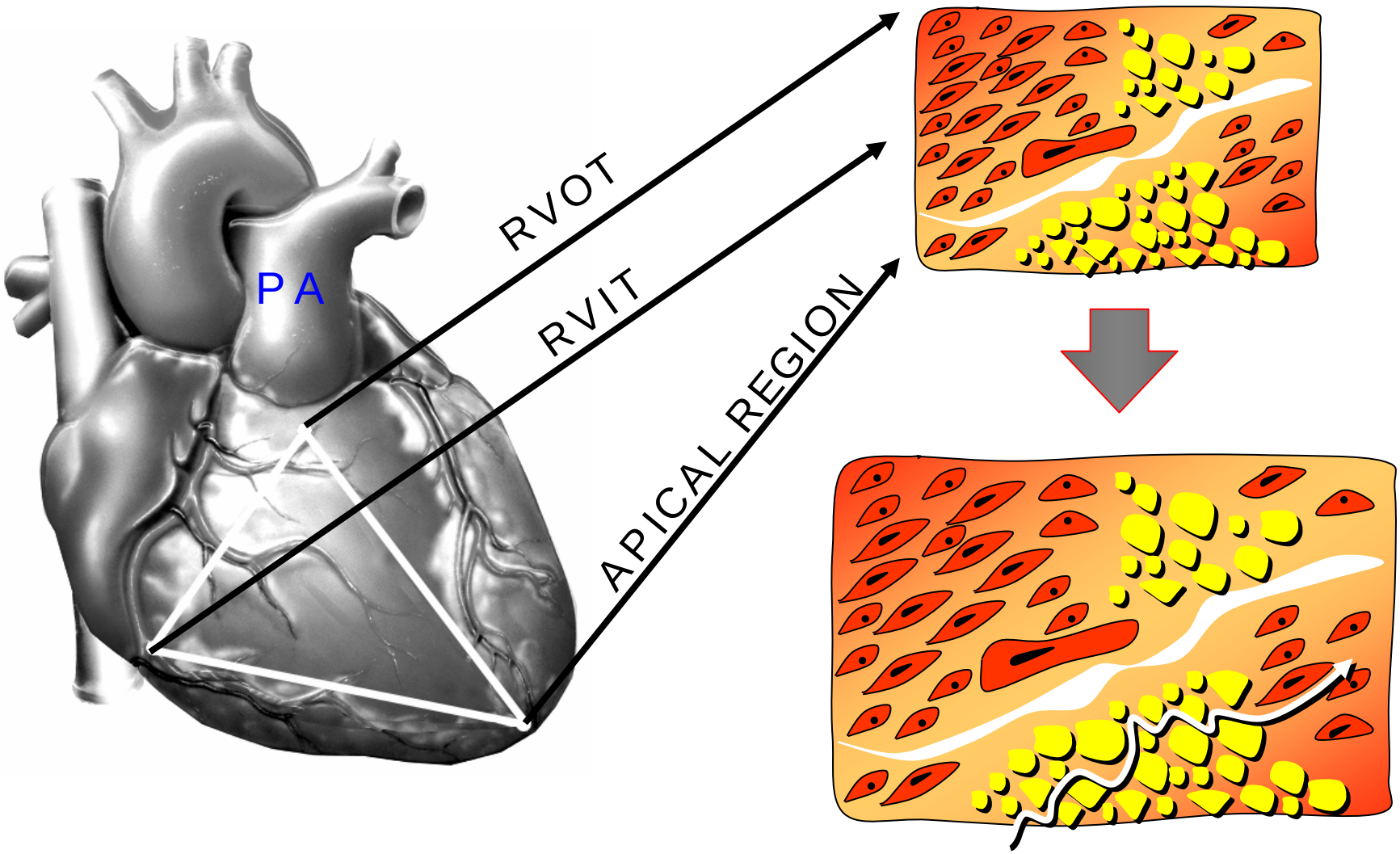
A prolonged S-wave upstroke in V1 through V3 is the most frequent ECG finding in ARVC/D and should be considered as a diagnostic ECG marker.



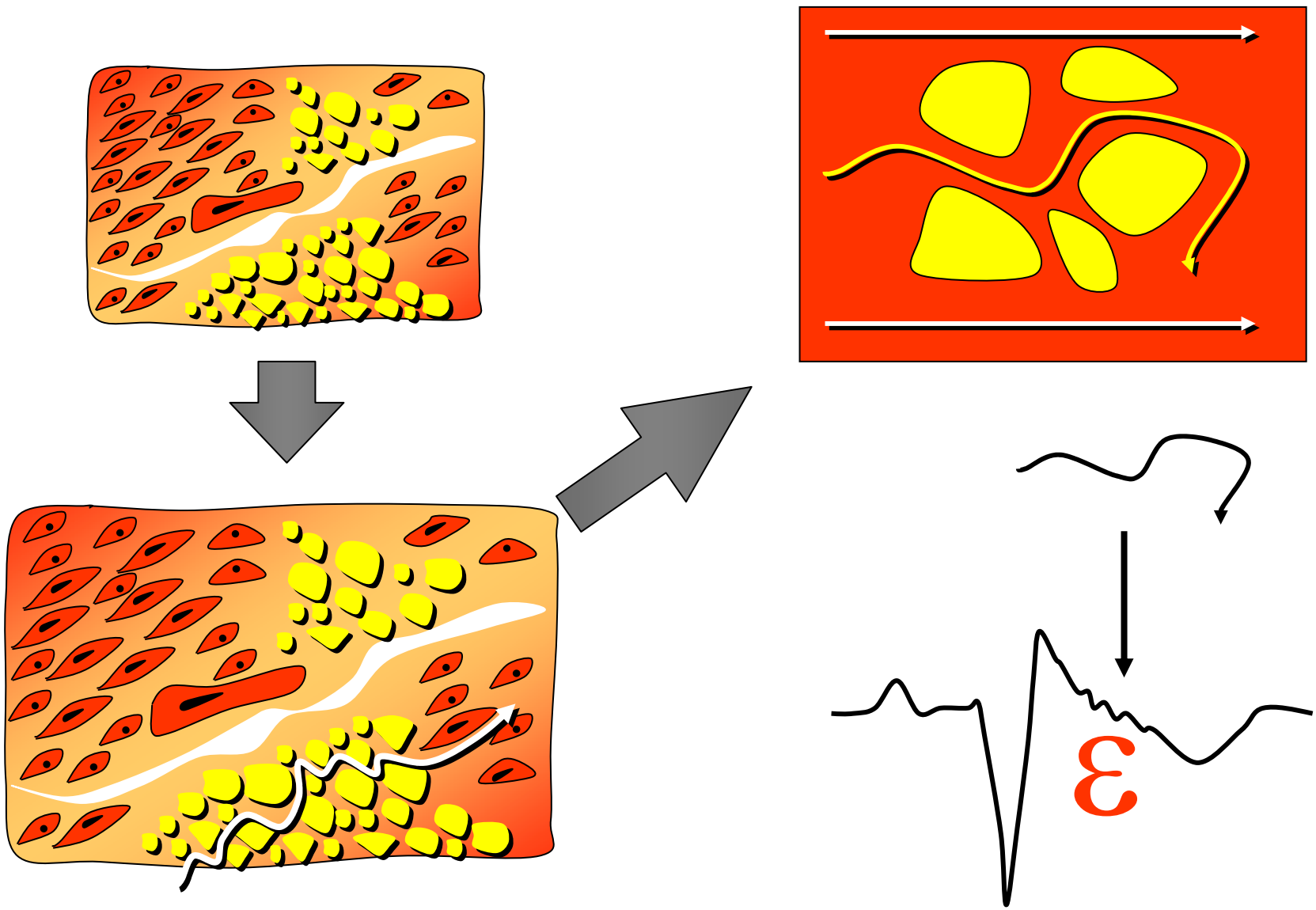


1. **Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004 Sep 21;110:1527-1534.**

TRIANGLE OF DYSPLASIA IN ARVD



TRIANGLE OF DYSPLASIA



Outline of Epsilon wave in ARVC/D.

CHARACTERISTICS OF EPSILON OR FONTAINE WAVE

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

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

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

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

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

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

6) High resolution ECG: observed more frequently with this method.

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

1. **Hurst JW. Naming of the waves in the ECG, with a brief account of their genesis. Circulation. 1998 Nov 3;98:1937-1942.**
2. ***McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 1994; 71:215-218.***

CHARACTERISTICS OF EPSILON OR FONTAINE WAVE

7) Pathognomonic character: in spite of the characteristics in ARVC/D, they are not pathognomonic, since they have been described in other diseases associated with and without myocardial damage: acute right, inferior or dorsal ventricular infarction, (1), sarcoidosis,(2) sickle cell anemia,(3) and Brugada syndrome(4; 5). Specific ECG markers that reflect ventricular conduction delay in ARVC/D are commonly observed in subjects with spontaneous or drug-induced type 1 ECG pattern of BrS as well. These depolarization abnormalities may be related to subtle underlying structural abnormalities.

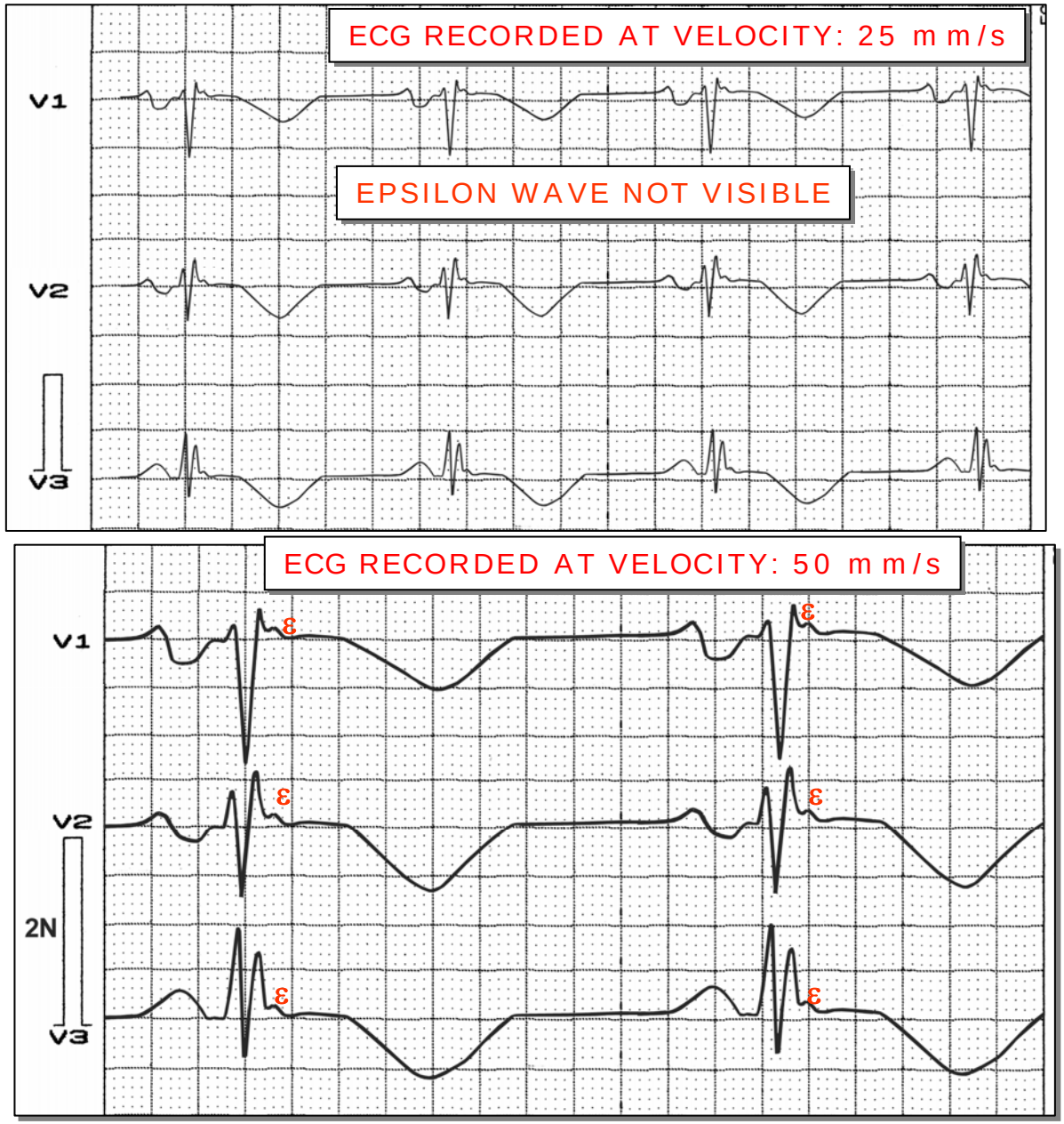
8) Association with Inversion of T wave Association with Inversion of T wave in leads V1-V3 and/or ε wave found in 70% of patients with ARVC/D.

1. **Zorio E, Arnau MA, Rueda J, et al.The presence of epsilon waves in a patient with acute right ventricular infarction. Pacing Clin Electrophysiol. 2005 Mar;28:245-247.**
2. **Santucci PA, Morton JB, Picken MM, et al. Electroanatomic mapping of the right ventricle in a patient with a giant epsilon wave, ventricular tachycardia, and cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2004 Sep;15:1091-1094.**
3. **Hurst JW. Naming of the waves in the ECG, with a brief account of their genesis. Circulation. 1998 Nov 3;98:1937-1942.**
4. **Letsas KP, Efremidis M, Weber R, et al. Epsilon-like waves and ventricular conduction abnormalities in subjects with type 1 ECG pattern of Brugada syndrome. Heart Rhythm. 2011 Jun;8:874-878.**
5. **Ozeke O, Cavus UY, Atar I, et al. Epsilon-like electrocardiographic pattern in a patient with Brugada syndrome. Ann Noninvasive Electrocardiol. 2009 Jul;14:305-308.**

CHARACTERISTICS OF EPSILON OR FONTAINE WAVE

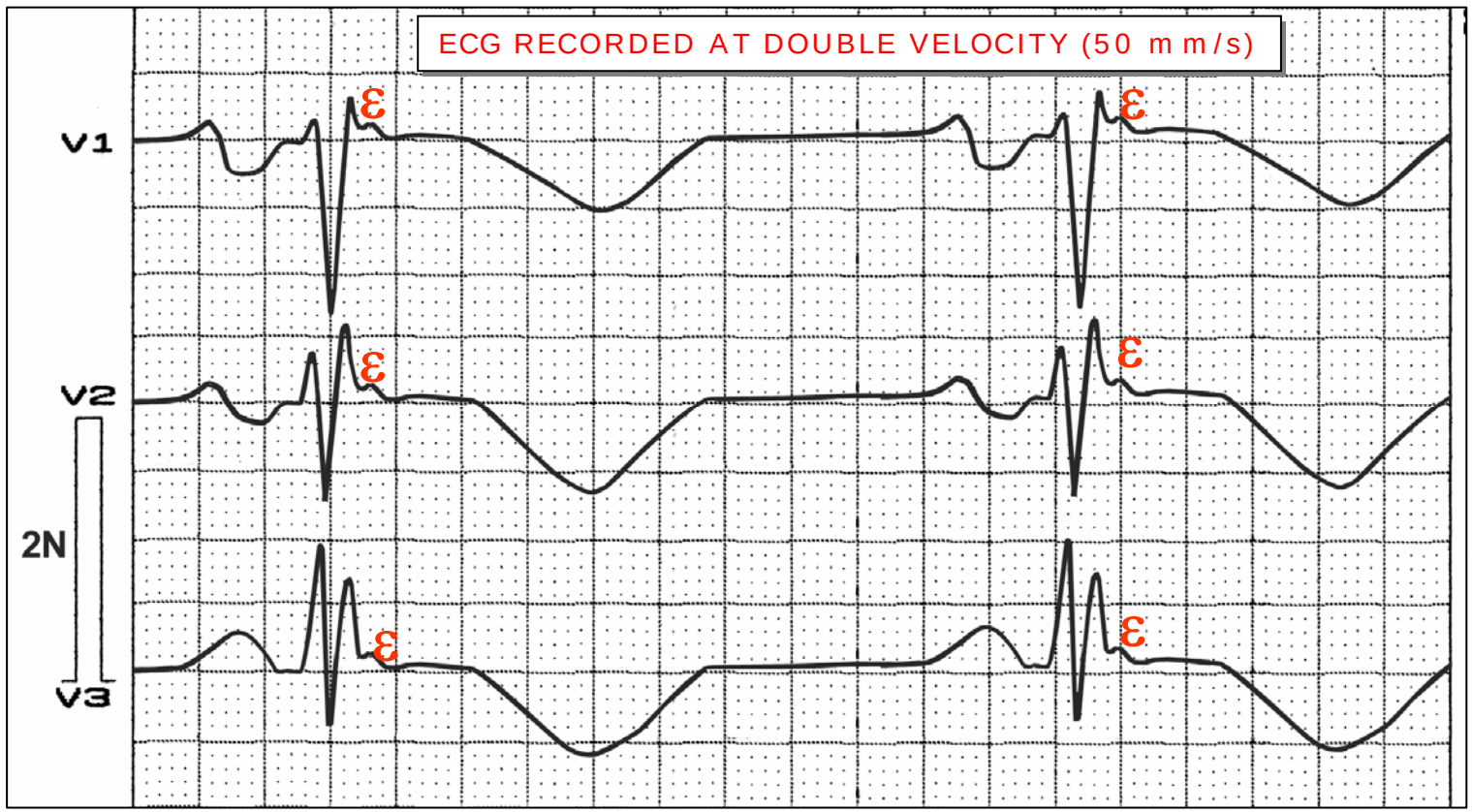
9) Epsilon wave and relationship to VT: the simple presence of these waves indicate slow and fragmented conduction, which favors reentry circuits, which in turn result in M-VT runs with CLBBB morphology by originating in the RV.(1)
10) Electrocardiographic algorithms: including localized right precordial QRS prolongation, prolonged S-wave upstroke, and epsilon potentials, with the use of the normal recording technique and the amplified and modified recording technique at a paper speed of 50 mm/s contribute significantly to the noninvasive diagnosis of ARVC/D(2).
11) QRS fragmentation in ARVC/D: has a high diagnostic value similar to epsilon potentials by a highly amplified and modified recording technique.(3)

1. **Sajeev CG, Jayakumar TG, Krishnan MN, et al. Epsilon wave. Int J Cardiol. 2004 Feb;93:315.**
2. **Peters S, Trümmel M, Koehler B, et al. The value of different electrocardiographic depolarization criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Electrocardiol. 2007 Jan;40:34-37.**
3. **Peters S, Trümmel M, Koehler B. QRS fragmentation in standard ECG as a diagnostic marker of arrhythmogenic right ventricular dysplasia-cardiomyopathy. Heart Rhythm. 2008 Oct;5:1417-1421.**



Epsilon wave characteristics in ARVC/D.

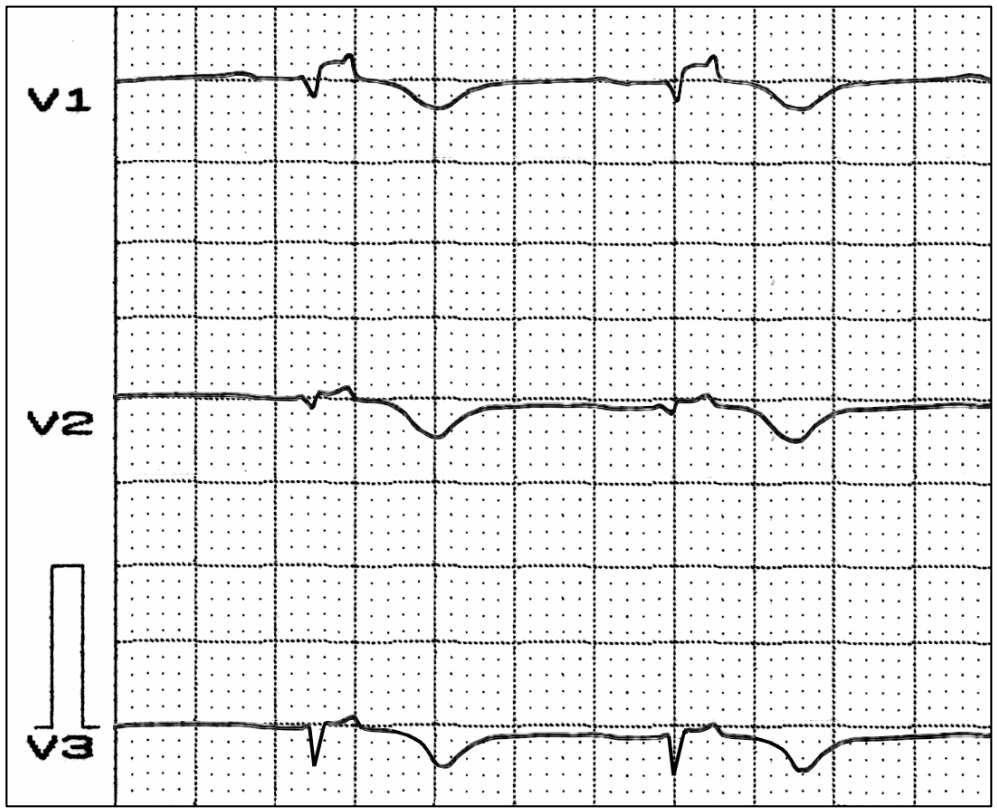
EPSILON WAVE (ε)



Double amplitude (20 mm/mV)

CLASSIFICATION PROPOSSAL OF EPSILON WAVE

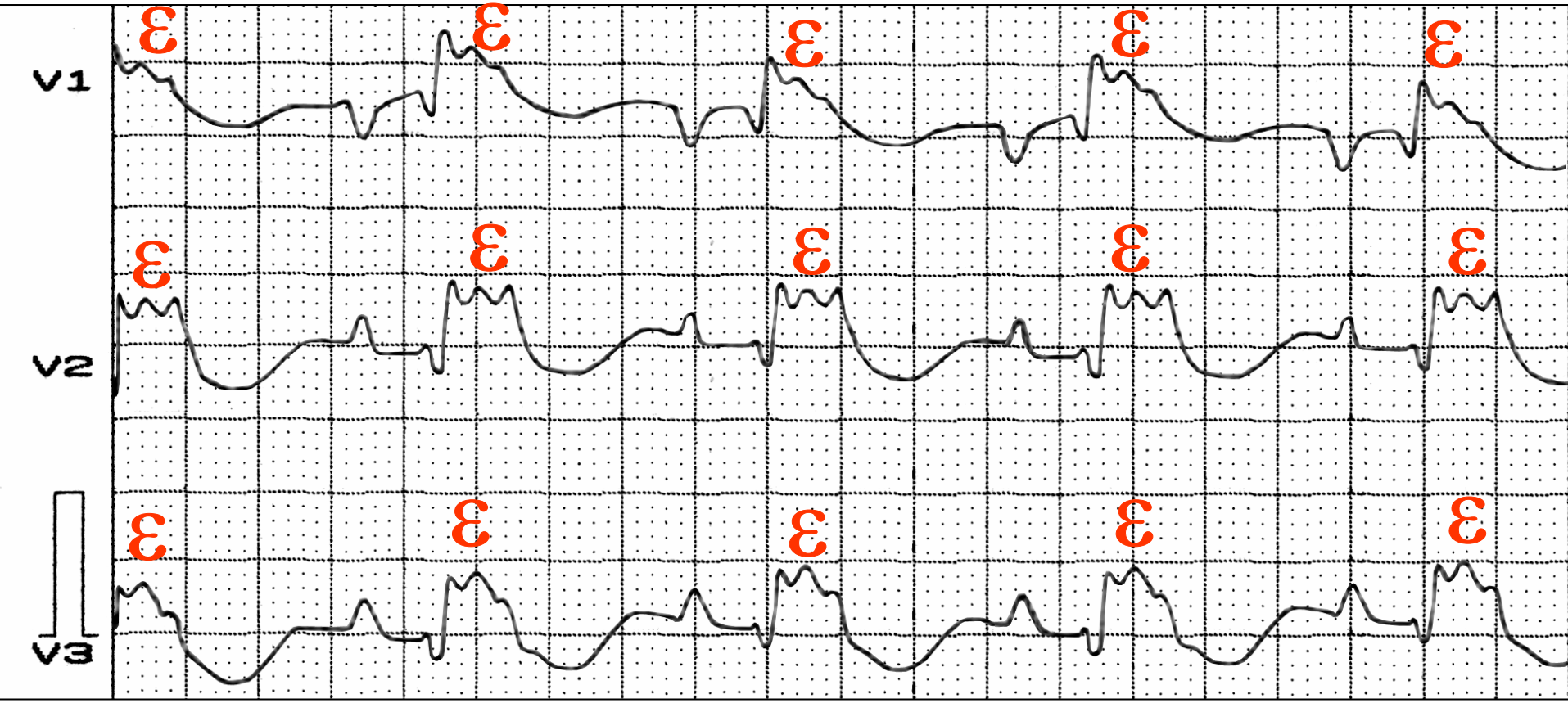
SINGLE DEFLECTION



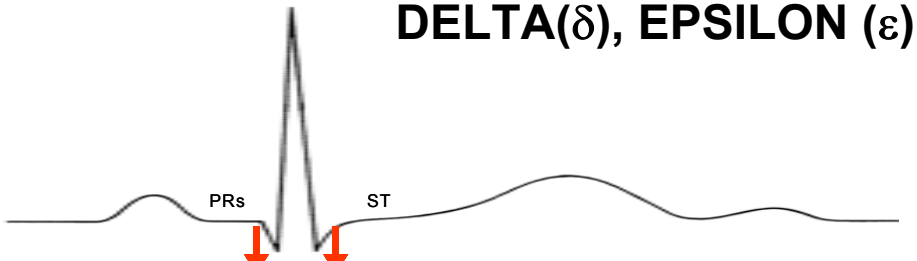
Epsilon wave characteristics in ARVC/D

CLASSIFICATION PROPOSSAL OF EPSILON WAVE

MULTIPLE DEFLECTION



DELTA(δ), EPSILON (ε), J and LAMDA waves



J wave

DELTA WAVE δ

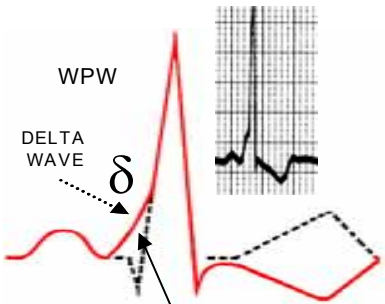
EPSILON WAVE ε

J POINT

HYPERCALCEMIA

WPW

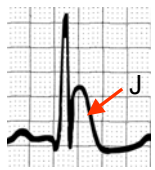
DELTA WAVE δ



ARVD

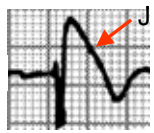
EPSILON

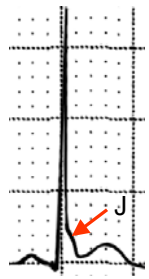
HYPOTHERMIA



50mm/sec
2N

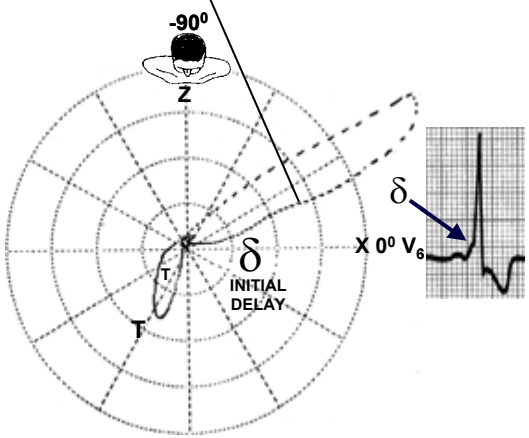
BRUGADA SYNDROME





SHORT QT INTERVAL
THE ST SEGMENT IS ALMOST ABSENT

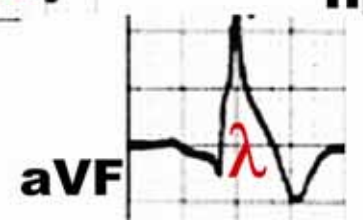
DELTA



In WPW type ventricular preexcitation, a wave located at the Ja point (end of PR segment and onset of QRS complex) is observed, called delta wave (δ). Following the Greek alphabet, the wave should be called Epsilon (ε), located near the J point (end of QRS complex and onset of ST segment).

LAMDA wave

Idiopathic VF/ malignant early repolarization



The detection rate of Epsilon wave is significantly higher in probands (65%) than involved family members (22%).

In the conventional ECG as well as Fontaine leads, Epsilon wave detection rate were (37%) in probands and 57% in family members.

The prevalence of diffuse right ventricle involvement, T-wave inversion and signal-averaged ECG are significantly different between the ARVC/D patients with Epsilon wave and without Epsilon wave.

It is significantly correlated between Epsilon wave and the progressive ARVC/D.(1)

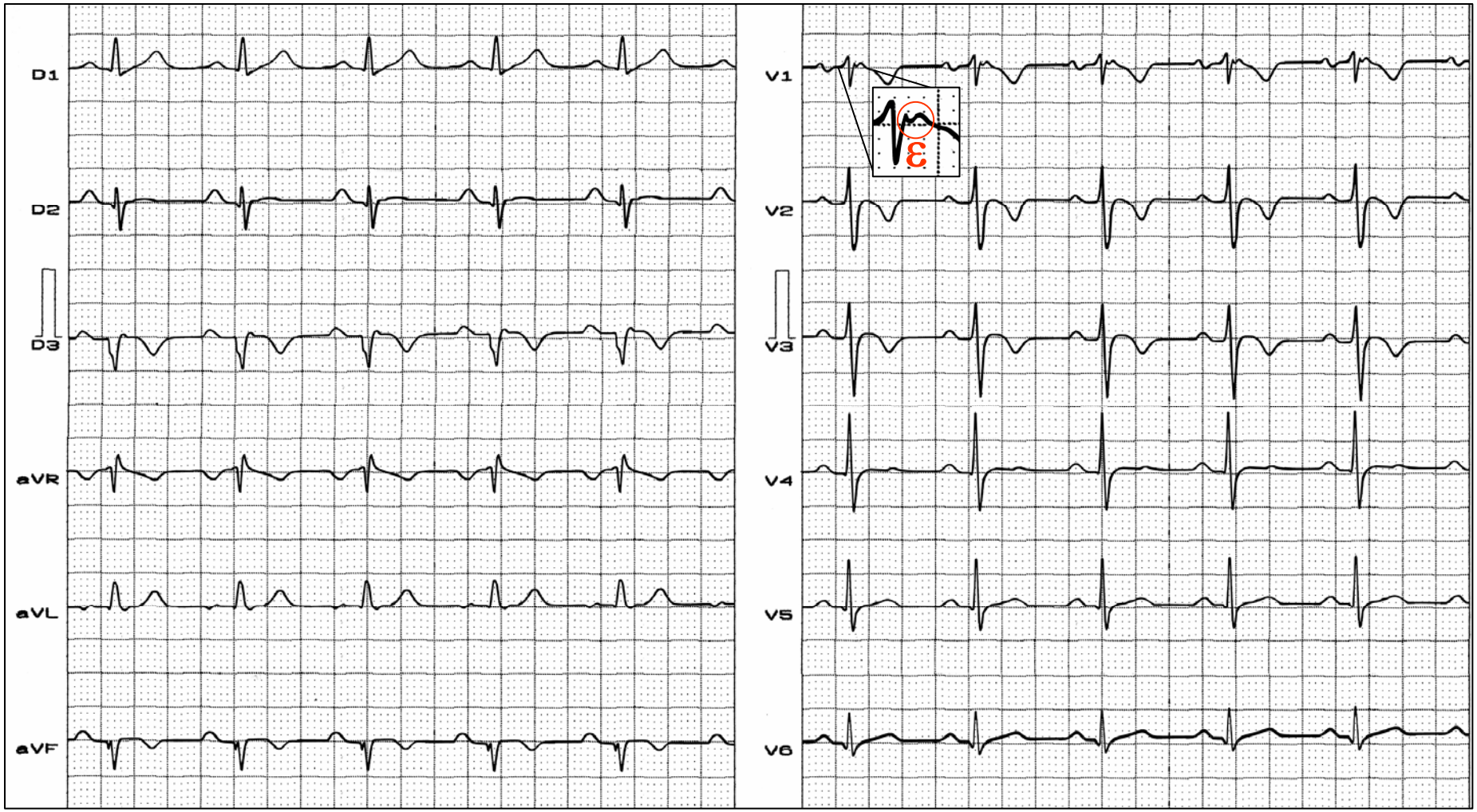
1. **Wu S, Wang P, Hou Y, et al. Epsilon wave in arrhythmogenic right ventricular dysplasia/cardiomyopathy.Pacing Clin Electrophysiol. 2009 Jan;32:59-63.**

MODIFIED PROTOCOL TO OBTAIN ECG IN PATIENTS WITH SUSPICION OF ARVD

1) 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 Epsilon waves.

2) 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.

Characteristics of modified protocol for patients suspected of ARVC/D.



Clinical diagnosis: cardiac sarcoidosis.
ECG diagnosis: SAQRS -60º, negative T wave from V1 to V3, Epsilon wave (ε) in V1.

Typical epsilon wave in a patient with Sarcoidosis.

DIFFERENTIAL DIAGNOSIS BETWEEN CARDIAC SARCOIDOSIS AND ARVC/D

	CARDIAC SARCOIDOSIS	ARVC/D
Family history:	Absent	Present in 30% to 50% of cases. When the disease is identified, genetic screening should be conducted among 1st degree relatives
Gender (M/F):	1 to 1.	2.9 to 1
Mean age of presentation:	Young people or adults in intermediary age	Adolescents and young adults. Rarely in children.
Multi-systemic involvement	Yes	No
Precordial pain	Intense precordial pain is described	No
Clinical manifestations of restrictive cardiomyopathy:	Possible	No
Mitral valve insufficiency	Common	Only lately when it involves the LV.
ECG pattern of pseudo infarction:	Frequent in extensive forms	No

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

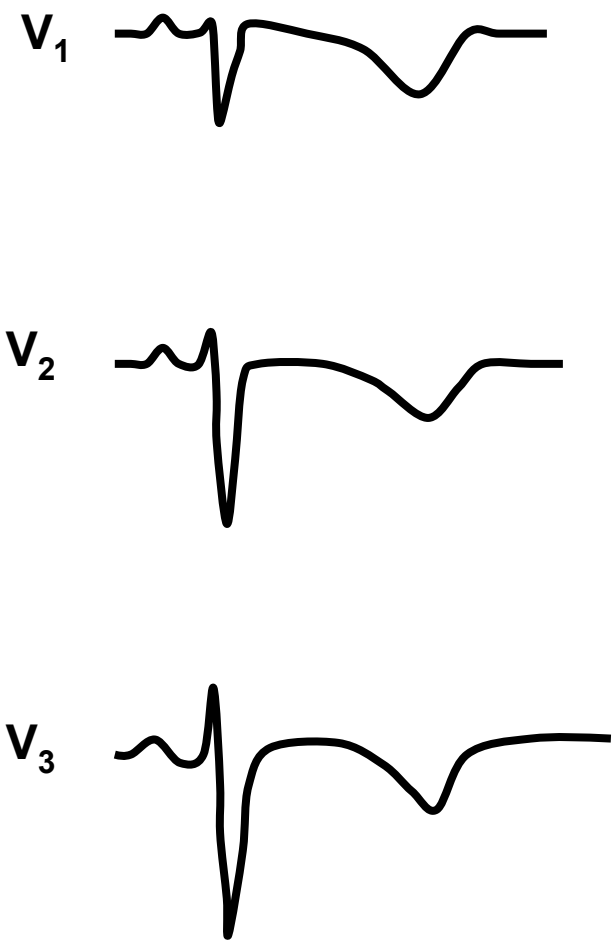
Differential diagnosis between ARVC/D and cardiac sarcoidosis

DIFFERENTIAL DIAGNOSIS BETWEEN CARDIAC SARCOIDOSIS AND ARVC/D

	CARDIAC SARCOIDOSIS	ARVC/D
Chest X-rays	Bilateral hiliar lymphoadenopathy.	Possible right cardiomegaly.
Pulmonary involvement	Present in >90% of cases. Frequent COPD.	No
Pathological anatomy:	Non-cancerous granulomas that sometimes form fibrotic scars.	RV fibro-fatty substitution in the triangle of dysplasia.
Cardiac location involved more frequently:	LV free wall and interventricular septum.	RVOT, RVIT and RV apex.
Pericardial effusion:	Frequent	Absent
Improvement of symptoms shown by MNR with use of corticoids:	Yes	No
Corticosteroids, chloroquine, methotrexate or cyclophosphamide:	Sometimes prescribed	No

Differential diagnosis between ARVC/D and cardiac sarcoidosis

POLARITY OF T WAVE FROM V1 TO V3 IN ARVC/D



In absence of CRBBB in patients >12 years old, negative T wave from V1 to V3 is a sign with great value for diagnosis.
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 patients carriers of ARVC/D, the ECG generally shows T wave inversion in V1 and V2, which may reach up to V6.(1).

In patients with VT of right ventricular origin, the presence of T-wave inversion in the right precordial leads during sinus rhythm supports the diagnosis of ARVC/D. (2)

1. **Fontaine G, Tsezana R, Lazarus A, et. al. Repolarization and intraventricular conduction disorders in arrhythmogenic right ventricular dysplasia. Ann Cardiol Angeiol (Paris). 1994 Jan; 43: 5-10.**
2. **Morin DP, Mauer AC, Gear K, et al. Usefulness of precordial T-wave inversion to distinguish arrhythmogenic right ventricular cardiomyopathy from idiopathic ventricular tachycardia arising from the right ventricular outflow tract. Am J Cardiol. 2010 Jun 15;105:1821-4.**

ARRHYTHMIAS IN ARVC/D

1) Monomorphic VT with CLBBB morphology, sustained or not, and frequent premature ventricular contractions (>100 in 24h).(1)

2) If SÂQRS of MVT with CLBBB morphology has inferior axis: it originates in RVOT.

3) If SÂQRS of MVT with CLBBB morphology has superior axis: it originates in the RVIT.

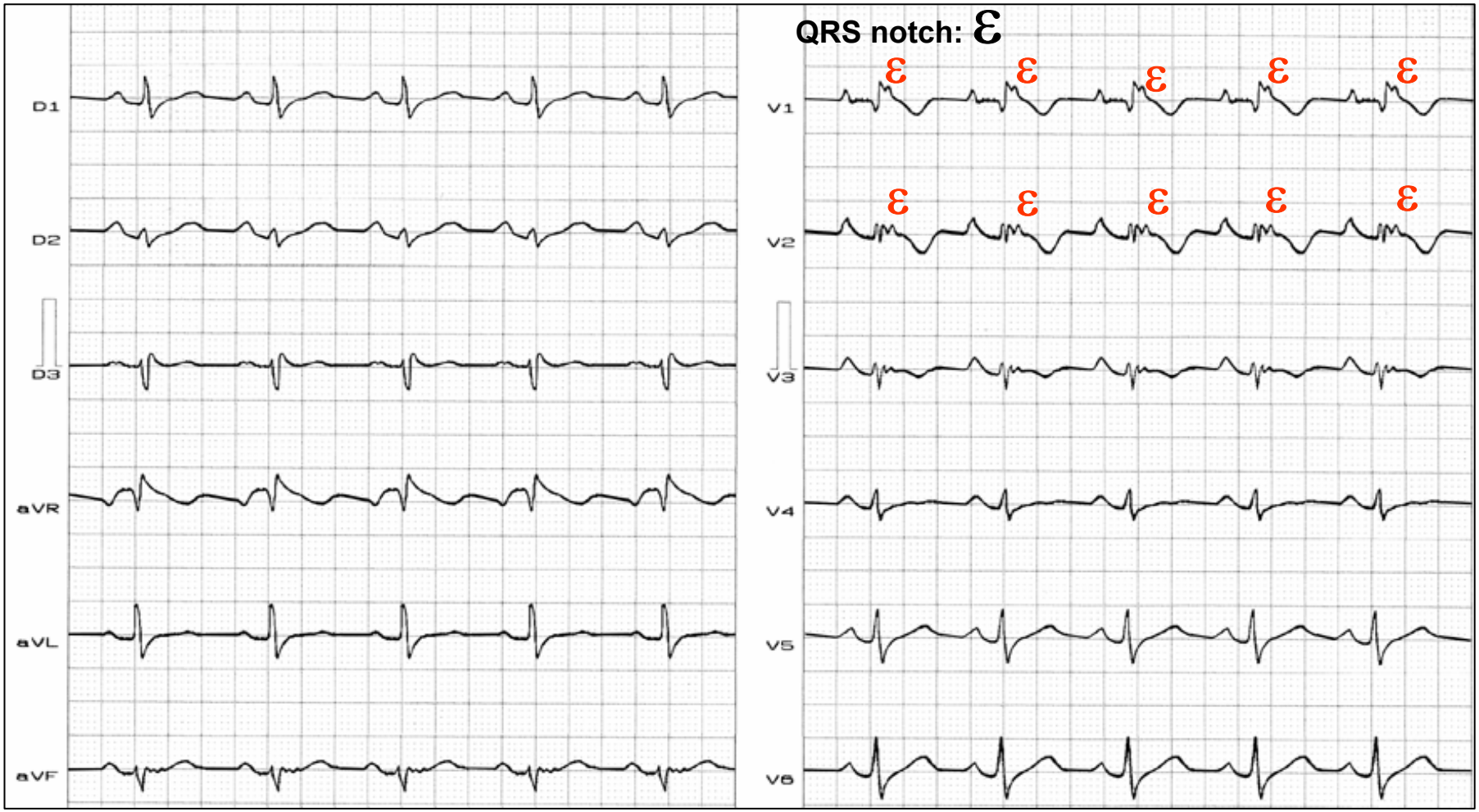
4) Multiple morphologies of VT during the electrophysiological study and abnormal angiogram of RV are usually observed in ARVC/D diagnosis.

5) QRST interval mapping reflects disparities in ventricular repolarization, which lead to vulnerability to arrhythmias. Integral mapping of QRST interval is considered an appropriate method to assess ventricular repolarization dispersion in patients with ARVC/D.(1)

6) ARVC/D associated to a high and significant incidence of inducibility for Supraventricular Tachyarrhythmias in the control population. Supraventricular Tachyarrhythmias may precede induced VT.

1. **Navarcikova S, Sulkova I, Celec P, et al. Body surface integral maps in patients with arrhythmogenic right ventricular cardiomyopathy.Bratisl Lek Listy. 2005;106:212-215.**

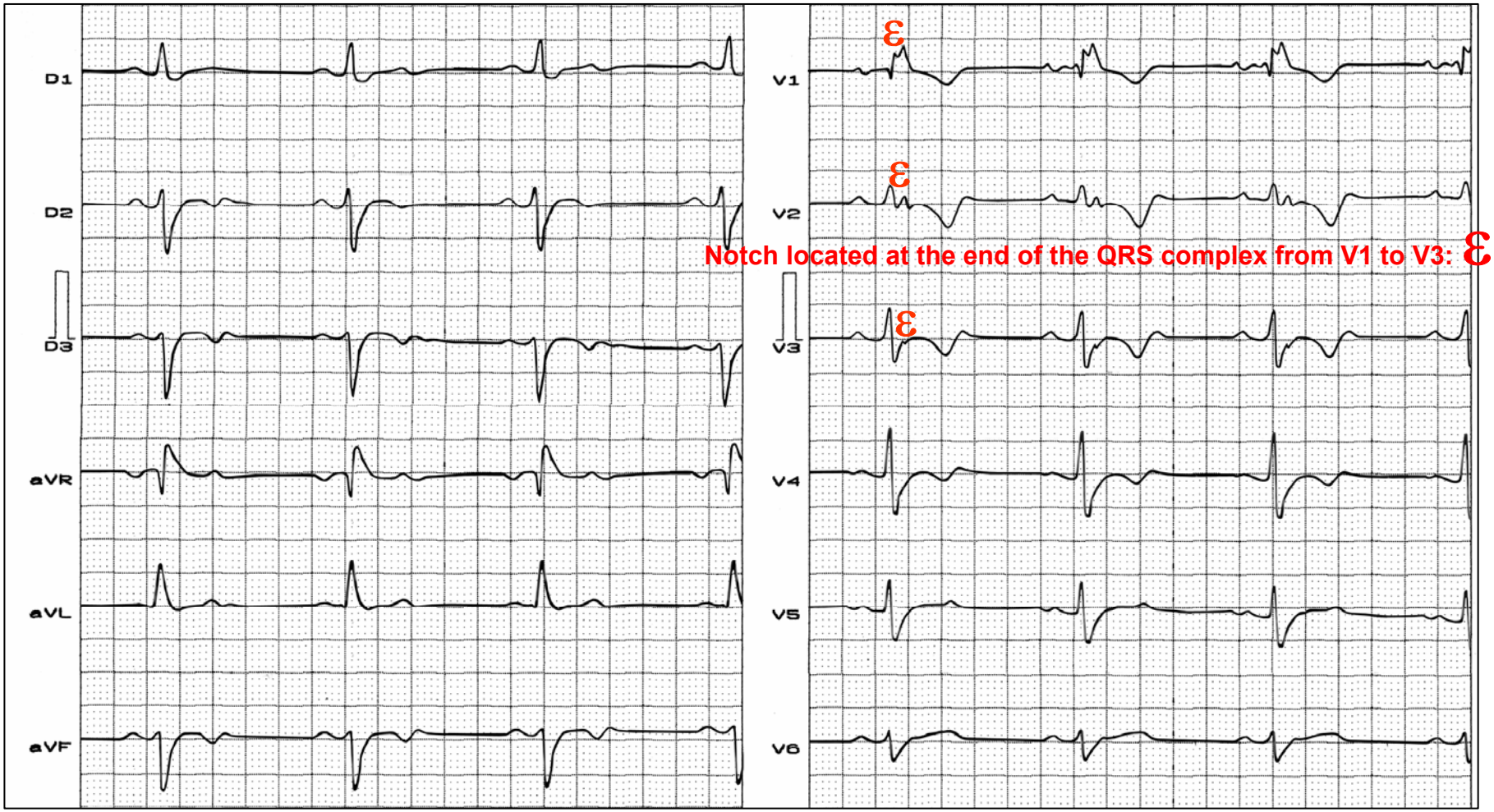
TYPICAL ECG OF ARVC/D



Sinus rhythm, CRBBB, terminal notch located in the J point (epsilon wave). The epsilon 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.

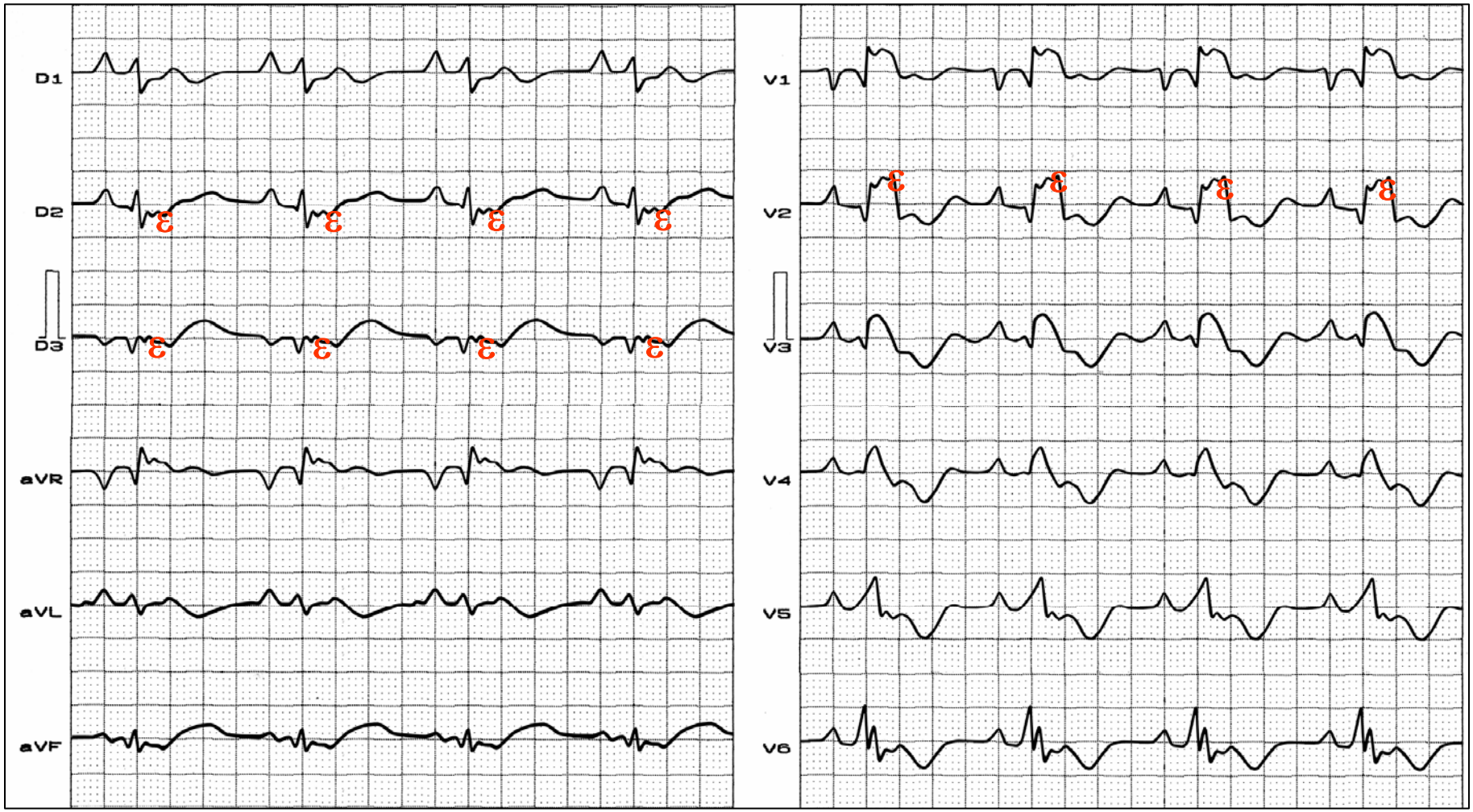
Typical ECG of ARVC/D: Epsilon wave, RBBB and negative T wave from V1 to V3.

TYPICAL ECG OF ARVC/D



Sinus rhythm, HF: 44 bpm, sinus bradycardia, PR interval: 175 ms, SAQRS: -85º, QRSD: 185 ms, SDIII > SDII, LAFB, atypical CRBBB (qR pattern), notch located near the J point (epsilon wave) visible from V1 to V3, characteristic of ARVD. Negative T wave from V1 to V4.

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

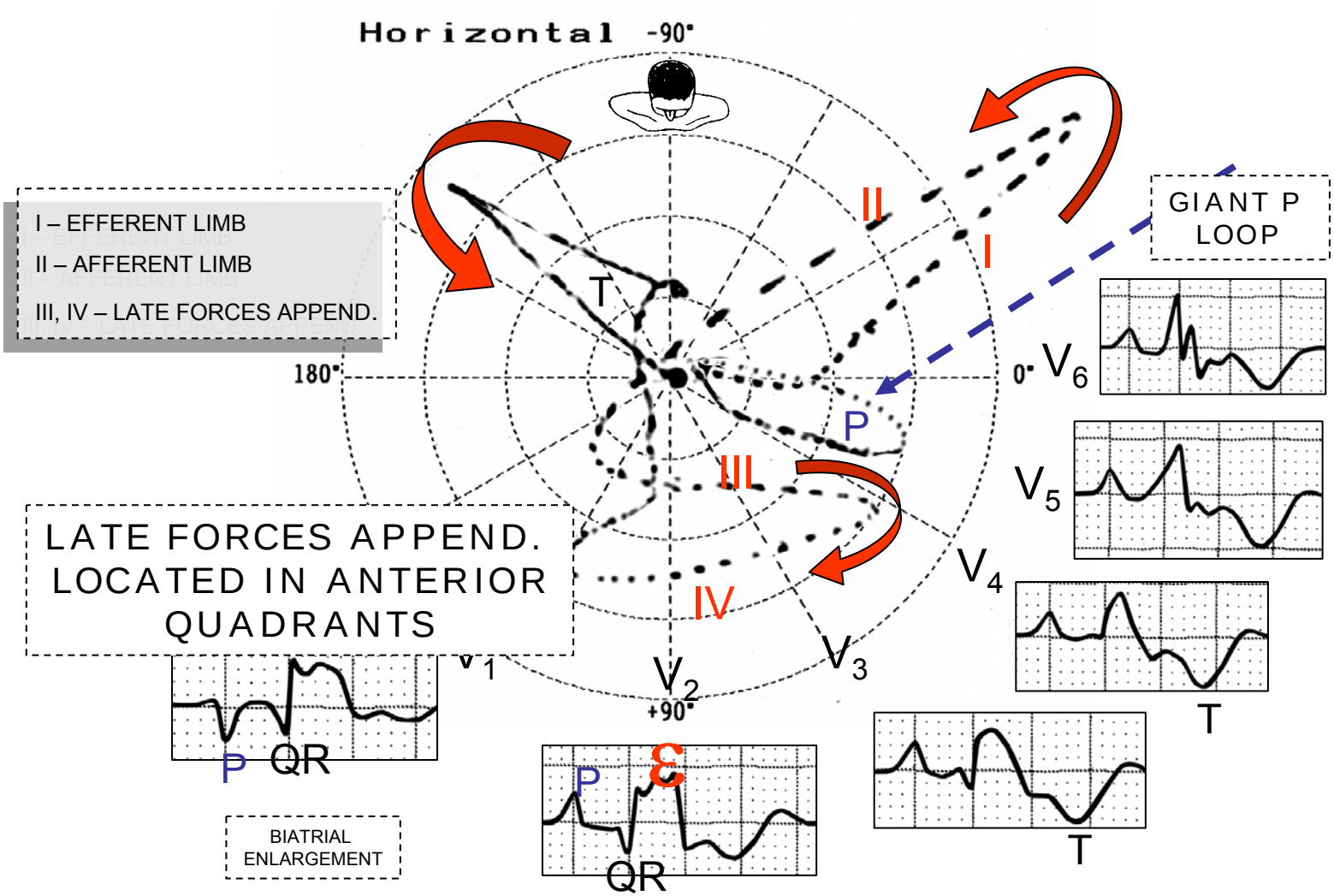


Clinical diagnosis: Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Severe right heart failure.

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); epsilon waves are observed in numerous leads.

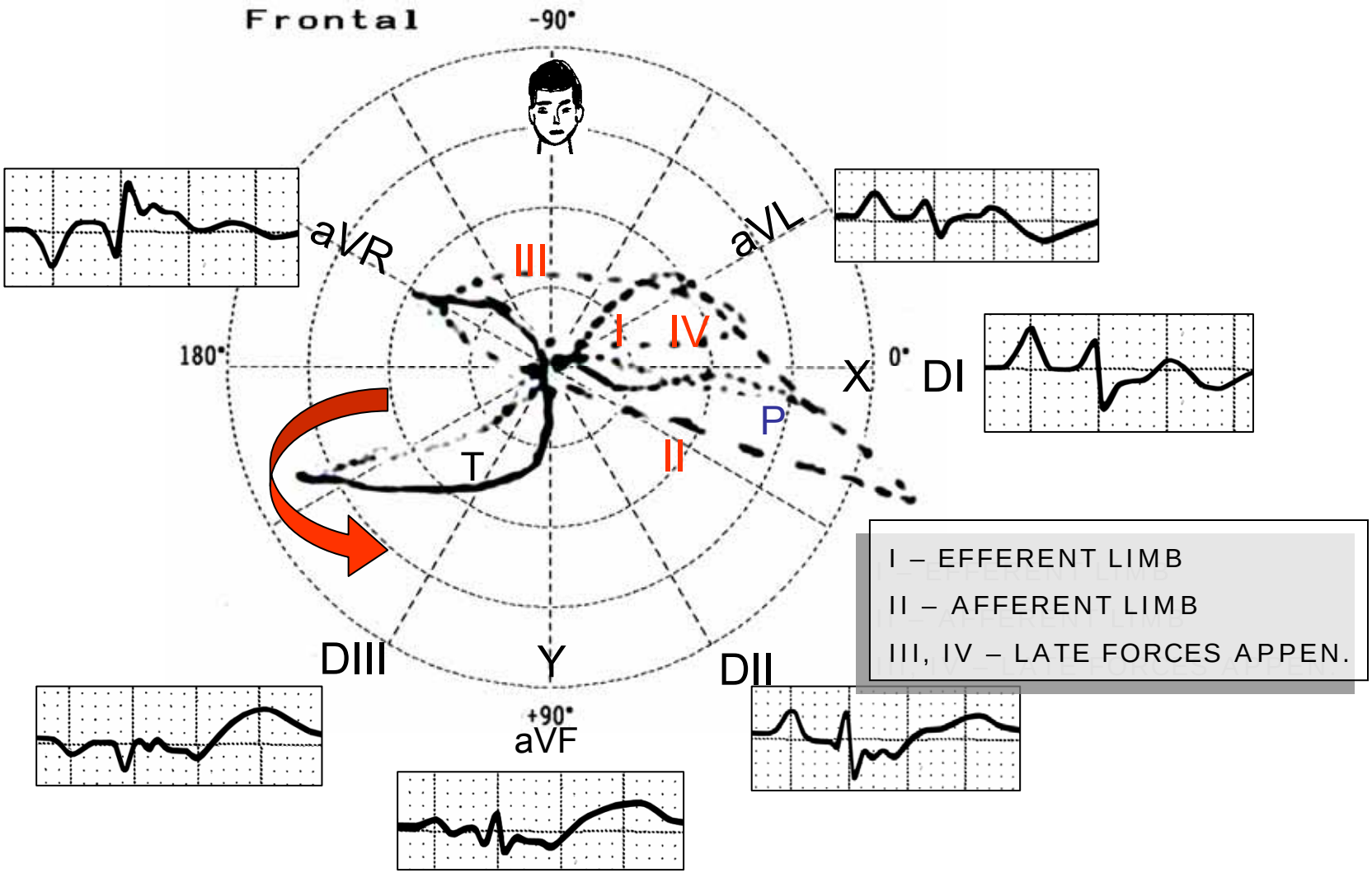
ARVD and severe right CHF.

ECG/VCG CORRELATION HORIZONTAL PLANE



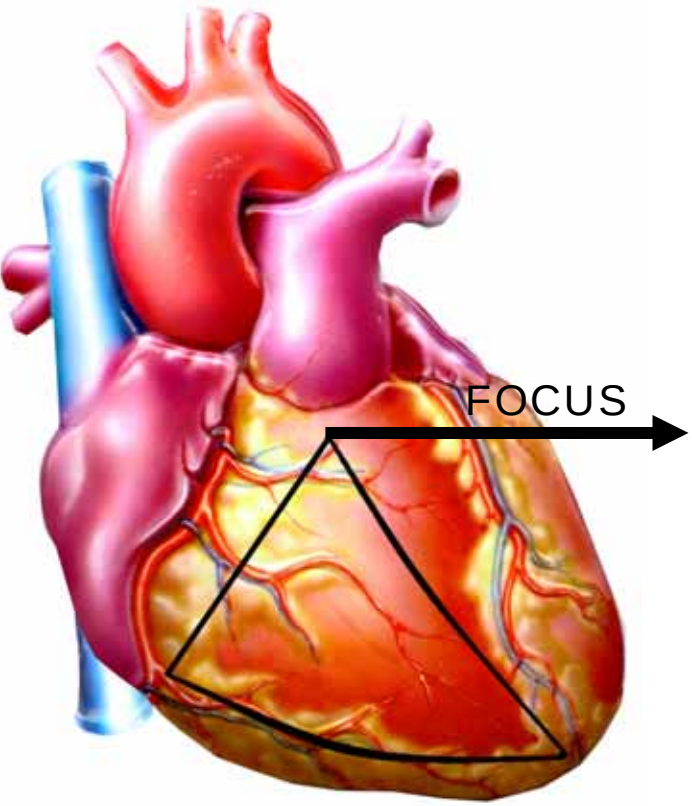
ECG/VCG sequence of a patient carrier of ARVC/D and severe right CHF.

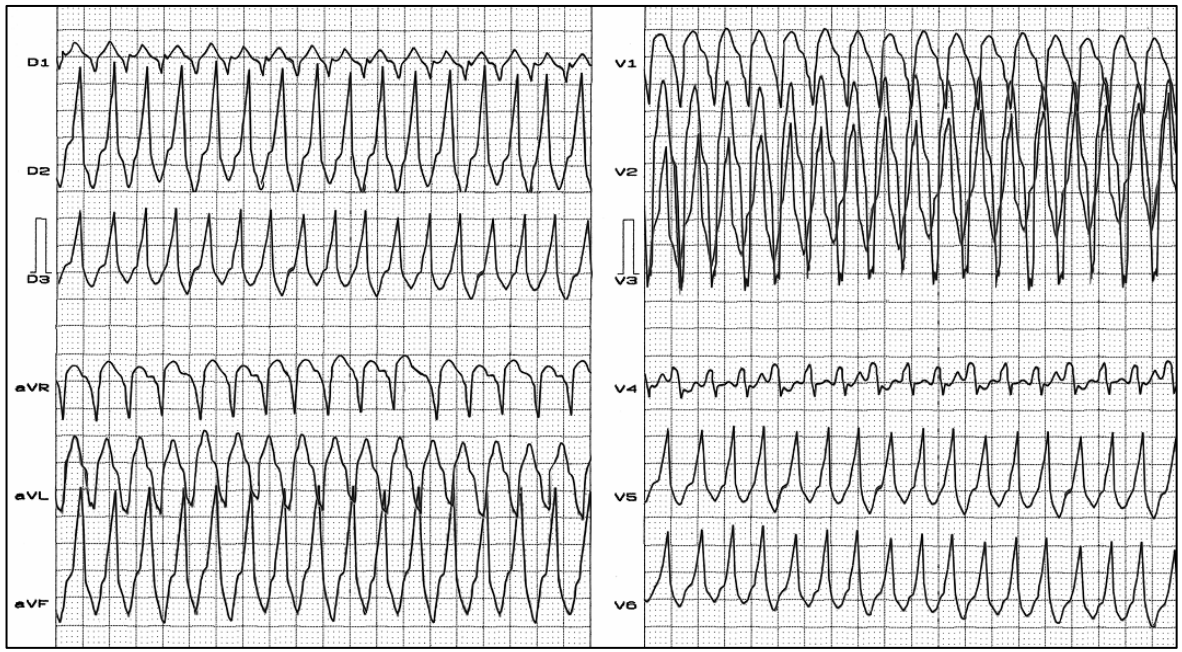
ECG/VCG CORRELATION FRONTAL PLANE



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

CHARACTERISTICS OF MVT THAT ORIGINATES IN THE RVOT

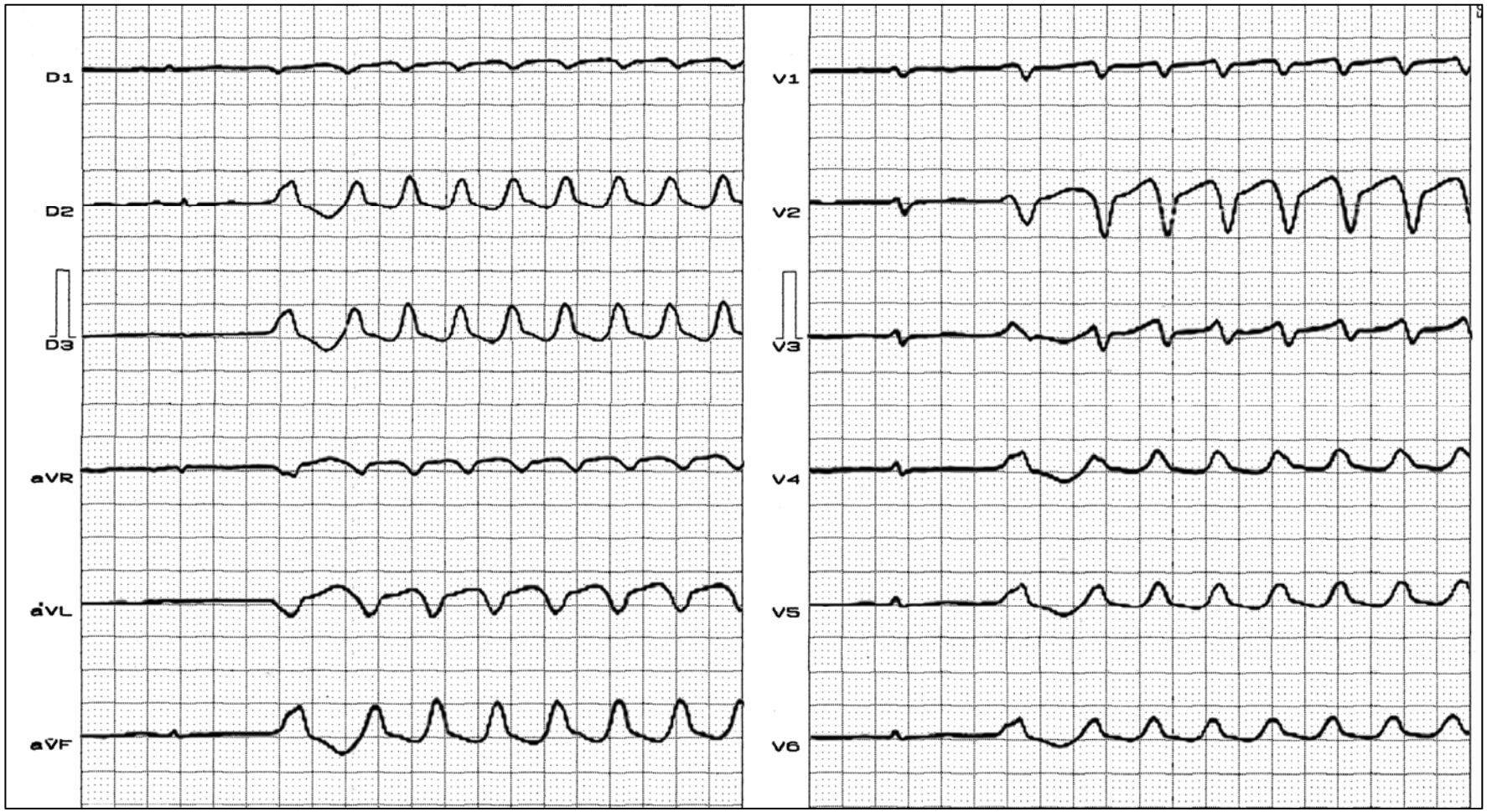




SMVT with Complete LBBB pattern and inferior axis in the frontal plane: positive complexes in inferior leads and negative in aVL and aVR. In this case, SÂQRS is located at the right of +90º, thus indicating origin in the RVOT. In these cases, SAQRS is between +90º and +120º ("QS" type QRS in I).

Relationship between TV's site of origin and ECG morphology.

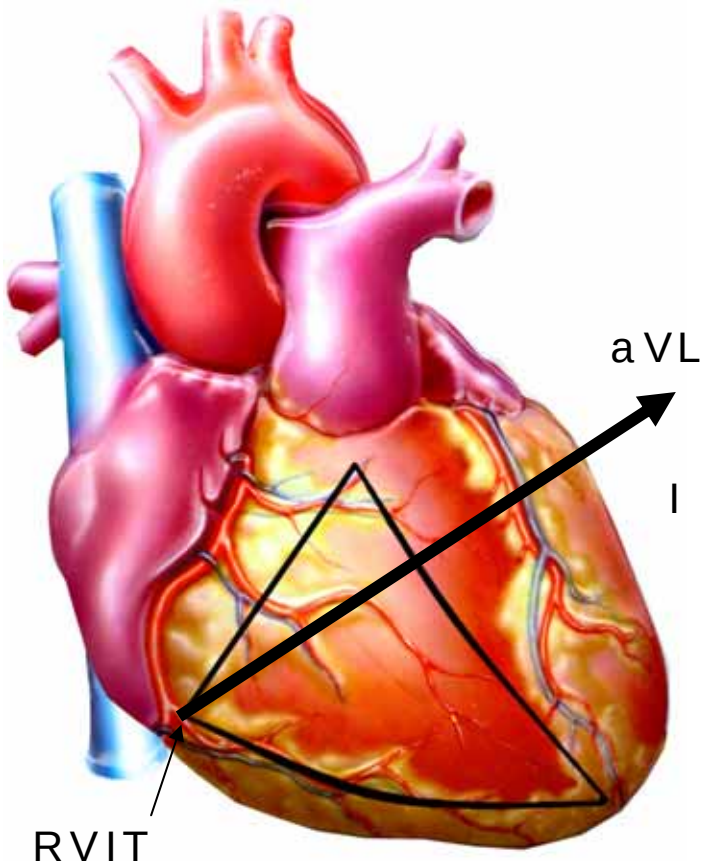
MVT THAT ORIGINATES IN THE RVOT (INFUNDIBULUM)

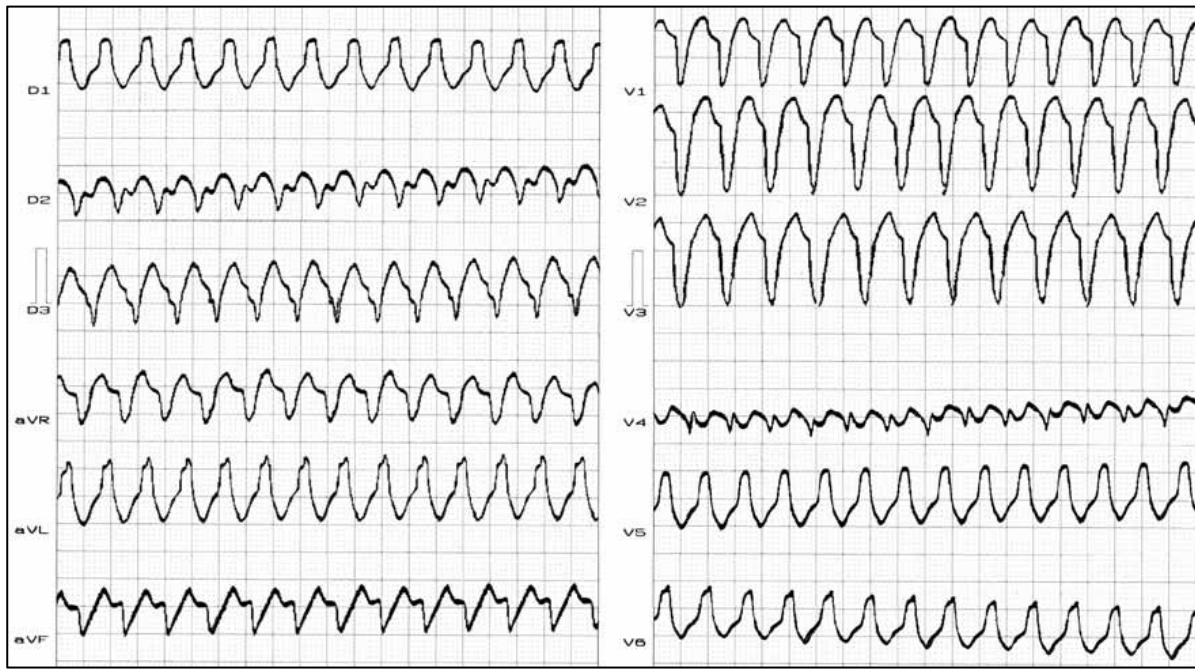


MVT that originates in the RVOT with CLBBB pattern and inferior QRS axis in patient carrier of ARVC/D after cardiac arrest.

Relationship between TV's site of origin and ECG morphology.

MVT THAT ORIGINATES IN THE RVIT

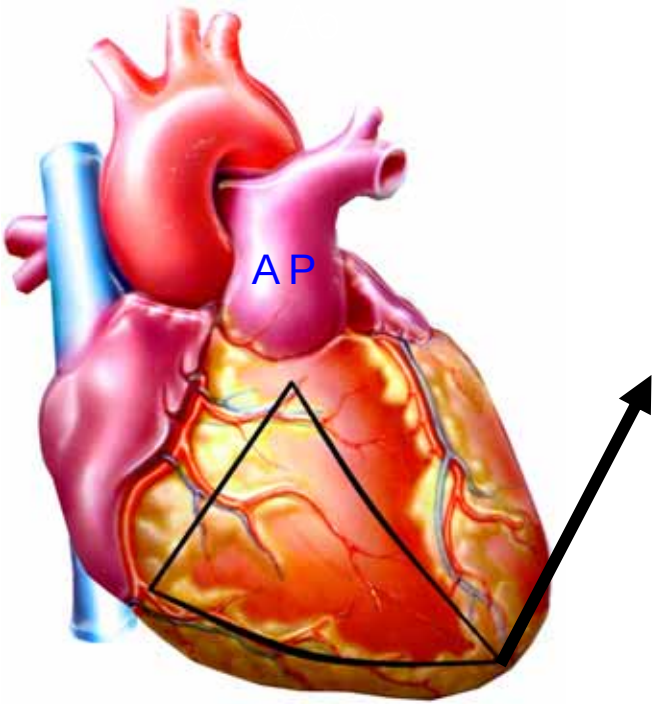


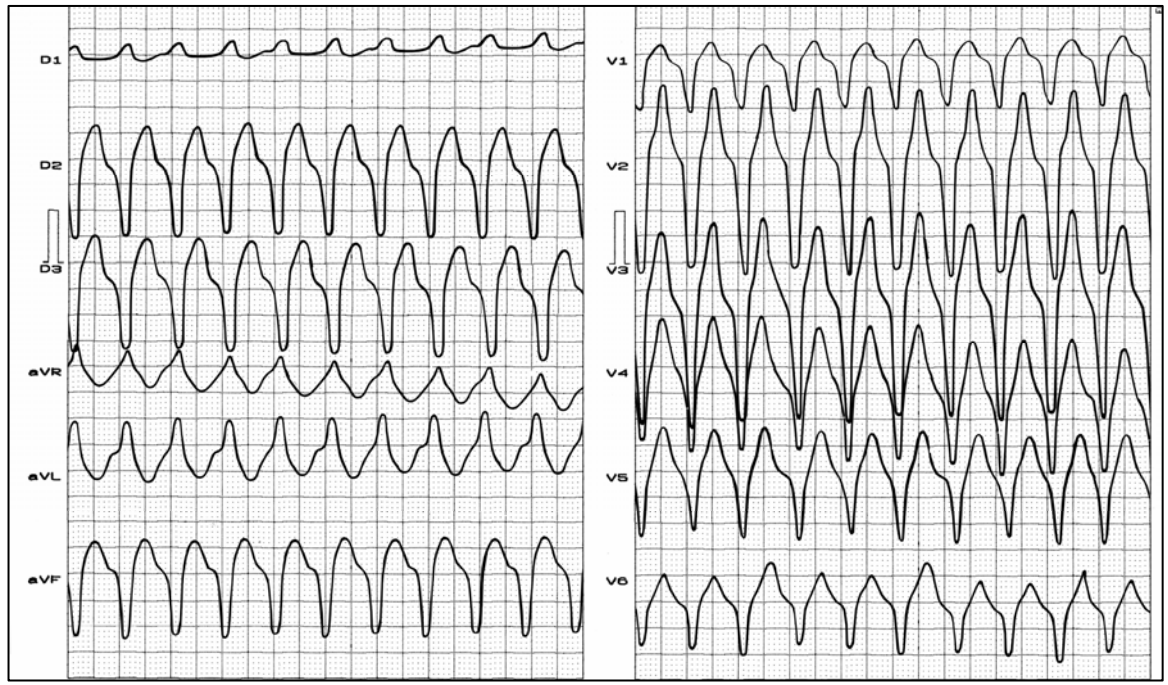


MVT with a heart rate of 214 bpm, pattern of CLBBB and electrical axis with extreme shift to the left: it originates in the RVIT. Positive QRS complexes in I and Avl, V5-V6,
This left QRS axis deviation indicates presence of structural heart disease.

Relationship between TV's site of origin and ECG morphology.

VT ORIGINATES IN THE RIGHT VENTRICLE APEX





VT with CLBBB morphology and SAQRS axis with extreme shift to the left: negative QRS complexes in inferior leads, positive in DI, aVL and aVR, associated to negative QRS complexes from V1 to V4 or V1 to V6, which indicate focus of origin in the RV apex (it indicates structural heart disease).

Relationship between TV's site of origin and ECG morphology.

ECG comparison of ventricular arrhythmias in patients with ARVC and RVOT tachycardia

	ARVC/D	RVOT-VT
QRS duration in lead I	150 ± 31 ms	123 ± 34 ms
Precordial transition in lead V5 or later	more often 17% Predicted	0%
Presence of notching on any QRS complex	Yes	No

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

PARIETAL BLOCK

Located prolongation has been described for QRSd interval from V1 to V3, related to $^{V1 + V2 + V3}$ / $_{V4 + V5 + V6}$ >1.2 in 97% of the cases of ARVC/D, and it is related with the amount of fibrotic tissue in patients with VT that originate in the RV.

The sensitivity of this criterion is not known in other entities and it speaks in favor of slow RV conduction.

One study shows that the sign is not specific, since it is found in Brugada syndrome with QT interval prolongation only from V1 to V3.(1)

If QT interval prolongation occurs only from V1 to V3, it is clear that this is due to depolarization time prolongation.

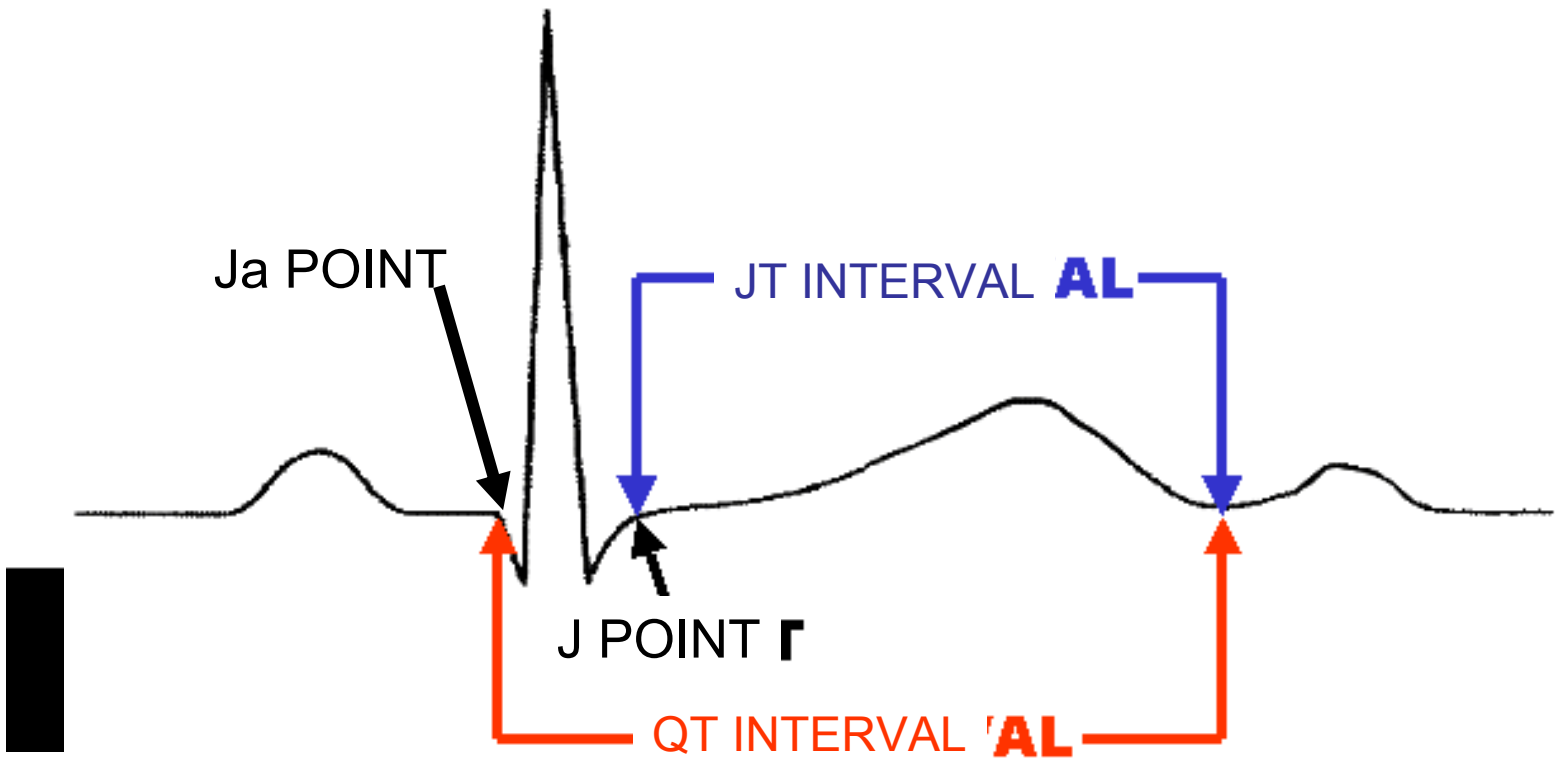
If we admit that in Brugada syndrome there is some degree of RBBB, this QT interval prolongation may be partially due to this fact.

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 (next slide).

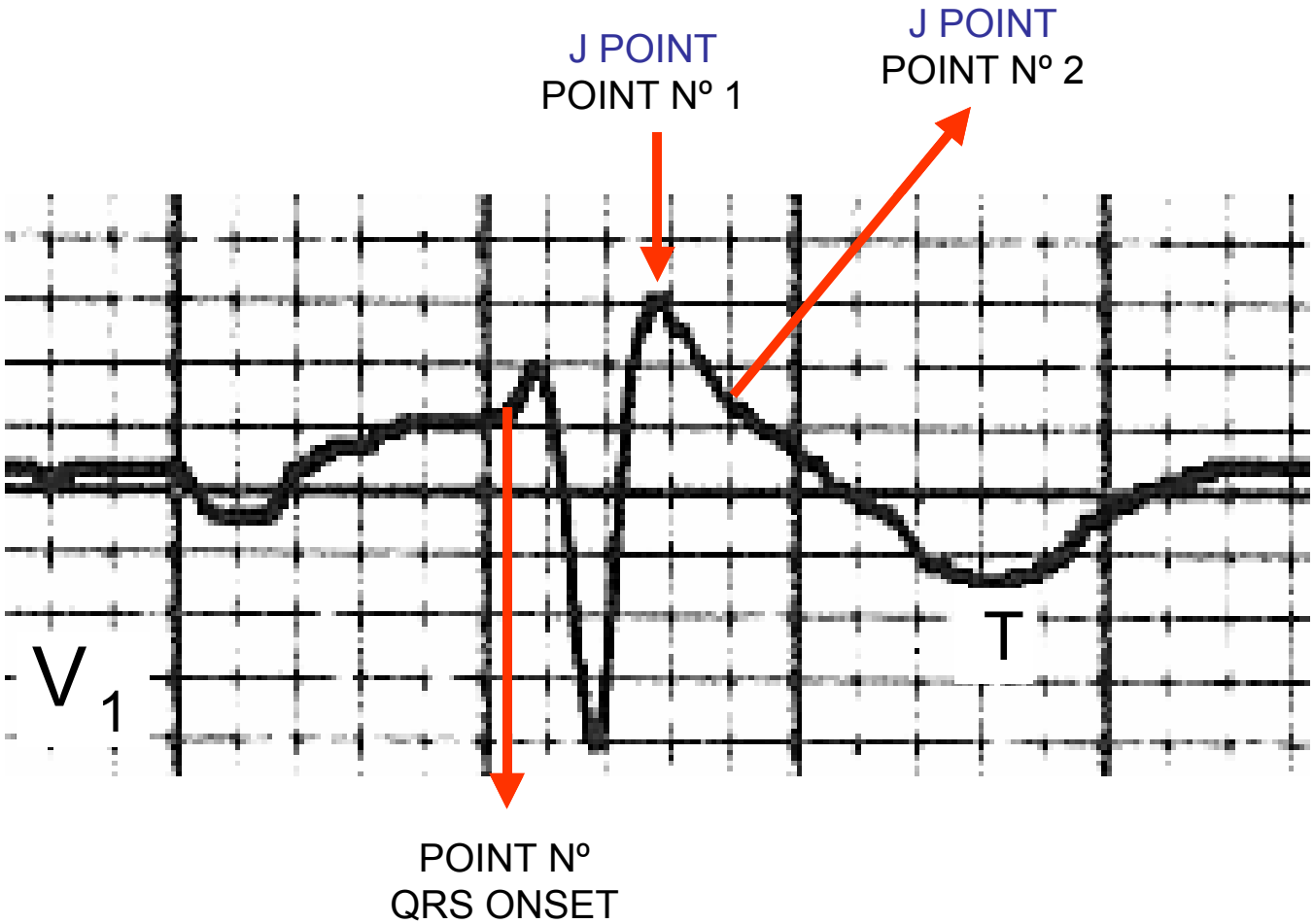
1) **Pitzalis MV, Anaclerio M, Iacoviello M, et al. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003 Nov 5;42:1632-1637.**

JT INTERVAL 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 additionof ventricular depolarization (QRS) and repolarization (ST/T = JT interval).If 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).

WHERE IS THE END OF QRS COMPLEX (J POINT)?



In certain cases as in Brugada syndrome, and in concealed forms of ARVC/D, it is difficult to determine accurately when the QRS complex ends and repolarization starts; in other words, it is difficult to know the precise location of the J point.

Problems to locate accurately the J point in concealed forms of ARVC/D and BrS.

VALUE OF VECTOCARDIOGRAM IN ARVC/D

In 1988, researchers from Padua (Italy) showed vectocardiographic tracings characterized by what is known today as right end conduction delay (RECD), by the superior fascicle of the right branch, in a series of 6 patients, 5 of which had ARVC/D as it was shown, and one of them was attributed to IVF.(1)

Tracings of this kind were interpreted as early repolarization.(2)

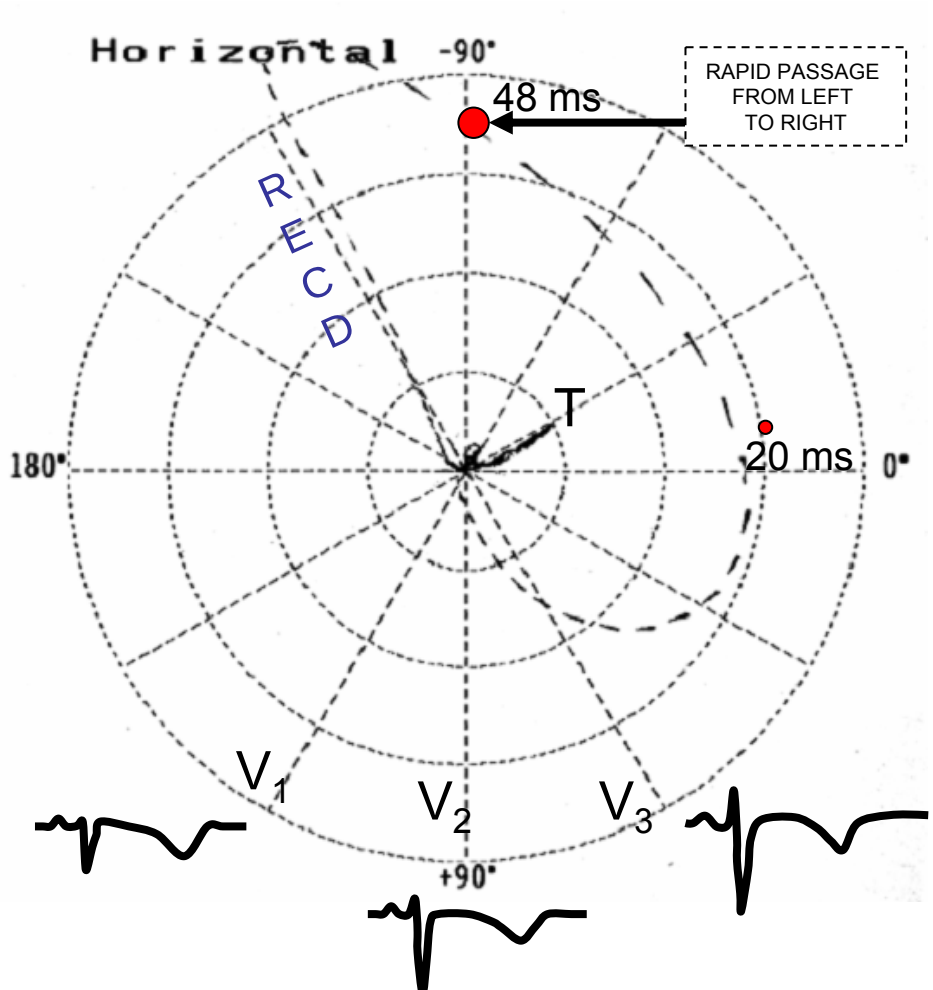
In ARVC/D, in 18% of cases, pattern of IRBBB or RECD are observed and in approximately 15% of the cases, Complete RBBB.

In this entity, there is evidence of right bundle fascicular block, which occurs in the RV free wall, after the trunk of the left branch splits at the tip of the RV, at the base of the papillary muscle of the tricuspid valve. The mechanism responds to dysplastic involvement of the free wall, in the so-called Dysplasia Triangle, the angles of which are formed by the RVOT, RVIT and the apex. (3)

Its characteristic is the presence of RECD by the right branch, by one of the fascicles, known as selective, peripheral, parietal, monofascicular RBBB or RECD. This disorder is vectocardiographically characterized by:

1. **Nava A, Canciani B, Buja G, et al. Electrovectorcardiographic study of negative T waves on precordial leads in arrhythmogenic right ventricular dysplasia: relationship with right ventricular volumes. J Electrocardiol. 1988 Aug;21:239-245.**
2. Nava A, et al. Mises a Jour Cardiologiques 1988; 17:157-159.
3. Fontaine G, et al. Arch Mal Coeur Vaiss. 1984; 77:872-879.

VCG IN ARVCD – HORIZONTAL PLANE



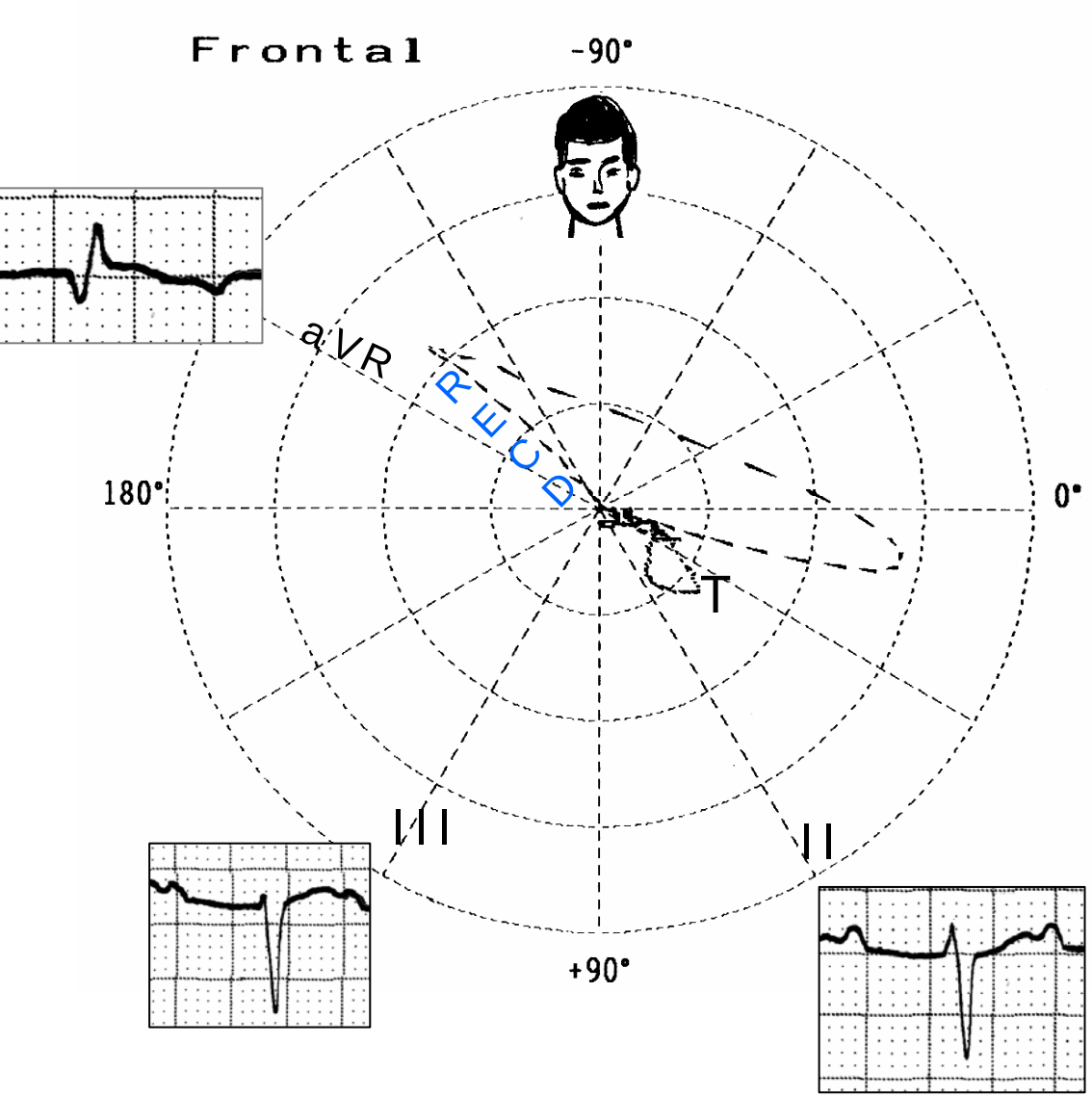
1. **Initial 10 to 20 ms vector heading predominantly forward and rightward (in normal conditions, this vector in 85% of the cases is heading forward and rightward).**

2. **QRS loop displays rapid passage from left to right between 40 and 60 ms in both planes (FP and HP).**

3. **RECD on posterior right quadrant**

4. **T loop located on left posterior quadrant (negative T waves form V1 to V3.**

VCG IN ARVC/D – FRONTAL PLANE



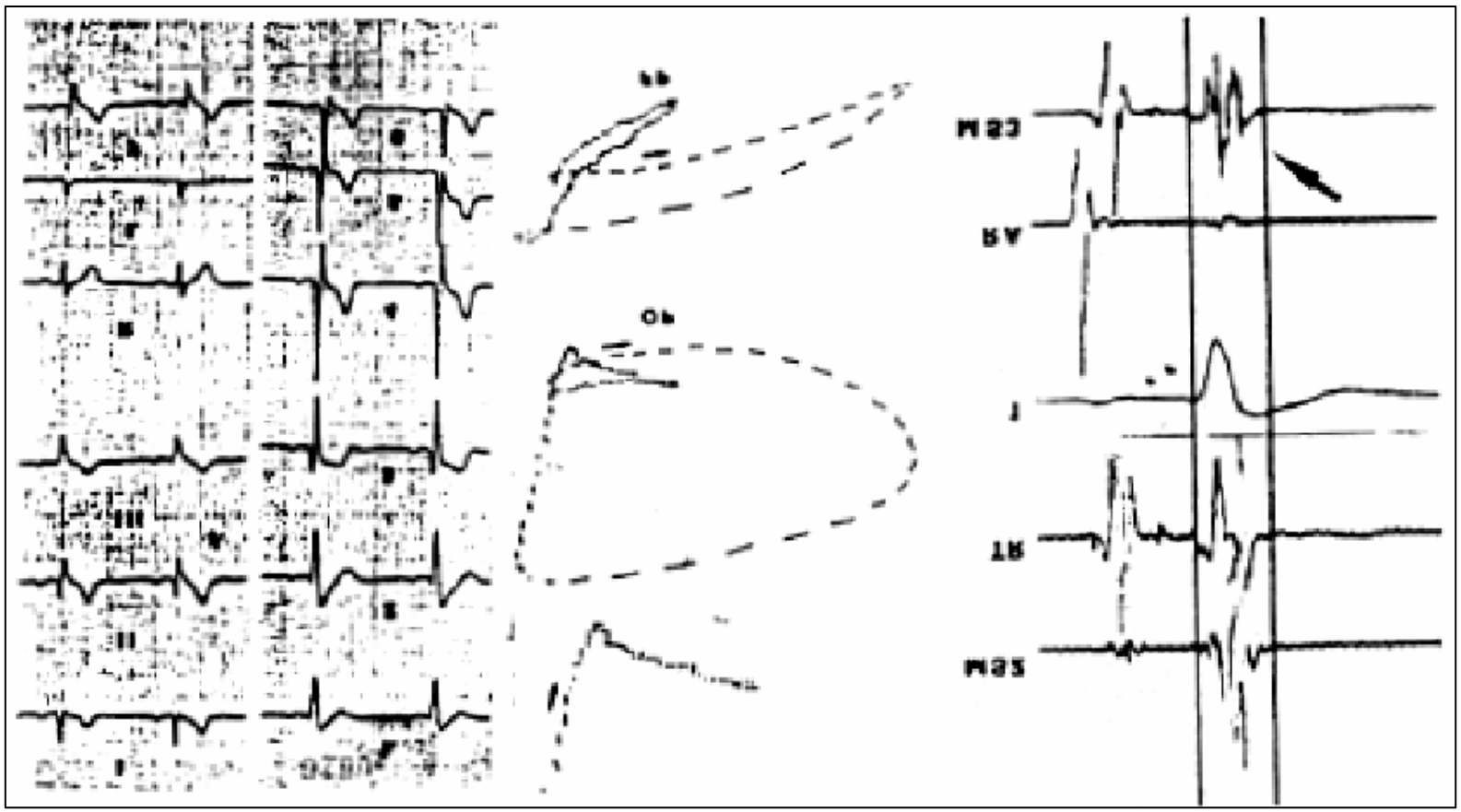
1. **Possible extreme shift of QRS axis in the frontal plane (FP) located between -30° and -90°**

2. **S II > S III in most cases (element of great significance for differential diagnosis with LAFB).**

3. **QRS loop with significant RECD (30 ms or more of very close dashes) after 60 ms, visible at least in 2 planes**

4. **RECD located in in the right superior quadrant in FP with prominent final R wave in aVR.**

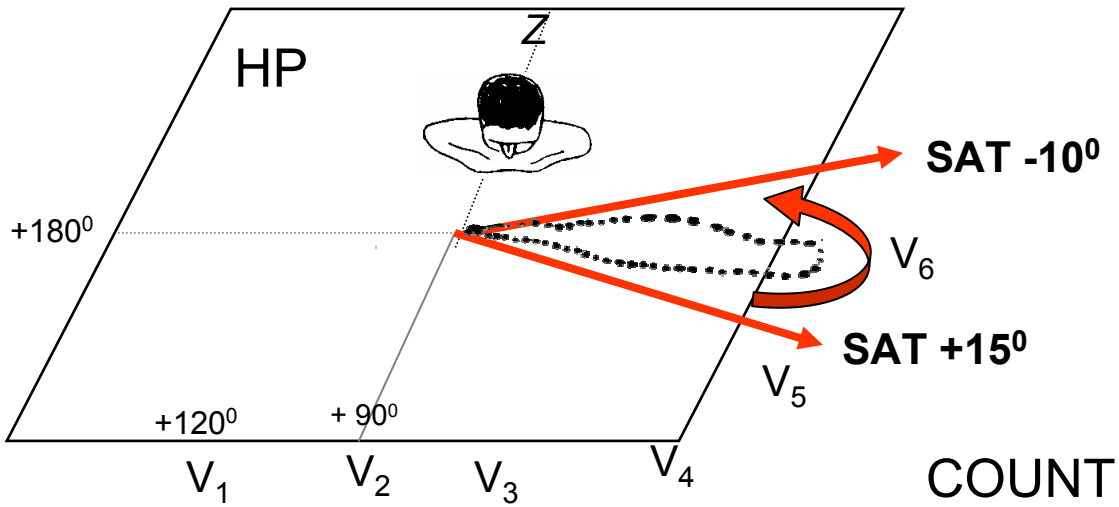
36 YEARS OLD, EPISODE OF VF



The authors interpreted this tracing as early repolarization. Today we know that this is the typical type 1 Brugada pattern, which from the vectocardiographic point of view is diagnosed as RECD by one of the RB fascicles

1) **Nava A, et al. Mises a Jour Cardiologiques 1988;17:157-159.**

T LOOP BEHAVIOR IN ARVC/D AND ITS RELATIONSHIP WITH RV END DIASTOLIC VOLUME

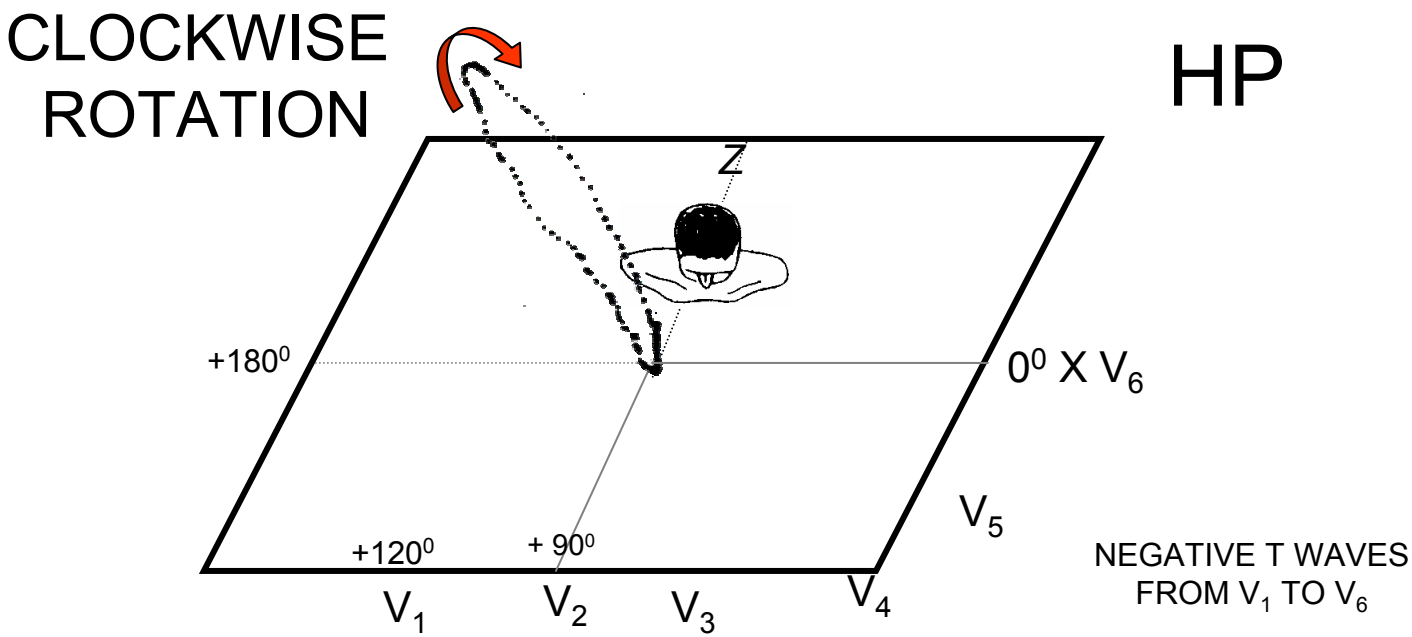


COUNTERCLOCKWISE ROTATION

When the RV end diastolic volume is not very increased (in average 100 ml/m^2).

The T loop presents counterclockwise rotation in the HP and axis between +15° y –10° (average +5^0).

T LOOP BEHAVIOR IN ARVD AND ITS RELATIONSHIP WITH RV END DIASTOLIC VOLUME

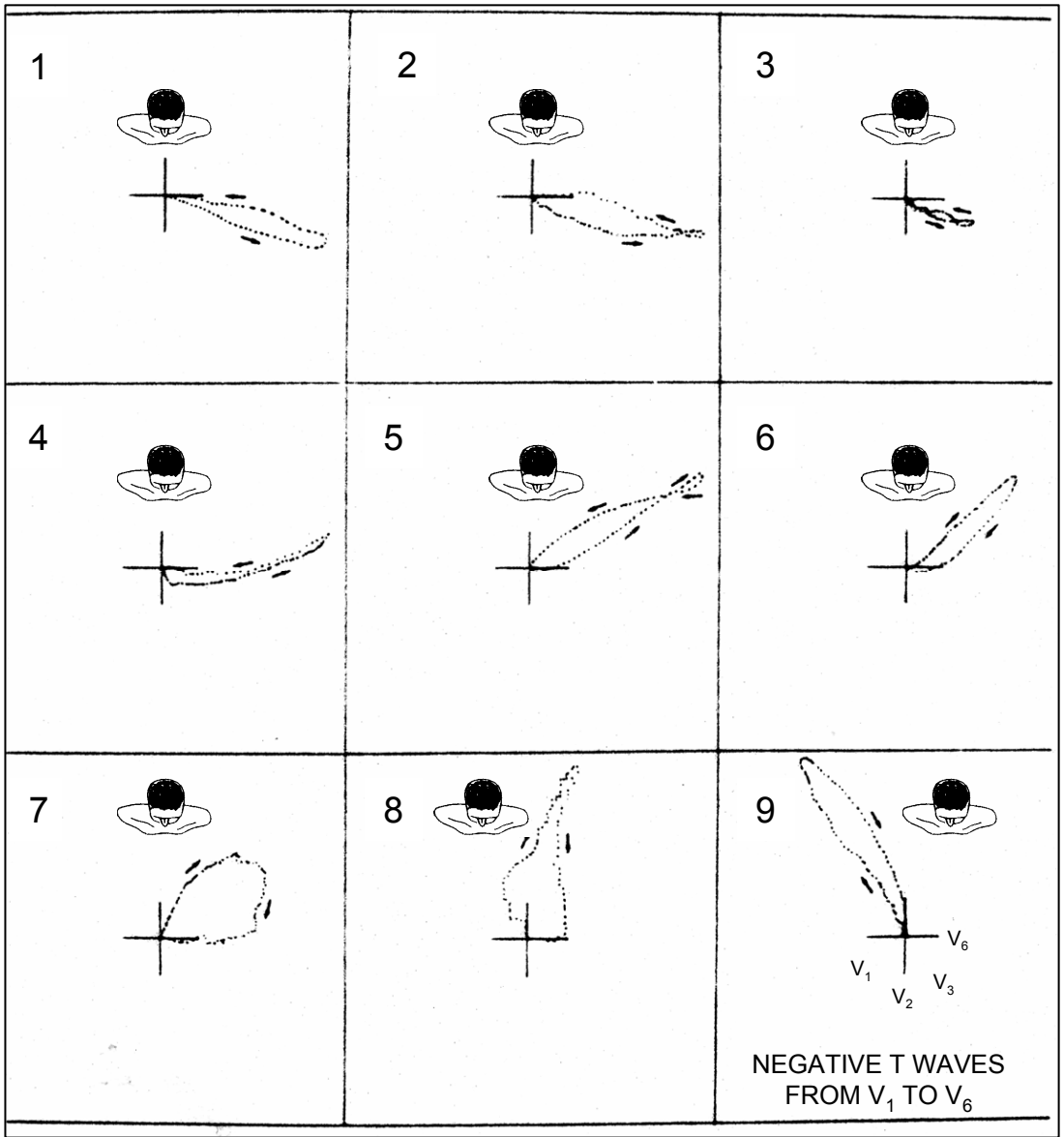


When the RV end diastolic volume is large (in average 320 ml/m^2), the T loop displays clockwise rotation in the HP and is located in the right posterior quadrant, which justifies the negative T wave in all precordial leads[1].

Note: the presence of T loop of clockwise rotation, indicates the presence of underlying heart disease.

1) Friedman HH. Diagnostic Electrocardiography and Vectorcardiography. 3rd Edition. Chapter 6. Pg 116; 1985.

T LOOP BEHAVIOR IN ARVD AND ITS RELATIONSHIP WITH RV END DIASTOLIC VOLUME

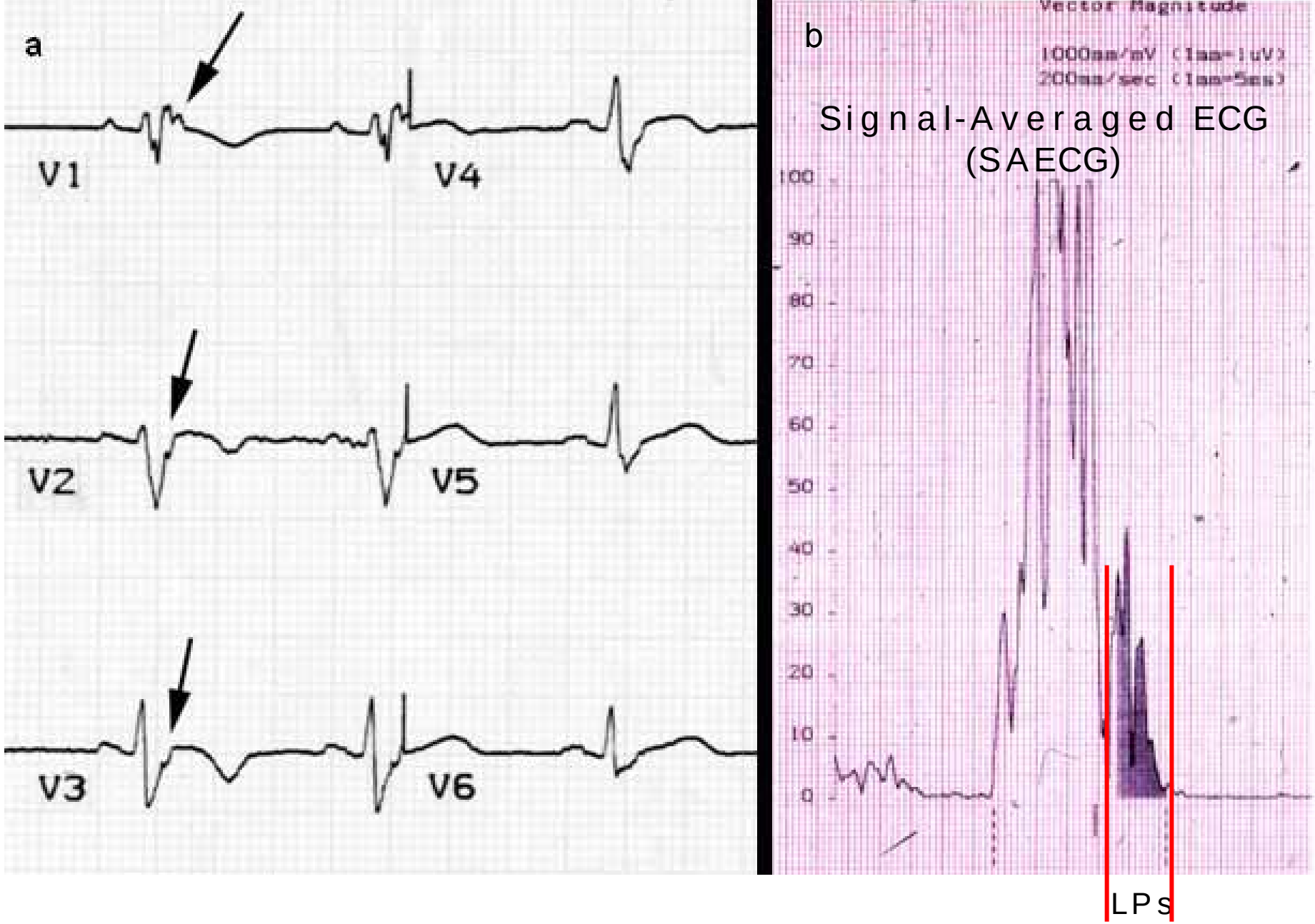


T loop in 9 patients in the HP, carriers of ARVC/D. T loops are arranged on the basis of progressive RVH.

T loop (nº 1) has a RV end diastolic volume of 100 ml/m^2 and the last loop (nº 9) has 320 ml/m^2.

Note the progressive alteration of the T loop from 1 to 9. The present case correspond to type 9.

1. **Nava A, Canciani B, Buja G, et al. Electrovectorcardiographic study of negative T waves on precordial leads in arrhythmogenic right ventricular dysplasia: relationship with right ventricular volumes. J Electrocardiol. 1988 Aug;21:239-245.**



ECG recording: (a) post-excitation epsilon wave (arrows) in right precordial leads; (b) positive late potentials

VALUE OF SAECG IN ARVC/D

- In ARVC/D, high resolution ECG 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.(1)
- SAECG is used to detect late potentials (LP) and ε waves in ARVC/D carriers.
- Patients with positive high resolution ECG (presence of LP) have statistically significant increase of S-VT and/or SCD in comparison to those with normal SA ECG or branch block.
- SA ECG with LP constitutes a marker of arrhythmic events in patients with non-ischemic dilated cardiomyopathies. On the contrary, patients with dilated cardiomyopathies with normal high resolution ECG, display worsening only if they develop progressive CHF. (2)
- 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.
- SA ECG 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.(3)
- The combination of the analysis of time domain and frequency domain of high resolution ECG may be useful for screening patients carriers of ARVD. This combination of both domains increases sensitivity without reducing specificity.
- SAECG should be considered a standard test in the study of patients with suspicion or carriers of ARVC/D

1) **Gregor P. Vnitr Lek. 2003; 49:727-729.**
2) **Mancini DM, et al. Circulation. 1993;87:1083-1092.**
3) Oselladore L, et al. Am J Cardiol. 1995; 75:1038-1041.

VALUE SAECG IN ARVC/D

- Use of filters with a range between 20 and 250 Hz (substituting the classical ranges between 40 and 250 Hz).(1)
- The presence of LP in ARVD 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, high resolution ECG 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.(2)
- In absence of bundle branch block, the presence of LP in SA ECG is proportional to the size of the RV cavity, and thus is parallel to RV dysfunction.(3)
- 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 SA ECG may be helpful.
- ECG during VT and high resolution ECG may be useful to differentiate both entities. In the case of ARVD, VT presents QS in V1 and QRSD related to the amount of fibrous tissue existing in the RV.(4)
- 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.(3)
- There is a narrow correlation between the result from SAECG and the extension of the disease, with the presence of VT.
- SA ECG 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.(5)

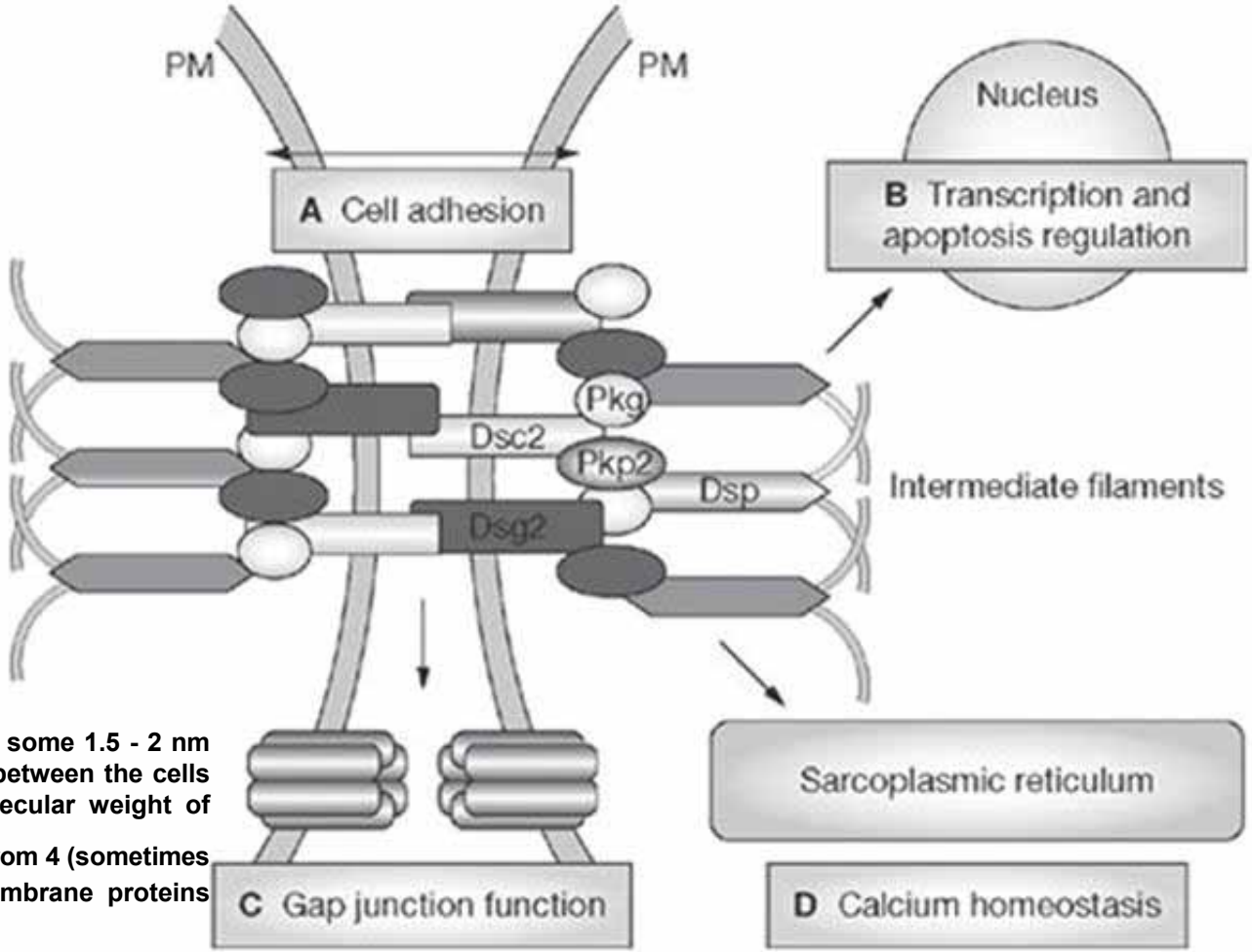
1) **Kinoshita O, et al. Circulation.1995;91:715-721.**
2) **Fauchier JP, et al. Pacing Clin Electrophysiol. 1996;19:231-244.**
3) **Mehta D, et al. J Am Coll Cardiol. 1996; 28:713-719.**
4) **Kazmierczak J, et al. Heart. 1998; 79:388-393.**
5) Nava A, et al. Eur Heart J. 2000; 21:58-65.

VALUE SAECG IN ARVC/D

- In comparison to 12-lead ECG, SA ECG 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.(1)
- The anatomopathological process of ARVC/D also considers ventricular LPs, which when they are registered as LP in SA ECG, indicate electrical stability worsening associated to rapid progression of SAECG, while clinical parameters remain unchanged. This fact suggests that progression parameters in SA ECG are markers of electrical instability increase.(2)
- Sensitivity, specificity, predictive value and accuracy of the different criteria of high resolution ECG 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.(3) The average of presence of LPs 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;SA ECG is a very useful resource to follow the evolution of the disease;
- In relatives of patients, high resolution ECG presents a positivity of LP between 4-16%;
- Detecting LPs improves by using 25 Hz filters and specificity is better observed in the orthogonal lead Z.
- 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;

1) **Sekiguchi K, et al. Jpn Heart J. 2001;42:287-294.**
2) Bauce B, et al. Pacing Clin Electrophysiol. 2002; 25:362-364.
3) Nasir K, et al. Pacing Clin Electrophysiol. 2003; 26: 1955-1960.
4) Nasir K, et al. Ann Noninvasive Electrocardiol. 2003;8:112-120.

ARVC/D is a cardiomiopathy mainly caused by mutations in genes encoding desmosomal proteins.

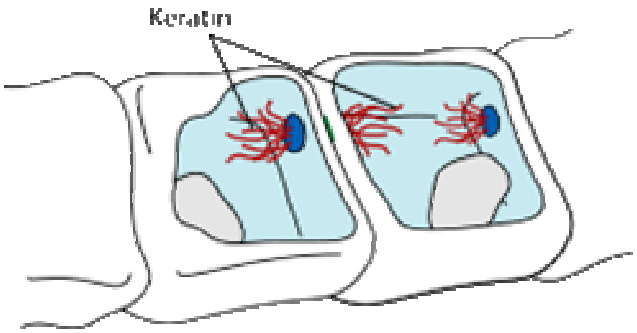


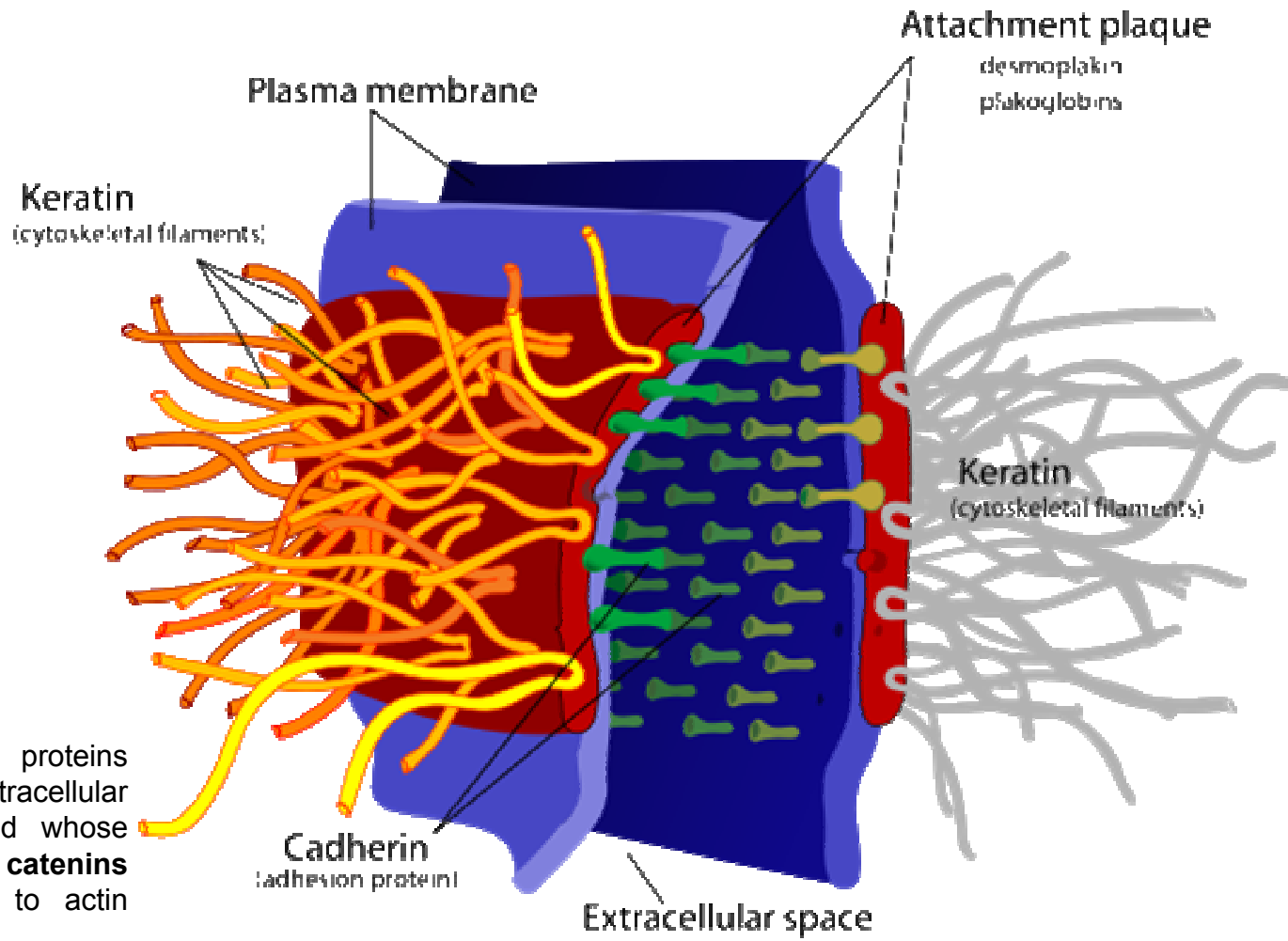
Gap junctions **are intercellular channels some 1.5 - 2 nm in diameter. These permit the free passage between the cells of ions and small molecules (up to a molecular weight of about 1000 daltons). They are constructed from 4 (sometimes 6) copies of one of a family of a transmembrane proteins called connexins**

The cardiac desmosome and proposed roles of the desmosome in (A) supporting structural stability through cell-cell adhesion, (B) regulating transcription of genes involved in adipogenisis and apoptosis, and maintaining proper electrical conductivity through regulation of (C) gap junctions and (D) calcium homeostasis. Abbreviations: Dsc2, desmocollin-2; Dsg2, desmoglein-2; Dsp, desmoplakin; Pkg, plakoglobin; Pkp2, plakophilin-2; PM, plasma membrane. Awad MM, et a(1)

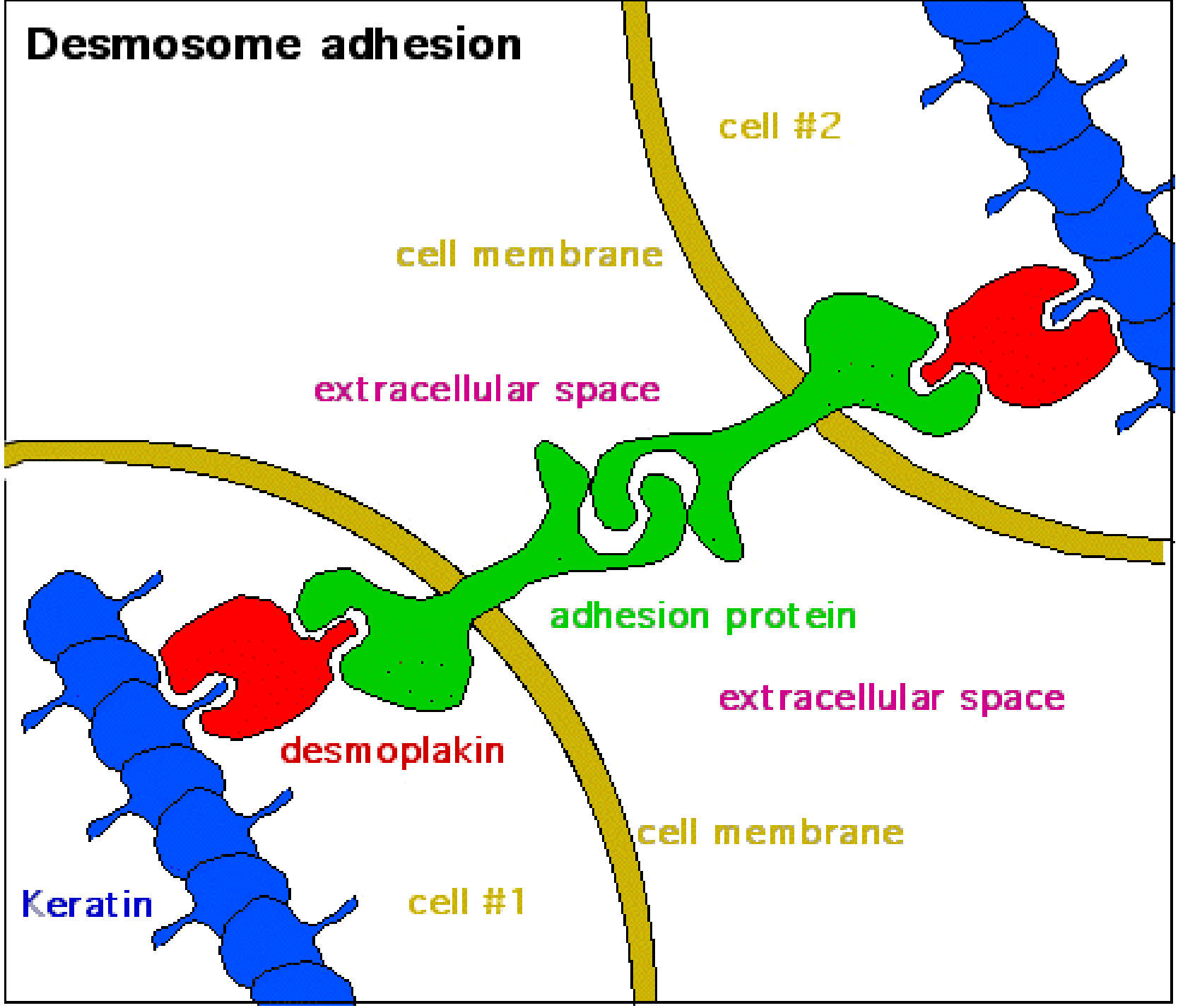
1. **Awad MM, Calkins H, Judge DP. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Nat Clin Pract Cardiovasc Med. 2008 May;5:258-67.**

Components of the cardiac desmosome. Dysfunctional desmosomes resulting in defective cell adhesion proteins, such as plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP-2), and desmoglein-2 (DSG-2) consequently cause loss of electrical coupling between cardiac myocytes, leading to myocyte cell death, fibrofatty replacement and arrhythmias.





Cadherins are transmembrane proteins (shown in green) whose extracellular segments bind to each other and whose intracellular segments bind to **catenins** (yellow). Catenins are connected to actin microfilaments


Desmosome adhesion
cell #2
cell membrane
extracellular space
adhesion protein
extracellular space
desmoplakin
cell membrane
Keratin
cell #1

GAP JUNCTIONS: ANOTHER MECHANISM FOR HETEROGENEITY OF REPOLARIZATION ACROSS VENTRICULAR WALL

By Andrés Ricardo Pérez-Riera

Intercalated discs are the sites of the membrane where cardiomyocytes connect. Adherens or desmosomes, and gap junctions are located in intercalated discs, and ensure the mechanical coupling, thus enabling cardiac electrical impulse to spread.
Arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) is an entity that affects these structures, and consequently the mechanical coupling with electric organic defficiency, and a tendency to fatal arrhythmias occurrence. (1)

In boxer dogs, one of the animal models of ARVC/D, severe mechanical and electrical modifications were observed in cell-to-cell interaction, with a significant reduction in gap junctions density, a factor that promotes the appearance of malignant ventricular arrhythmias. This model may help in the advancement of our understanding of molecular basis, pathophysiology, and potential therapeutic approach in patients carriers of ARVC/D(2).
Gap junctions are electrical points of continuity between cardiac cells and between smooth muscle fibers. These structures are protein channels with low resistance, dodecameric (12 structures), constituted by hexagonal hemichannels, arranged around a central watery pore with a 9 to 11 nm diameter, and located in the sarcolemma of neighbor cells. This pore enables the passage of molecules of up to 1000 daltons, and provides access to the cytoplasm of the two neighbor cells.

1. **Noorman M, van der Heyden MA, van Veen TA, Cox MG, Hauer RN, de Bakker JM, van Rijen HV.Cardiac cell-cell junctions in health and disease: Electrical versus mechanical coupling.** ***J Mol Cell Cardiol. 2009 Jul; 47:23-31.***
2. ***Oxford EM, Everitt M, Coombs W, et al . Molecular composition of the intercalated disc in a spontaneous canine animal model of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Heart Rhythm. 2007 Sep;4:1196-1205.***

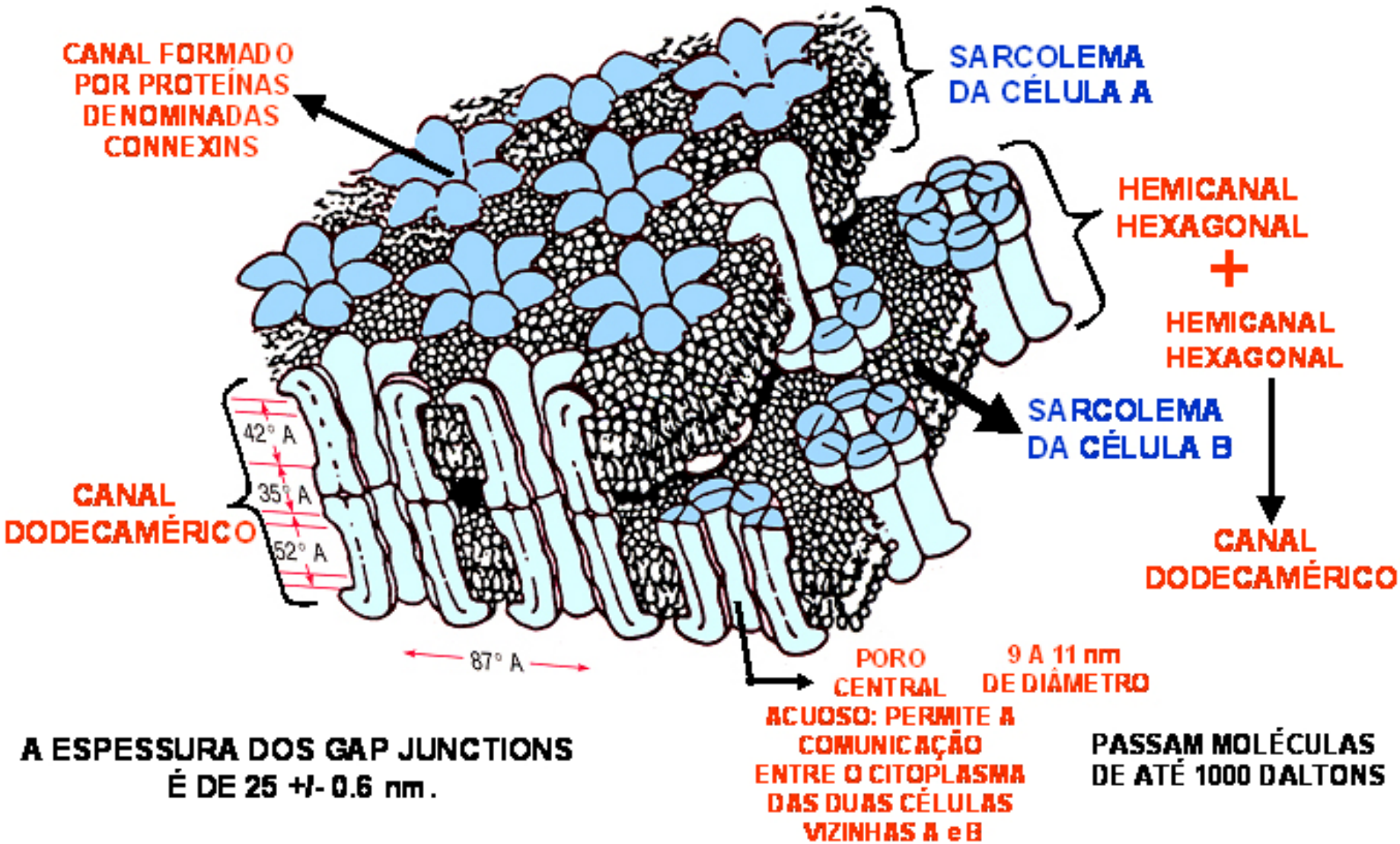
A dodecameric structure of gap junctions, is composed by 2 hexagonal hemichannels that surround a central watery pore, which enables the passage of small molecules. These structures are made up by proteins called connexins(1).

Which are the functions of gap junctions?

1. Enabling the electrical binding between two adjacent cells, thus AP spreads more easily from fiber to fiber;
2. Cardiac gap junction channels are crucial for conducting electrical impulse between cardiomyocytes;
3. Structurally, they may be constituted by connexin 40 (Cx40), connexin 43 (Cx43), and connexin 45 (Cx45). A fourth isoform, Cx37, expresses in the endothelium;
4. Enabling a greater conduction velocity in the site where they are. Because they are located in the longitudinal direction of the fiber, conduction velocity is two to three times greater in the longitudinal direction than in the transversal direction (anisotropic conduction). This longitudinal arrangement of gap junctions explains why dromotropic disorders and blocks occur more frequently in the longitudinal direction;
5. Providing a biochemical coupling by enabling cell-to-cell movement of small molecules such as high-energy phosphates (energetic support, growth control, and embryogenesis), e.g. ATP. These are small molecules that may go through, because gap junctions enable the passage of elements of up to 1000 daltons.
6. Suppression of tumor genes (Cx43, Cx32, and Cx36);
7. Adhesive function, independent from dromotropic properties.

1. **van Veen TA, van Rijen HV, Jongsma HJ Physiology of cardiovascular gap junctions. Adv Cardiol. 2006; 42: 18-40.**

ILLUSTRATION OF A GAP JUNCTION



The proteins that make up the gap junctions are known as connexins. The most abundant connexin is found in the heart, and is connexin 43, and to a lesser degree, connexin 40 (Cx40) and 45 (Cx45) (1).

In the ventricles, there is a large amount of connexin 43 and 45, and a very small amount of connexin 40. SA and AV nodes only have connexins 40 and 45, and in the atria, there is a large amount of three types, however, connexin 40 (Cx40) and the largest gap-junction protein in atrial muscle tissue. Cx40 expressed abnormally increases the vulnerability to occurrence of atrial fibrillation, which is triggered by alteration in the genetic formation of thoracic veins (2).

Connexin 43 is the main decisive factor between the electrical properties of the cardiac muscle (3). Closure of gap junctions at the level of this connexin causes negative dromotropism.

Purkinje cells have a greater concentration of gap junctions in comparison to bundle cells, which explains why the septal fascicle of the His bundle left branch (AF) activates the left middle surface earlier than the anterior fascicle and posterior fascicle (PF). This Purkinje cell has very prominent and abundant gap junctions, with a rapid termino-terminal and side-to-side transmission. The termino-terminal one is mainly constituted by connexin 43.

1. **Teunissen BE, Jansen AT, Mutsaers NA, Vuerhard MJ, Vos MA, Bierhuizen MF.Primary structure, organization, and expression of the rat connexin45 gene. DNA Cell Biol. 2007 Feb;26:108-115.**

2. **Chaldoupi SM, Loh P, Hauer RN, et al. The role of connexin40 in atrial fibrillation.The role of connexin40 in atrial fibrillation. Cardiovasc Res. 2009 Oct 1;84:15-23.**

3. **Xia Y, Gong KZ, Xu M, et al.Regulation of gap-junction protein connexin 43 by beta-adrenergic receptor stimulation in rat cardiomyocytes. Acta Pharmacol Sin. 2009 Jul;30:928-934.**

The entities that hamper gap junction conduction have arrhythmogenic potential. On the contrary, drugs that open these structures could potentially be used as another management strategy for arrhythmias. Peptide ZP123 increases conductance in gap junctions, significantly decreasing their closure during acidosis. This property of decreasing intracellular binding in these conditions, shows the antiarrhythmic potential of the drug in conditions of acidosis.

Gap junctions are properly developed in Purkinje cells and in cells with which bundle fibers bind, and ventricular myocardial cells; they are very prominent and abundant, with fast termino-terminal and side-to-side transmission. The first one is mainly made up by connexin 45.

Note: Purkinje cells usually make up groups of three, yielding an aspect of Y. This arrangement is the anatomical basis for the main mechanism of arrhythmias: anatomical reentry.

These cells are located in the His bundle, Purkinje branches and arborizations, with less density in the baseline region of the ventricles, and tip of papillary muscles. Additionally, they are observed in a low amount in the preferential pathways or interatrial bundles.

Substantial heterogeneity in ion channel density and expression exists in cells isolated from various regions of the heart. Cell-to-cell coupling in the intact heart, however, is expected to attenuate the functional expression of the ion channel heterogeneities. Due to limitations of conventional electrophysiological recording techniques, the extent to which cellular electrical heterogeneities are functionally present in intact myocardium remains unknown. High-resolution optical mapping with voltage-sensitive dyes was used to measure transepicardial and transmural repolarization gradients in the Langendorff perfused guinea pig ventricle and the canine wedge preperation, respectively. Diversity of repolarization kinetics in the transepicardial direction modulated dispersion of repolarization in a biphasic fashion as premature coupling interval was shortened. Moreover, modulation of repolarization paralleled arrhythmia vulnerability in a predictable fashion. Transmural optical mapping revealed significant gradients of repolarization across the ventricular wall that were markedly increased in a surrogate model of LQTS.

Transmural gradients of repolarization in LQTS were associated with an enhanced susceptibility to TdP. Therefore, despite strong cell-to-cell coupling in the normal heart, heterogeneities in the ionic make-up of cells across the epicardial and transmural surfaces result in functional heterogeneities of repolarization leading to arrhythmias.

Electrophysiological (EP) heterogeneities between subepicardial and midmyocardial cells can form a substrate for reentrant ventricular arrhythmias. However, cell-to-cell coupling through gap junctions is expected to attenuate transmural heterogeneities between cell types spanning the ventricular wall. Because connexin43 (Cx43) is the principal ventricular gap junction protein, Gap junctions are critical to maintaining synchronized impulse propagation and repolarization. Heterogeneous expression of the principal ventricular gap junction protein connexin43 (Cx43) is associated with APD dispersion across the anterior ventricular wall. Little is known about Cx43 expression patterns and their disparate impact on regional electrophysiology throughout the heart. Strom et al. aimed to determine whether the anterior and posterior regions of the heart are electrophysiologically distinct. Multisegment, high-resolution optical mapping was performed in canine wedge preparations harvested separately from the anterior left ventricle (aLV; n = 8) and posterior left ventricle (pLV; n = 8). Transmural APD dispersion was significantly greater on the aLV than the pLV. Conduction velocity dispersion was also significantly higher across the aLV than the pLV. Carbenoxolone perfusion significantly enhanced APD and conduction velocity dispersion on the aLV, but not the pLV and produced a 4.2-fold increase in susceptibility to inducible arrhythmias in the aLV. Confocal immunofluorescence microscopy revealed significantly greater transmural dispersion of Cx43 expression on the aLV compared with the pLV wall, suggesting that regional expression of Cx43 expression patterns may account for regional electrophysiological differences.

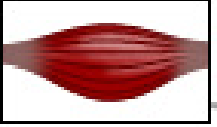
Computer simulations affirmed that localized uncoupling at the epicardial-midmyocardial interface is sufficient to produce APD gradients observed on the aLV. These data demonstrate that the aLV and pLV differ importantly with respect to their electrophysiological properties and Cx43 expression patterns. Furthermore, local underexpression of Cx43 is closely associated with transmural electrophysiological heterogeneity on the aLV. Therefore, regional and transmural heterogeneous Cx43 expression patterns may be important mechanism underlying arrhythmia susceptibility, particularly in disease states where gap junction expression is altered (1).

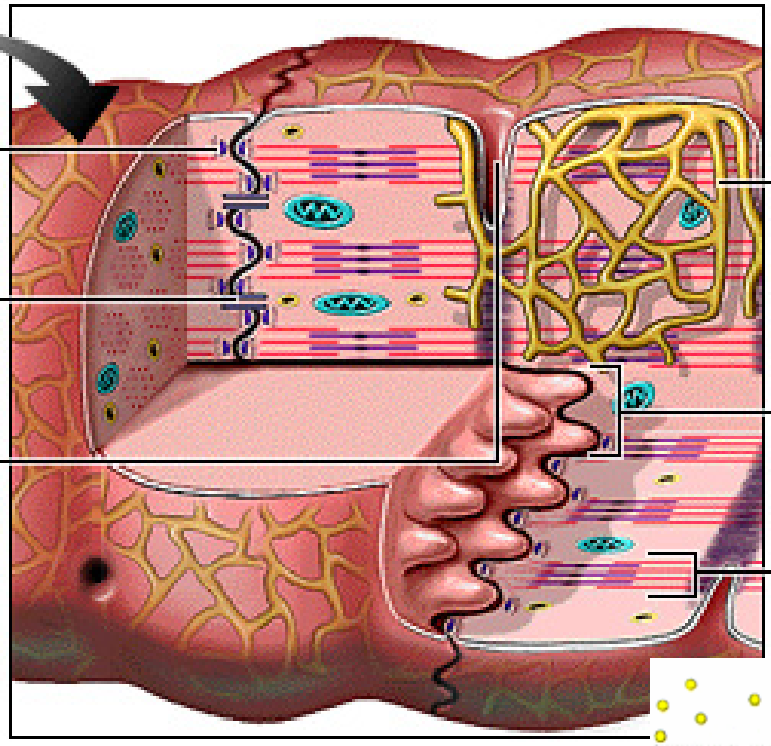
Additionally, in heart failure, midmyocardial Cx43 expression is heterogeneously reduced. This is associated with increased transmural dispersion in refractoriness and conduction, and with increased arrhythmia inducibility(2).

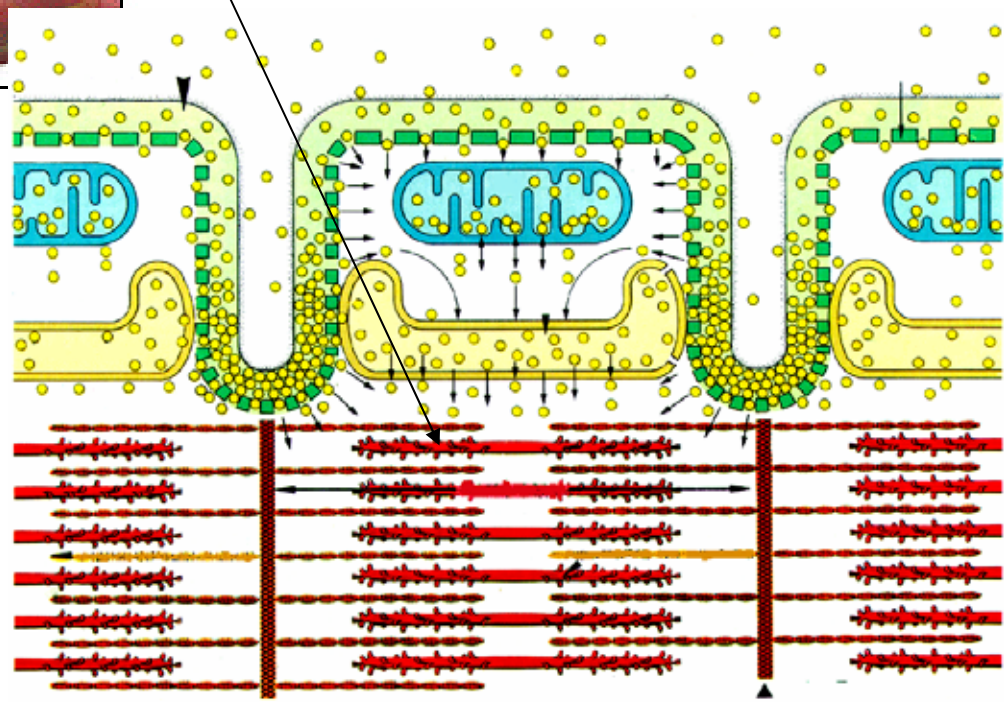
Heterogeneous Cx43 expression is closely associated with functionally significant EP heterogeneities across the transmural wall. Therefore, Cx43 expression patterns can potentially contribute to arrhythmic substrates that are dependent on transmural electrophysiological heterogeneities (3).

1. **Strom M, Wan X, Poelzing S, Ficker E, Rosenbaum DS. Gap junction heterogeneity as mechanism for electrophysiologically distinct properties across the ventricular wall. Am J Physiol Heart Circ Physiol. 2010 Mar;298:H787-94.**
2. **Wiegerinck RF, van Veen TA, Belterman CN, Schumacher CA, Noorman M, de Bakker JM, Coronel R. Transmural dispersion of refractoriness and conduction velocity is associated with heterogeneously reduced connexin43 in a rabbit model of heart failure. Heart Rhythm. 2008 Aug;5:1178-1185.**
3. **Poelzing S, Akar FG, Baron E, Rosenbaum DS. Heterogeneous connexin43 expression produces electrophysiological heterogeneities across ventricular wall. Am J Physiol Heart Circ Physiol. 2004 May; 286:H2001-2009.**

DESMOSOME, GAP JUNCTION AND CARDIAC SARCOMERE CONECTION







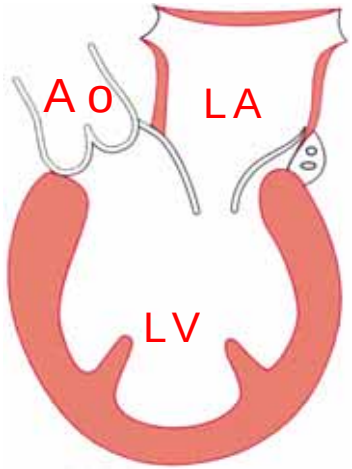
CARDIOMYOPATHIES CLASSIFICATION BASED ON GENOMIC

1. **Dilated (Congestive) Cardiomyopathy (DCM):** Cytoskeletal cardiomyopathy or "cytoesqueletalopathy. This impair force transmission.
2. **Hypertrophic Cardiomyopaty (HCM):** Sarcomeric cardiomyopathy or " sarcomyopathy". These impairing force production.
3. **Restrictive Cardiomyopathy (RCM):** Sarcomeric cardiomyopathy or " sarcomyopathy
4. **Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) and cardiocutaneous syndromes:** desmosomal (desmosomalopathies),
5. **Ion channels cardiomyopathy "cannelopaties":** long QT syndrome, short QT syndromes, Brugada syndrome, Lènegre disease, and catecholaminergic polymorphic ventricular tachycardia. These nonstructural inherited arrhythmic conditions should be regarded as cardiomyopathies because the myocyte is abnormal, although the heart is apparently intact. It is time for a new classification of cardiomyopathies taking into account the underlying gene mutations and the cellular level of expression of encoded proteins,
6. **Unclassifield:** It includes a few cases that do not fit readily into any group (endocardial fibroelastosis, noncompacted myocardium, systolic dysfunction with minimal dilatation, Fiedler´s myocarditis, histiocytoid cardiomyopathy and mitochondrial disease.

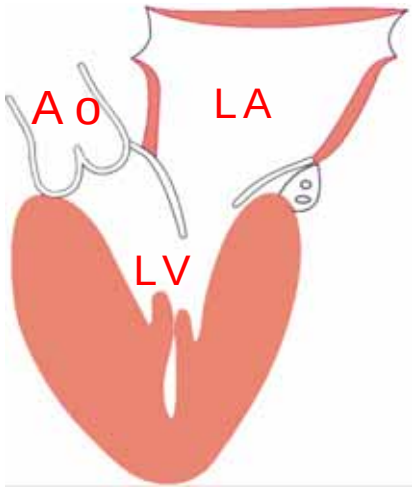
1. ***Thiene G, Corrado D, Basso C. Revisiting definition and classification of cardiomyopathies in the era of molecular medicine. Eur Heart J. 2008 Jan;29:144-146.***
2. ***Corrado D, Basso C, Thiene G. Is it time to include ion channel diseases among cardiomyopathies? J Electrocardiol. 2005 Oct;38(4 Suppl):81-7.***
3. ***Thiene G, Corrado D, Basso C. Cardiomyopathies: is it time for a molecular classification? Eur Heart J. 2004 Oct;25:1772-1775.***

CLASSIFICATION OF CARDIOMYOPATHIES

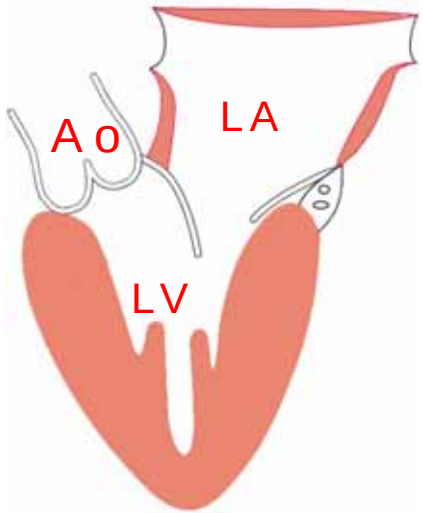
I) DILATED OR CONGESTIVE



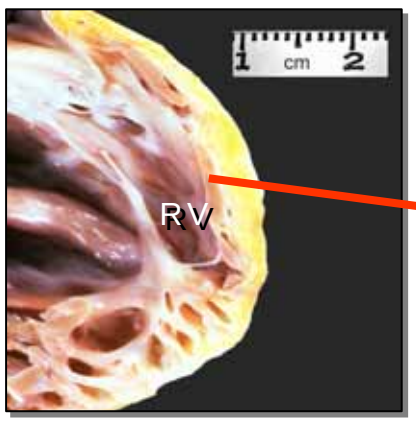
II) HYPERTROPHIC



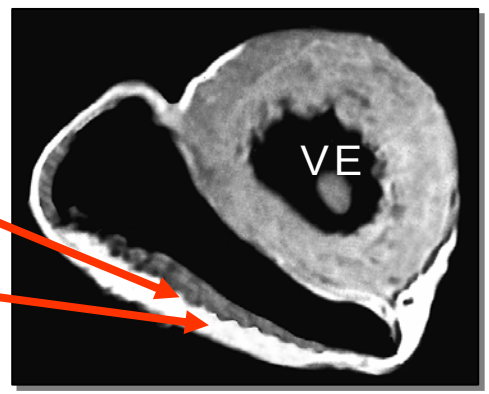
III) RESTRICTIVE



IV) ARRHYTHMOGENIC OR ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

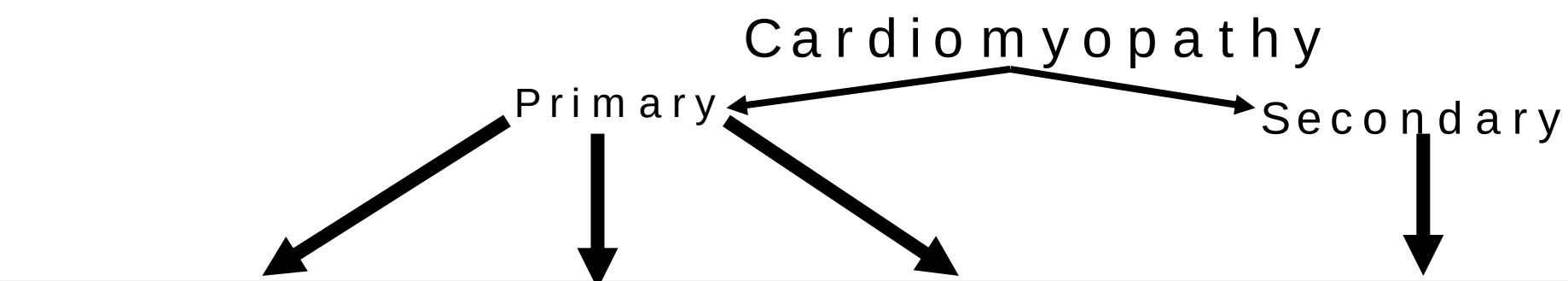


THE CHARACTERISTIC FOUND IS FIBRO-FATTY REPLACEMENT OF RIGHT VENTRICULAR MYOCARDIUM



Richardson P, et al. Circulation. 1996;93:841-842.

The four main types of cardiomyopathy.

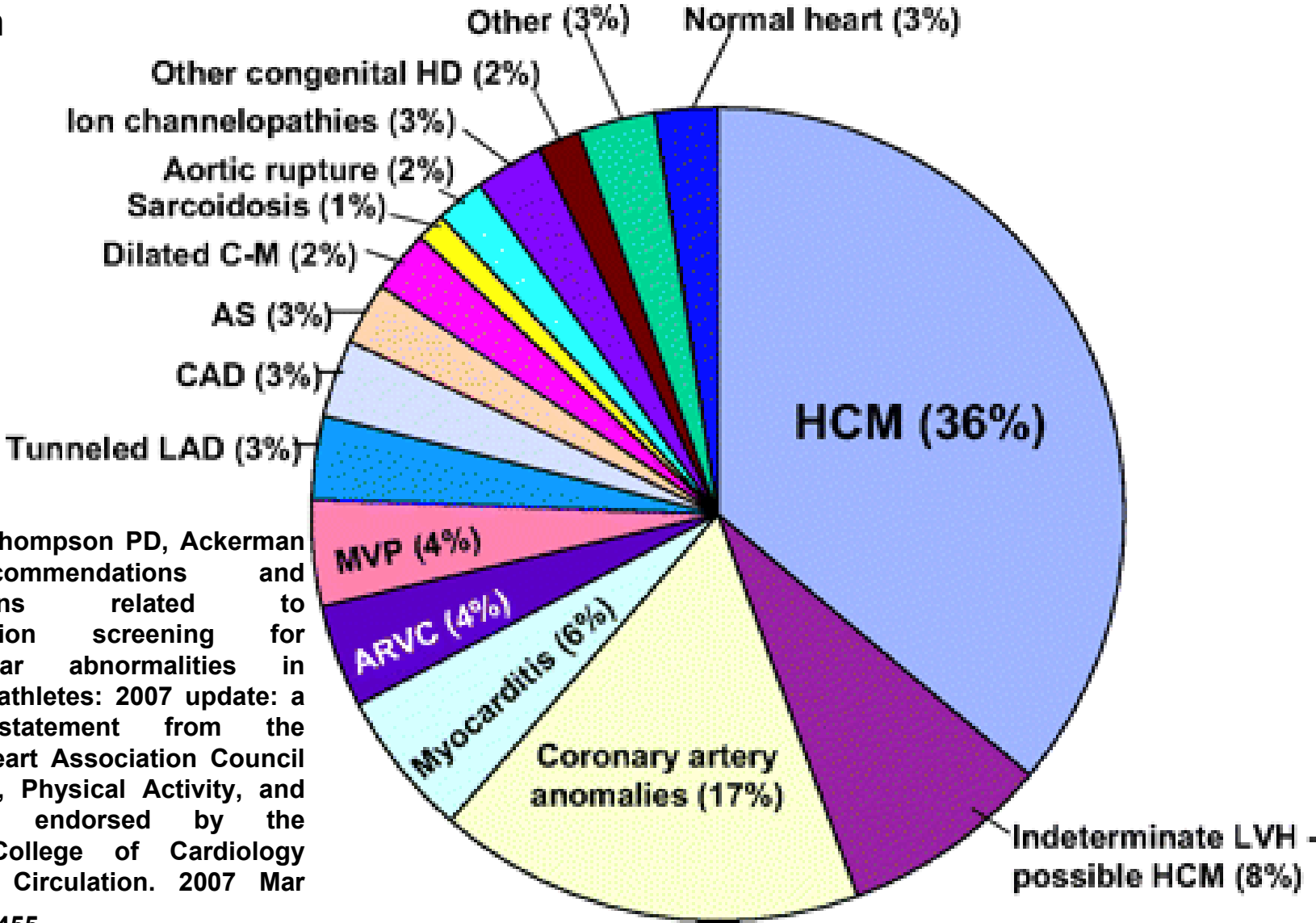


Genetic	Mixed	Acquired	Infiltrative (Amyloid,Gaucher)
HCM	**DCM**	**Inflammatory Myocarditis**	**Storage (Fabry´s, Pompes, Hemochromatosis)**
ARVC/D	**Restrictive**	**Stress induced (tako-tsubo)**	**Toxicity(drugs, heavy meatals, endomyocardial fibrosis, hypereosinophilic**
LVNC		**Peripartum**	**Inflamatory Sarcoidosis**
Glycogen storage		**Tachycardia induced**	**Endocrinel DM, Thyroid dysfunction, Acromegaly**
Conduction defects			**Autoimmune SLE, RA**
Channelopaties			**Neuromuscular disorders(Friederich Ataxia)**

Type	OMIN	GENE/ inheritance pattern	LOCUS
ARVC/D1	107970	*TGFB3* Autosomal dominant	mapped to chromosome 14q23-q24 (*Rampazzo et al., 1994*)
ARVC/D2	600996	*Ryr2* Autosomal dominant	mapped to chromosome 1 long arm (1q42-q43) (*Rampazzo et al., 1995*)
ARVC/D3	602086	??? Autosomal dominant	mapped to chromosome 14 long arm (14q12-q22) (*Severini et al., 1996*)
ARVC/D4	602087	Autosomal dominant	mapped to chromosome 2 long arm (2q32.1-q32.3) (*Rampazzo et al., 1997*)
ARVC/D5	604400	Autosomal dominant	mapped to chromosome 3 short arm (3p23) (*Ahamad et al., 1998*)
ARVC/D6	604401	Autosomal dominant	mapped to chromosome 10 short arm (10p12-p14) (*Li D. et al., 2000*)
ARVC/D7	609160	Autosomal dominant	mapped to chromosome 10 long arm (10q22) (*Melberg ed al., 1999*)
ARVC/D8	607450	Autosomal dominant	mapped to chromosome 6 short arm (6p24) (*Rampazzo ed al., 2002*)
ARVC/D9	609040	*PKP2*	mapped to chromosome 12 12p11
ARVC/D10	610193	*DSG2*	mapped to chromosome 18 18q12.1-q12
ARVC/D11	610476	*DSC2*	mapped to chromosome 18 18q12.1
ARVC/D12	611528	Autosomal recessive *JUP Naxos disease*	mapped to chromosome 17 17q21

THE CAUSES OF ARRHYTHMIC SUDDEN DEATH IN YOUNG ATHLETES (35yo) (AVERAGE AGE: 17 Y0)

The overall burden of sports-related sudden death was 4.6 cases per million population



1. **Maron BJ, Thompson PD, Ackerman MJ, Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2007 Mar 27;115:1643-455.**

Although such data are available for young competitive athletes, the prevalence, characteristics, and outcome of sports-related sudden death have not been assessed previously in the general population. A prospective and comprehensive national survey was performed throughout France from 2005 to 2010, involving subjects 10 to 75 years of age. Case detection for sports-related sudden death, including resuscitated cardiac arrest, was undertaken via national ambulance service reporting and Web-based screening of media releases.

The overall burden of sports-related sudden death was 4.6 cases per million population per year, with 6% of cases occurring in young competitive athletes.

Sensitivity analyses used to address suspected underreporting demonstrated an incidence ranging from 5 to 17 new cases per million population per year.

More than 90% of cases occurred in the context of recreational sports.

The age of subjects was relatively young (mean±SD 46±15 years),

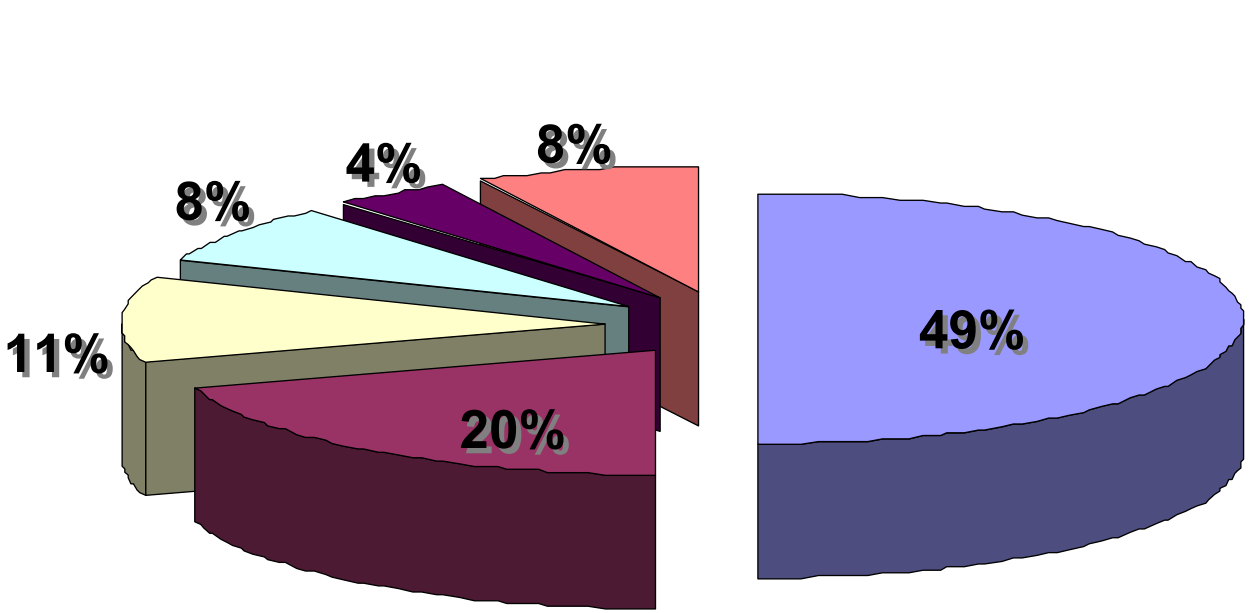
Gender predominance of men (95%).

Although most cases were witnessed (93%), bystander cardiopulmonary resuscitation was only commenced in 30.7% of cases. Bystander cardiopulmonary resuscitation (odds ratio 3.73, 95% confidence interval 2.19 to 6.39, $P<0.0001$) and initial use of cardiac defibrillation (odds ratio 3.71, 95% confidence interval 2.07 to 6.64, $P<0.0001$) were the strongest independent predictors for survival to hospital discharge (15.7%, 95% confidence interval 13.2% to 18.2%).

Sports-related sudden death in the general population is considerably more common than previously suspected. Most cases are witnessed, yet bystander cardiopulmonary resuscitation was only initiated in one third of cases. Given the often predictable setting of sports-related sudden death and that prompt interventions were significantly associated with improved survival, these data have implications for health services planning.

1. **Marijon E, Tafflet M, Celermajer DS, et al. Sports-related sudden death in the general population. Circulation. 2011 Aug 9;124:672-681.**

SUDDEN DEATH CAUSES IN ATHLETES (>35 YEARS OLD)



Chagas disease or aortic stenosis

The annual incidence of SCD) is estimated at 1 per 1,000 for adults over the age of 35 years, and 1 per 100,000 for adolescents and young adults.

1. **Junttila MJ, Castellanos A, Huikuri HV, Myerburg RJ. Risk markers of sudden cardiac death in standard 12-lead electrocardiograms.Ann Med. 2011 Jul 11. [In press]**

THE CAUSES OF ARRHYTHMIC SUDDEN DEATH IN YOUNG ATHLETES(< 35 years) (AVERAGE AGE: 17 YEARS)

1. **Hypertrophic cardiomyopathy (HCM):** **is recognized as by far the most common cause of sudden cardiac death in young athletes in the United States, responsible for at least one-third of cases. In nonathletic populations, the underlying causes of SCD are more varied.**
2. **Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)** **is a predominantly genetically determined and heritable form of cardiomyopathy that is characterized pathologically by the replacement of myocytes by adipose and fibrous tissue and leads to RV failure, arrhythmias, and SCD. The estimated prevalence of ARVC/D in the general population ranges from 1 in 2,000 to 1 in 5,000, men are more frequently affected than women, with an approximate ratio of 3:1. ARVC/D can be inherited as an autosomal dominant disease with reduced penetrance and variable expression, autosomal recessive inheritance is also described. There have been 12 genes identified which are linked to ARVC/D, encoding several components of the cardiac desmosome. Dysfunctional desmosomes resulting in defective cell adhesion proteins, such as plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP-2), and desmoglein-2 (DSG-2) consequently cause loss of electrical coupling between cardiac myocytes, leading to myocyte cell death, fibrofatty replacement and arrhythmias. Diagnosis is based on the finding a combination of characteristic abnormalities in family history, ECG, ECGAR, Holter monitoring, cardiac imaging as well as endomyocardial biopsy (original task force criteria). Therapeutic options remain limited because of the progressive nature of ARVC/D. Competitive athletics should be avoided. Patients with ARVC/D with a history of having been resuscitated from SCD, patients with syncope, very young patients, and those who have marked RV involvement are at the highest risk for arrhythmic death and also, the presence of LV involvement is a risk factor. Patients who meet the Task Force criteria for ARVC/D are at high risk for SCD and should undergo ICD placement for primary and secondary prevention, regardless of electrophysiologic testing results. The role of electrophysiologic study and VT catheter ablation in ARVC/D remains poorly defined, and is frequently used as a palliative measure for patients with refractory VT. The progressive nature of ARVC/D suggests that catheter ablation would not be a long-term curative procedure. Sotalol proved to be highly effective in patients with ARVC/D and inducible as well as non-inducible VT; if it is ineffective in inducible VT response to other antiarrhythmic drugs is unlikely and therefore non-pharmacological therapy without further drug testing should be considered. Orthotopic heart transplantation is considered in patients with sever progressive heart failure and intractable recurrent ventricular arrhythmias.**

3. **Congenital coronary artery anomalies:** secondary to anatomic coronary artery anomalies (particularly the left main coronary originating from the right sinus of valsalva or anomalous RCA arising from the left sinus (ARCA) is a known cause of SCD, particularly in young athletes.
4. **Commotio cordis**
5. **Idiopathic left ventricular hypertrophy**
6. **Myocarditis**
7. **Marfan Syndrome**
8. **Aortic stenosis**
9. **Dilated cardiomyopathy**
10. **Mitral valve abnormalities/Mitral valve prolapse**
11. **Ion Channelopathies or primary electrical diseases**
12. **Cardiac sarcoidosis**
13. **Pre-excitation syndromes**
14. **Other congenital heart diseases**
15. **Cocaine abusers and others Illicit drugs** **Forensic pathologists have shown that over three per cent of all SDs in south-west Spain are related to the use of cocaine. They believe their findings can be extrapolated to much of the rest of Europe, indicating that cocaine use is a growing public health problem in Europe and that there is no such thing as "safe" recreational use of small amounts of the drug(1).** ECG abnormalities are common among asymptomatic, chronic cocaine abusers, with a higher prevalence in blacks. During acute cocaine abuse, abnormalities are more prevalent and QT is prolonged. ST-T changes are frequent(2)

1. **Lange RA, Hillis LD. Sudden death in cocaine abusers. Eur Heart J. 2010 Feb;31:271-273.**
2. **Chakko S, Sepulveda S, Kessler KM, et al. Frequency and type of electrocardiographic abnormalities in cocaine abusers (electrocardiogram in cocaine abuse). Am J Cardiol. 1994 Oct 1;74:710-7133.**

American Heart Association recommended screening elements Pre-participation Athletes candidates

I) INTERROGATORY

Personal history

1. Heart murmur
2. High blood pressure
3. Chest pain or discomfort with exertion
4. Syncope/near-syncope
5. Exercise intolerance
6. In older athletes (>35 y0), a history of coronary risk factors, including a family history of ischemic heart disease, is useful in identifying at-risk individuals.

Family history

1. History of cardiomyopathy, long QT syndrome,SQTS, BrS, CPVT, Marfan syndrome or abnormal heart rhythms
2. Sudden or unexplained cardiac death before age 50
3. History of disability from heart disease before age 50

II) PHYSICAL EXAMINATION

1. Physical stigmata of Marfan syndrome
2. Cardiac auscultation supine and standing Auscultation performed in the standing position (or with Valsalva maneuver) mayunmask a loud murmur due to dynamic left ventricular outflow obstruction
3. Brachial artery blood pressure (sitting position)
4. Femoral pulses to exclude aortic coarctation

III) The 12-lead ELECTROCARDIOGRAM

European investigators have promoted the 12-lead ECG as a practical and cost-efficient strategy for population-based screening. ECGs are abnormal in >90% of patients with HCM and ARVC/D) and can detect ion channelopathies such as LQTS and BrS. However, the resting ECG is usually normal in CPVT, and exercise testing is required for diagnosis. The ECG has relatively low specificity as a screening test in athletic populations largely because of the high frequency of ECG alterations associated with the normal physiological adaptations of the trained athlete's heart.

In the United States, screening results have been reported only in relatively small studies of high school and college athletes (250 to 2000 subjects) with diverse study designs, including one using the ECG as a primary screening test. In general, these efforts yielded few important cardiovascular abnormalities, likely because of the small cohort sizes. In screening older trained athletes, routine application of exercise testing for the detection of coronary artery disease would have the limitation of low specificity and pretest probability.

1. ***Maron BJ, McKenna WJ, Danielson GK, et al . American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines, Committee to Develop an Expert Consensus Document on Hypertrophic Cardiomyopathy. J Am Coll Cardiol.2003;43:1687-1713,***

Revised Task Force Criteria 2010(1)

I.Global or regional dysfunction and structural alterations*

Mayor

By 2D echo:

• Regional RV akinesia, dyskinesia, or aneurysm• *and* 1 of the following (end diastole):

— PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2)

— PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2)

— *or* fractional area change ≤33%

By MRI:

• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction• *and* 1 of the following:

— Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female)

— *or* RV ejection fraction ≤40%

By RV angiography:

• Regional RV akinesia, dyskinesia, or aneurysm

Minor

By 2D echo:

• Regional RV akinesia or dyskinesia

• *and* 1 of the following (end diastole):

— PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2)

— PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2)— *or* fractional area change >33% to ≤40%

By MRI:

• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction• *and* 1 of the following:

— Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female)

— *or* RV ejection fraction >40% to ≤45%

II. Tissue characterization of wall

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

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

III. Repolarization abnormalities

• Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 ms)

• Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6

• Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

IV. Depolarization/conduction abnormalities

Major

• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)

Minor

• 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

1. **Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria.Circulation. 2010 Apr 6;121:1533-1541.**

V. Arrhythmias

Major

• Nonsustained or sustained VT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)

Minor

• Nonsustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis

• >500 ventricular PVCs per 24 hours (Holter)

VI. Family history

Major

• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria

• ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative• Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation

Minor

• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria

• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

VALUE OF MAGNETIC RESSONANCE IMAGE (MRI) IN ARVC/D

MRI Right Ventricular Aneurism ⇒ YES ⇒ ARVC/D

⇓

NO

MRI fatty replacement in RV free wall ⇒ YES ⇒ ARVC/D (I-II)

⇓

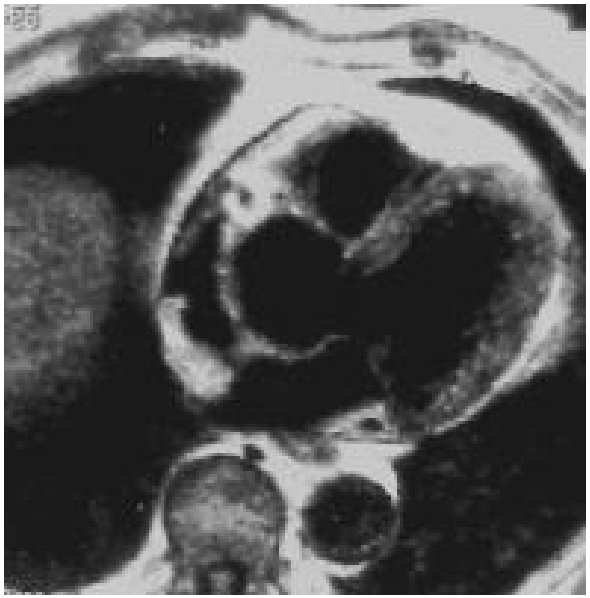
NO

MRI prominent trabecular in the right ventricle ⇒ YES ⇒ ARVC/D

⇓

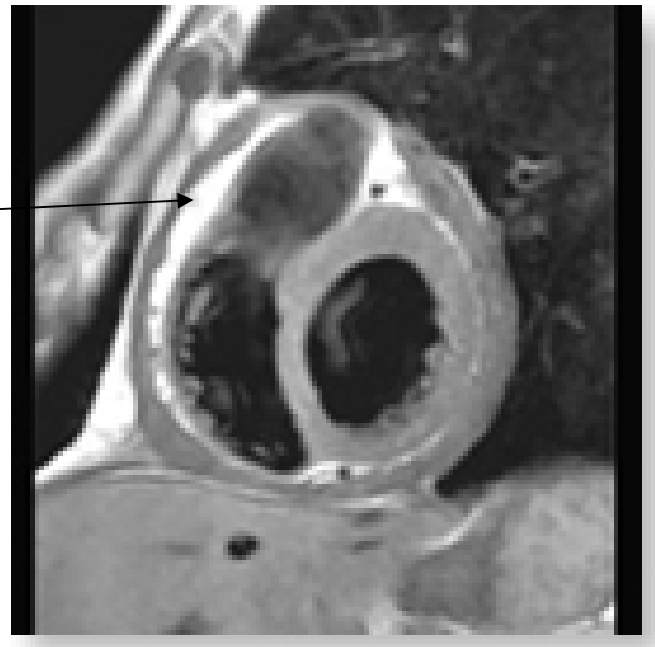
NO

I



Prominent epicardial fat in the RVOT.

II

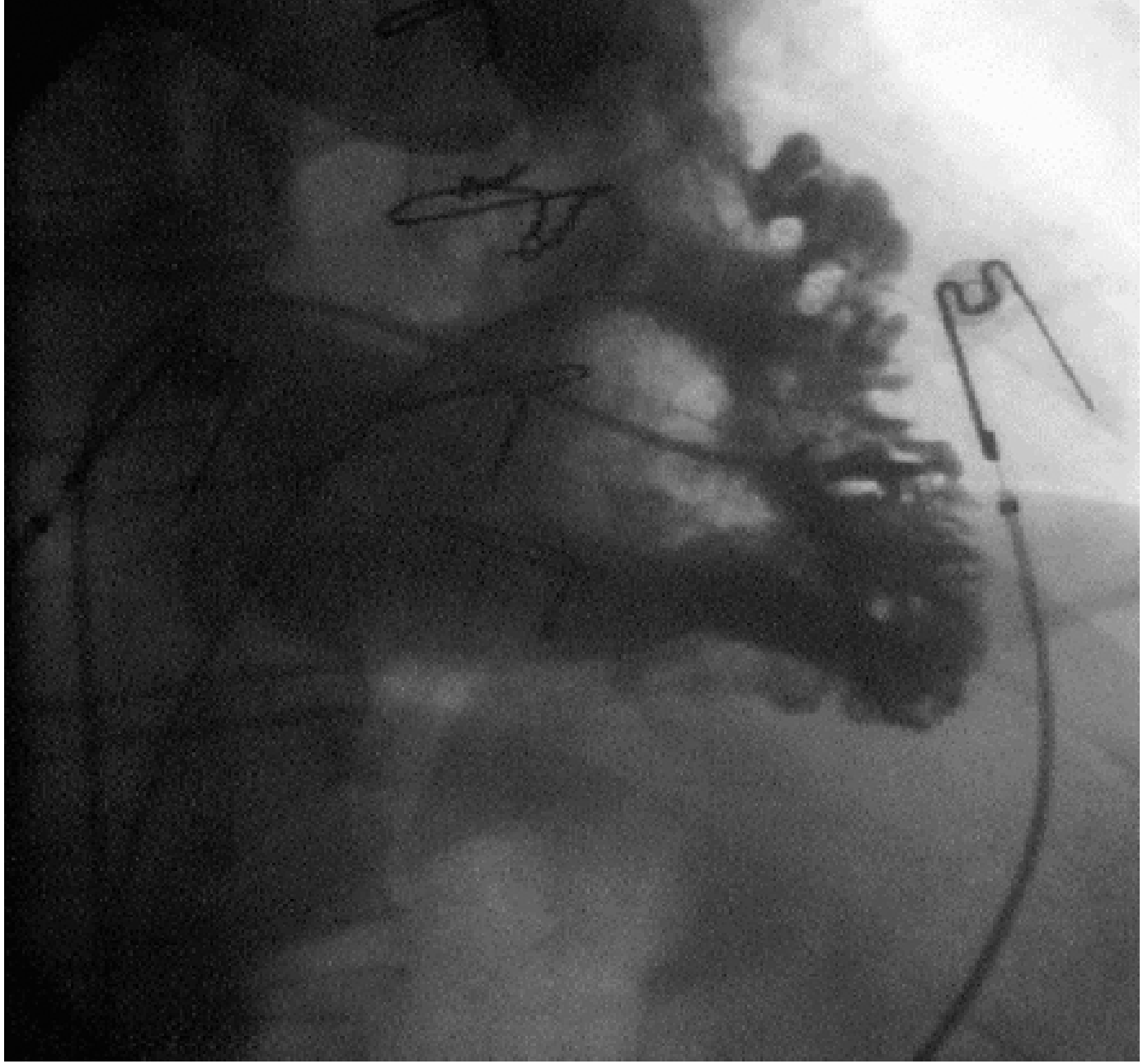


SORT: KEY RECOMMENDATIONS FOR PRACTICE IN ARVC/D

Clinical recommendation	*Evidence rating*	*References*
Although the best imaging technique is debatable, magnetic resonance imaging of the heart can provide noninvasive localization of structural changes and regional dysfunction.	C	**1;2**
Electrophysiologic studies can be used to distinguish between idiopathic right ventricular arrhythmias and ARVD.	C	**3, 4, 5**
For chronic management of ARVD, treatment with sotalol (Betapace), beta blockers, propafenone (Rythmol), and amiodarone (Cordarone), alone or in combination, can be used with variable success.	B	**6; 7**
Placement of an automatic implantable cardioverter-defibrillator should be considered strongly in patients with drug-refractory arrhythmias.	B	**8;9**

A = ***consistent, good-quality patient-oriented evidence;***
B = ***inconsistent or limited-quality patient-oriented evidence;***
C = ***consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1313 or http://www.aafp.org/afpsort.xml.***

1. Blake LM, et al. MR features of arrhythmogenic right ventricular dysplasia. *AJR Am J Roentgenol*. 1994;162:809–812.
2. Auffermann W, et al. Arrhythmogenic right ventricular disease: MR imaging vs angiography. *AJR Am J Roentgenol*. 1993;161:549–555.
3. O'Donnell D, et al.Clinical and electrophysiological differences between patients with arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia. *Eur Heart J*. 2003;24:801–810.
4. Iesaka Y, et al. Usefulness of electrophysiologic study and endomyocardial biopsy in differentiating arrhythmogenic right ventricular dysplasia from idiopathic right ventricular tachycardia. *Heart Vessels*. 1990;5(suppl):65–9.
5. Niroomand F, et al. Electrophysiological characteristics and outcome in patients with idiopathic right ventricular arrhythmia compared with arrhythmogenic right ventricular dysplasia. *Heart*. 2002;87:41–47.
6. Wichter T, et al. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. *Circulation*. 1992;86:29–37.
7. Fontaine G, et al.Arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Anesthesiology*. 2001;95:250–4.
8. Kayser HW, et al. Diagnosis of arrhythmogenic right ventricular dysplasia: a review. *Radiographics*. 2002;22:639–50.
9. Gregoratos G,, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2002;40:1703–19.



Angiogram of the RV in a patient with ARVC/D shows heavy trabeculation and aneurysmal bulges of the RVOT.

TREATMENT

(1) – Pharmacological Approach
- (1.1) – Empirical Drug Therapy
- (1.2) – Anticoagulant Therapy
- (1.3) – Treatment of CHF

(2) – Radiofrequency Catheter Ablation (RFCA)

(3) – Implantable Cardioverter-Defibrillator (ICD) or Automatic Implantable Cardioverter/Defibrillator (AICD)

(4) – ICDs in combination with Drugs and/or RFCA.

(5) – Cardiac Transplant Orthotopic Heart Transplantation (OHT)

(6) – Anterior Dynamic Cardiomyoplasty.

(7) – Cellular Cardiomyoplasty (Cell Transplantation for Cardiac Repair).

GUIDELINES FOR PATIENTS AND RELATIVES ON THE MEDICAL ASPECTS OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC/D)

By the Medical Advisory-Committee of The Cardiomyopathy Association

1.All patients diagnosed as having ARVC/D should ask their general practitioner and cardiologist about the complications of the disease, the purposes and methods of treatment and the benefits, disadvantages and risks of the proposed medication or suggested operations

.2. Although ARVC/D is not strictly curable, much can now be done by attention to appropriate lifestyle and administration of suitable drugs treatments. Ongoing research is opening up promising new possibilities.

3.It is important that relatives of patients should be examined by expert cardiologists to detect the disease if present.

4.Situations to avoid.

Strenuous exercise: always seek the advice of your consultant and general practitioner on how much exercise you should take

Acute severe loss of blood or body fluid: haemorrhage. diarrhoea, vomiting
Prolonged standing in hot conditions that might predispose to fainting which can be dangerous
Very hot baths/showers
During anaesthesia: including an epidural, special attention is required to avoid a sudden drop in blood pressure.
Pregnancy and childbirth
There is no special information on this. People with heart disease are more prone to problems during pregnancy and childbirth.

The most important goal of management of ARVC/D is to decrease the incidence of SCD. This raises a clinical dilemma: How to prophylactically treat the asymptomatic patient who was diagnosed during family screening.
Certain subgroups of individuals with ARVC/D are considered at high risk for SCD. Characteristics associated with high risk of SCD include:
Young age;
Competitive sports activity;
Malignant familial history;
Extensive RV disease with decreased RVEF;
LV involvement;
Syncope;
Episode of VT.
Management options include pharmacologic approach, (empirical drug therapy, anticoagulant therapy and inprove RV or or biventricular systolic dysfunction.), Radiofrequency Catheter Ablation (RFCA), Implantable Cardioverter-Defibrillator (ICD), ICDs in combination with drugs and/or RFCA and exceptionally surgery.
Prior to the decision of the treatment option, PES in the electrophysiology laboratory may be performed for additional prognostic information.

Goals of PES include:

Assessment of the disease's arrhythmogenic potential;

Evaluate the hemodynamic consequences of S-VT;

Determine whether the VT can be interrupted via antitachycardia pacing.

Regardless of the management option chosen, the individual is typically suggested to undergo lifestyle modification, including avoidance of strenuous exercise, cardiac stimulants (ie: caffeine, nicotine, pseudoephedrine) and alcohol. If the individual wishes to begin an exercise regimen, an exercise stress test may have added benefit.

Pharmacologic Approach

Pharmacologic management of ARVC/D involves arrhythmia suppression, prevention of thrombus formation and improve RV or or biventricular systolic dysfunction.

(1.1) – Empirical Drug Therapy

Sotalol, beta-blockers, carvedilol (alpha and beta blocker) and amiodarone are used.

Beta-blockers are the drugs of choice in the cases where the arrhythmias are clearly induced for the efforts. In patients with ARVC/D, regional abnormalities of sympathetic innervation are frequent and can be demonstrated by 123I-MIBG scintigraphy. Sympathetic denervation appears to be the underlying mechanism of reduced 123I-MIBG uptake and may be related to frequent provocation of ventricular arrhythmias by exercise or catecholamine exposure in ARVC/D. Therefore, in patients with ARVC/D, the noninvasive detection of localized sympathetic denervation by 123I-MIBG imaging may have implications for the early diagnosis and for the choice of antiarrhythmic drugs in the treatment of arrhythmias. (1)

1. **Wichter T, Hindricks G, Lerch H, et al. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy. An analysis using 123I-meta-iodobenzylguanidine scintigraphy. Circulation. 1994; 89:667-683.**

Sotalol, a beta-blockers and a class III antiarrhythmic agent, is the most effective antiarrhythmic agent in ARVC/D**.(1)** Treatment with sotalol cause eventually severe, symptomatic sinus bradycardia in ARVC/D patients requiring permanent pacing.(2).Additonally, coronary vasospasm may be induced by the non-selective beta-blocking properties of sotalol.(3)

Carvedilol is not only useful for controlling arrhythmia but also for improving LV function in some patients with ARVC/D. Sympathetic overactivity is reported to cause SCD, so carvedilol may be a first-line drug for some patients with ARVC/D. (4)

Other antiarrhythmic agents used include amiodarone and conventional beta blockers (ie: metoprolol). If antiarrhythmic agents are used, their efficacy should be guided by series ambulatory Holter Monitoring, to show a reduction in arrhythmic events. Amiodarone and beta-blockers can both be effective, in addition there appears to be a synergistic affect when they are used together.

1. **Wichter T, Borgreffe M, Haverkamp W, *et al*. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. *Circulation* 1992; 86:29-37**.
2. **Kazmierczak J, Kornacewicz-Jach Z, Wojtarowicz A. Atrial epicardial pacing with long stimulus to P wave interval in a patient with arrhythmogenic right ventricular dysplasia complicated by right atrial thrombosis.Pacing Clin Electrophysiol. 1999;22:1111-1113**.
3. **Muto S, Ashizawa N, Arakawa S, et al. Sotalol-induced coronary spasm in a patient with dilated cardiomyopathy associated with sustained ventricular tachycardia. Intern Med. 2004;43:1051-1055.**
4. **Hiroi Y, Fujiu K, Komatsu S, et al. Carvedilol therapy improved left ventricular function in a patient with arrhythmogenic right ventricular cardiomyopathy. Jpn Heart J. 2004; 45:169-177.**

(1.2) – Anticoagulant Therapy

Individuals will decreased RVEF with dyskinetic portions of the RV may benefit from long-term anticoagulation with warfarin to prevent thrombus formation and subsequent pulmonary embolism. Its drugs prevent risk of thromboembolic complications **(1)**

(1.3) – Treatment of CHF

While angiotensin converting enzyme inhibitors (ACE Inhibitors) are well known for slowing progression in other cardiomyopathies, they have not been proven to be helpful in ARVC/D, In those patients who evolve for severe RV or biventricular CHF we must include ACE Inhibitors, espironolactone, furosemide, carvedilol and sometime digital.

1. **Corrado D, Basso C, Nava A, et al. Arrhythmogenic right ventricular cardiomyopathy: current diagnostic and management strategies.Cardiol Rev. 2001;9:259-265.**

(2) – Radiofrequency Catheter Ablation (RFCA)

RFCA is an invasive and non-surgical technique that disrupts (destroys) parts of the abnormal electrical pathway that is causing arrhythmia (abnormal heart rhythm). During RFCA, is insert a special electrode catheter (long, flexible wire) into the heart. They position the catheter so that it lies close to the abnormal electrical pathway, and then pass heat energy through it. The tip of the catheter heats up and destroys the small area of heart tissue that contains the abnormal pathway. RFCA is an invasive procedure developed in 1990 that, unlike treatment using medication, offers the opportunity to cure many types of cardiac arrhythmias.

RFCA may be used to treat intractable ventricular tachycardia. It has a 60-90% success rate. Unfortunately, due to the progressive nature of the disease, recurrence is common (60% recurrence rate), with the creation of new arrhythmogenic foci. Indications for RFCA include drug-refractory VT and frequent recurrence of VT after ICD placement, causing frequent discharges of the ICD. In patients with VT due to structural heart disease, RFCA is used as adjunctive therapy to the ICD, eg, in patients with frequent ICD discharges. Approximately 50% the cases of VTs associated with structural heart disease can be palliated by RFCA. Extensive scarring in these ventricles may limit the efficacy of the relatively small lesions made by RFCA, and multiple VT circuits may also contribute to this moderate success rate. In practice, many of these patients have ICDs, and RFCA is used as adjunctive therapy for frequent device activations.

The electroanatomic mapping system Carto ((R)) with its combination of anatomic and electrophysiologic information has substantially improved our understanding of arrhythmia mechanisms and substrates in patients with VT and structural heart disease. In about 75-90% of the patients, the target VT can be ablated with acute success and the patients remain free of any VT recurrence in up to 75%. First results of electroanatomically guided ablation in patients with ARVC/D are promising.(1)

1.Wetzel U, Hindricks G, Dorszewski A, et al. Electroanatomic mapping of the endocardium. Implication for catheter ablation of ventricular tachycardia. Herz. 2003; 28:583-590.

RFCA was complete or partial success in 71% patients with ARVC/D and VT recurred in 48%.
In the IMVT-RVOT patients, RFCA was a complete success in 97% with recurrent VT in 6%.
Long-term success in the RVOT patients was 95% in both patients with and without MRI abnormalities. (1)
VT in ARVC/D shows many of the characteristics of VT due to myocardial infarction. Entrainment mapping techniques can be used to characterize reentry circuits in ARVC/D. The use of entrainment mapping to guide ablation is feasible. (2)
The reentrant circuit sites were clustered predominantly around the tricuspid annulus and in the RVOT. Sites classified as exits, central/proximal, inner loop, outer loop, remote bystander and adjacent bystander were identified by entrainment criteria.
In patients with ARVC/D and VT:
Perivalvular electrogram abnormalities represent the commonly identified substrate and source of most VT;
LV perivalvular endocardial electrogram abnormalities and VT can occasionally be identified;
Aggressive ablative therapy provides long-term VT control.(3)

1. **O'Donnell D, Cox D, Bourke J, Mitchell L et al. Clinical and electrophysiological differences between patients with arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia. Eur Heart J. 2003; 24:801-810.**
2. **Ellison KE, Friedman PL, Ganz LI, et al. Entrainment mapping and radiofrequency catheter ablation of ventricular tachycardia in right ventricular dysplasia. J Am Coll Cardiol. 1998; 32:724-728.**
3. **Marchlinski FE, Zado E, Dixit S, et al.Electroanatomic substrate and outcome of catheter ablative therapy for ventricular tachycardia in setting of right ventricular cardiomyopathy.Circulation. 2004; 110:2293-2298.**

Multiple morphologies, hemodynamic instability, or noninducibility may limit VT ablation in patients with ARVC/D. Sinus rhythm CARTO mapping was performed by Verma et al. to define areas of "scar" (<0.5 mV) and "abnormal" myocardium (0.5 to 1.5 mV). RFCA was performed in "abnormal" regions, targeting sites with good pace maps compared with the induced VT(s). Linear lesions were created in these areas to connect the scar/abnormal region to a valve continuity or other scar or (2) encircle the scar/abnormal region.

Eighteen patients had ICDs, 15 had ICD therapies, and 7 had S-VT (6 with syncope). VTs (3+/-2 per patient) were induced (cycle length, 339+/-94 ms), and scar was identified in all patients. Scar areas were related to the tricuspid annulus, proximal RVOT, and anterior/inferior-apical walls. Lesions connected abnormal regions to the annulus (n=12) or other scars (n=4) and/or encircled abnormal regions (n=13). Per patient, a mean of 38+/-22 radiofrequency lesions was applied. Short-term success was achieved in 18 patients (82%). VT recurred in 23%, 27%, and 47% of patients after 1, 2, and 3 years' follow-up, respectively. Substrate-based ablation of VT in ARVC/D can achieve a good short-term success rate. However, recurrences become increasingly common during long-term follow-up. (1)

1. **Verma A, Kilicaslan F, Schweikert RA, et al.Short- and long-term success of substrate-based mapping and ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia. Circulation. 2005;111:3209-3216.**

(3) – Implantable Cardioverter-Defibrillator (ICD) or Automatic Implantable Cardioverter/Defibrillator (AICD)

ICD therapy appears to significantly reduce mortality in selected patients with nonischemic cardiomyopathy (NICM) **(1)**Indications for ICD placement in the setting of ARVC/D include:Cardiac arrest due to VT or VF, symptomatic VT that is not inducible during PES, failed PES-guided drug therapy; severe RV involvement with poor tolerance of VT, SCD of first-degree family member.
In patients with a prior history of S-VT/VF or cardiac arrest ICD is superior to amiodarone for secondary prophylaxis of SCD.. In a subset of Canadian Implantable Defibrillator Study (CIDS), the benefit of the ICD over amiodarone increases with time; most amiodarone-treated patients eventually develop side effects, have arrhythmia recurrences, or die. After a mean follow-up of 5.6+/-2.6 years, there were 28 deaths (47%) in the amiodarone group, compared with 16 deaths (27%) in the ICD group (P=0.0213). Total mortality was 5.5% per year in the amiodarone group versus 2.8% per year in the ICD group. In the amiodarone group, 49 patients (82% of all patients) had side effects related to amiodarone, of which 30 patients (50% of all patients) required discontinuation or dose reduction; 19 patients crossed over to ICD because of amiodarone failure (n=7) or side effects (n=12) (2)

1. **Desai AS, Fang JC, Maisel WH, et al. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA. 2004; 292:2874-2979.**
2. **Bokhari F, Newman D, Greene M, et al. Long-Term Comparison of the Implantable Cardioverter Defibrillator Versus Amiodarone. Eleven-Year Follow-Up of a Subset of Patients in the Canadian Implantable Defibrillator Study (CIDS). Circulation. 2004; 110: 112-116**.

Since ICDs are typically placed via a transvenous approach into the RV, there are complications associated with ICD placement and follow-up.
Patients with ARVD/C have a high arrhythmia rate requiring appropriate ICD interventions. The ICD therapy appears to be well tolerated and important in the management of patients with ARVD/C.(1)
Sixty patients from a single-center of long-term follow-up of 80+/-43 months (396 patient-years) multivariate analysis identified extensive RV dysfunction as an independent predictor of appropriate ICD discharge. The results of it study strongly suggest an improvement in long-term prognosis by ICD therapy in high-risk patients with ARVC/D.
However, meticulous placement and long-term observation of transvenous lead performance with focus on sensing function are required for the prevention and/or early recognition of disease progression and lead-related morbidity during long-term follow-up of ICD therapy in ARVC/D.(2)

1. **Roguin A, Bomma CS, Nasir K, et al. Implantable Cardioverter-Defibrillators in patients with arrhythmogenic right ventricular Dysplasia/Cardiomyopathy.J Am Coll Cardiol. 2004; 43:1843-1852.**
2. **Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. Circulation. 2004;109:1503-1508.**

Complications associated with ICD implantation

Due to the extreme thinning of the RV free wall, it is possible to perforation the RV during implantation, potentially causing pericardial tamponade;
Perforation of RV after RV defibrillation shock;
Because of this, every attempt is made at placing the defibrillator lead on the ventricular septum;
Need for lead repositioning;
After a successful implantation, the progressive nature of the disease may lead to fibro-fatty replacement of the myocardium at the site of lead placement. This may lead to undersensing of the individual's electrical activity (potentially causing inability to sense VT or VF), and inability to pace the ventricle;
System infection;
Lead fracture and insulation damage;
Change in thresholds secondary to production of mor fibrosis or association with myocarditis that incrases the threshold.
Deterioration of both RV and LV by superimposed extensive myocarditis with repetitives episodes of VF.
Inappropriate therapy: The most common etiology of inappropriate therapy is AF with rapid ventricular response (68%), atrial flutter (13%) and sinus tachycardia (11%). **(1)**

1. **Krivan L, Kozak M, Sepsi M, Svobodnik A, Spinar J.Specific complications in the treatment with implantable cardioverter-defibrillatorsCas Lek Cesk. 2004; 143:521-525.**

Arrhythmic storm: Patients with arrhythmic storm in history had significantly lower survival. The risk factors of cardiac nonsudden death are: age >66 years, LVEF <35% and arrhythmic storm history
Device related proarrhythmia;
Psychiatric complication: Anxiety and depression are common and they have an important effect on the quality of life. The unpredictable occurrence of painful, multiple and uncontrollable electrical shocks may induce a state of acute stress with stunning, (1)
ICDs can prevent premature death from an arrhythmia but may also prolong the dying process and make it more distressing. Individuals who choose to receive this device should have the opportunity to choose to discontinue it as death approaches. (2)
ICDs incorporating a multisite anti-bradycardiac function are more and more popular because of the close relationship between CHF and SCD.(3)
Patient-alert features are a useful additional tool facilitating early detection of serious ICD complications, but they do not substitute for regular ICD follow-up, because of their low sensitivity. (4;5)

1. **Goeb JL, Galloyer-Fortier A, Dupuis JM, et al. Psychiatric complication of an implanted automatic defibrillatorArch Mal Coeur Vaiss. 2003; 96:1235-1238.**
2. **Goldstein NE, Lampert R, Bradley E, et al. Management of implantable cardioverter defibrillators in end-of-life care. Ann Intern Med. 2004; 14111: 835-838.**
3. **Chauvin M, Jesel L, Douchet-Krebs MP. The implantable automatic defibrillatorArch Mal Coeur Vaiss. 2004; 97:1110-1115.**
4. **Becker R, Ruf-Richter J, Senges-Becker JC, et al. Patient alert in implantable cardioverter defibrillators: toy or tool? J Am Coll Cardiol. 2004; 44:95-98.).**
5. **Piccini JP, Dalal D, Roquin A, et al Predictors of appropriate implantable defibrillator therapies in patients with arrhythmogenic right ventricular dysplasia. Heart Rhythm. 2005; 2:1188-1194.**

The risk factors for SCD and indications for ICD placement in patients with ARVC/D are not well defined. Piccini et al from the Division of Cardiology, Department of Medicine, The Johns Hopkins Hospital, Baltimore, Maryland. studied which clinical and electrophysiologic variables best predict appropriate ICD therapies in patients with ARVC/D. Particular attention focused on whether the ICD was implanted for primary or second prevention. The authors enrolled 67 patients (mean age 36 +/- 14 years) with definite or probable ARVC/D who had undergone ICD placement. Appropriate ICD therapies were recorded, and Kaplan-Meier analysis was used to compare the event-free survival time between patients based upon the indication for ICD placement (primary vs secondary prevention), results of electrophysiologic testing, and whether the patient had probable or definite ARVC/D. Over a mean follow-up of 4.4 +/- 2.9 years, 40 (73%) of 55 patients who met task force criteria for ARVC/D and 4 (33%) of 12 patients with probable ARVC/D had appropriate ICD therapies for VT/VF; (P = .027). Mean time to ICD therapy was 1.1 +/- 1.4 years. Eleven of 28 patients who received an ICD for primary prevention (39%) and 33 of 35 patients who received an ICD for secondary prevention (85%) experienced appropriate ICD therapies (P = .001). Electrophysiologic testing did not predict appropriate ICD interventions in patients who received an ICD for primary prevention. Fourteen patients (21%) received ICD therapy for life-threatening (VT/VF >240 bpm) arrhythmias. There was no difference in the incidence of life-threatening arrhythmias in the primary and secondary prevention groups (P = .29). The authors concluded that patients who meet task force criteria for ARVC/D are at high risk for SCD and should undergo ICD placement for primary and secondary prevention, regardless of electrophysiologic testing results. (1)

1. **Piccini JP, Dalal D, Roquin A, et al Predictors of appropriate implantable defibrillator therapies in patients with arrhythmogenic right ventricular dysplasia. Heart Rhythm. 2005; 2:1188-1194**.

4.ICDs in combination with Drugs and/or RFCA

Drugs are used in association with ICD in case of frequent relapses of VT.
In-patient with poor tolerability or incessant VT ablation can be used.
An ICD is the most effective prevention against SCD. Due to the prohibitive cost of ICDs, they are not routinely placed in all individuals with ARVC/D. ICDs used alone or in combination with drug therapy, will probably play an increasing role in ARVC/D.

5. Cardiac Transplant Surgery or Orthotopic Heart Transplantation (OHT)

Cardiac transplant surgery or Orthotopic Heart Transplantation (OHT) is exceptional or rarely performed in ARVC/D. It may be indicated if the arrhythmias associated with the disease are uncontrollable or if there is severe bi-ventricular heart failure that is not manageable with pharmacological or others therapies. **(1;2)** The probability of survival at 1, 5 and 10 years in Spain were 76%, 66% and 54%, respectively. When survival rates for separate periods were considered, a significant improvement was seen in the last 5 years, with survival rates at of 81% at 1 year and 74% at 5 years. The most frequent causes of death were acute graft failure in the first month, infection and rejection in the first year, and a combination of vascular disease of the graft with SCD in the long term. Comparative analysis of survival rates shows that in it coutry long-term results are slightly better than those published in the literature, with a gradual tendency for survival rate to improve in recent years**.(3)**

1. **Fontaine G, Fontaliran F, Frank R, et al. Arrhythmogenic right ventricular dysplasia. A new clinical entity Bull Acad Natl Med. 1993; 177:501-512.**
2. **Canu G, Atallah G, Claudel JP, et al. Prognosis and long-term development of arrhythmogenic dysplasia of the right ventricle Arch Mal Coeur Vaiss. 1993; 86:41-48.**
3. **Almenar Bonet L.Spanish Registry of Heart Transplantation. 15th Official Report of the Working Group on Heart Failure, Heart Transplantation and Other Therapeutic Alternatives of the Spanish Society of Cardiology (1984-2003). Rev Esp Cardiol. 2004; 57:1197-1204.**

6 – Anterior Dynamic Cardiomyoplasty

Orthotopic Heart transplantation is the surgical procedure of choice for treatment of refractory heart failure. However, it benefits a small number of patients because of the limited number of donors and selection criteria of recipients. Anterior Dynamic Cardiomyoplasty is an alternative surgical procedure for heart failure. In properly selected patients, cardiomyoplasty and heart transplantation seem to be associated with improvement in survival and functional class at mid-term follow-up. Orthotopic Heart transplantation was more effective than cardiomyoplasty for functional class improvement.(1)

The mechanisms of action of dynamic cardiomyoplasty include the enhancement of LV systolic function, by the direct action of synchronized skeletal muscle flap contraction and the reversion of chamber remodeling. Moreover, both mechanisms seem to be responsible for improved diastolic function properties and for the decrease of ventricular wall stress.(2)

RV cardiac failure has been controlled by anterior dynamic cardiomyoplasty.(3)

The procedure has no effect on the microscopic structure of the RV myocardium.

1. **Bocchi EA, Bellotti G, Moreira LF, et al. Mid-term results of heart transplantation, cardiomyoplasty, and medical treatment of refractory heart failure caused by idiopathic dilated cardiomyopathy. J Heart Lung Transplant. 1996; 15:736-745.**
2. **Moreira LF, Bocchi EA, Stolf NA, Dynamic cardiomyoplasty in the treatment of dilated cardiomyopathy: current results and perspectives.J Card Surg. 1996;11:207-216.**
3. **Benvenuti LA, Moreira LF, Aiello VD, et al. Sequential histologic analysis of the myocardium after dynamic cardiomyoplasty: A study based on right ventricular endomyocardial biopsies. J Heart Lung Transplant. 2004; 23:1438-1440.**

7. Cellular Cardiomyoplasty (Cell Transplantation for Cardiac Repair)

Cell-based myocardial repair and regeneration heralds a new frontier in the treatment of cardiovascular disease. It provides an unprecedented opportunity to treat the underlying loss of cardiomyocytes that occurs after myocardial injury and that results in the cascade of events leading to CHF. In all mammals including humans, adult cardiocytes become post mitotic cells, while cardiac non-muscle cells still have the capacity to proliferate, and cardiac hypertrophy in adults is known to be due to cardiocyte hypertrophy and non-muscle cell hyperplasia.

Several new paradigms in cell biology have modified these views: the entire determinants of the cell cycle are now entirely known; apoptosis, and cardiac apoptosis, is central in the process of cell division, and has a rather complicated significance; telomeres are specialized DNA-protein structures that prevent end-to-end chromosome fusion, and are rather characteristic of germ and stem cells, these structures are maintained by telomerase. Using several markers, including telomerase activity, endogenous self-renewing, clonogenic and multipotent stem cells were identified in the adult myocardium in human, mice and rat. These cells are activated during cardiac overload or ischemia to produce new cardiocytes. New endothelial cells also appeared, and are likely to have a circulatory origin. The physiological importance of these new cells is debatable at the moment. Nevertheless, these findings provide an important new basis for cell cardiomyoplasty. It is also possible to envisage stimulation of the production and activity of these new cells to compensate for the lack of substance after myocardial infarction or myocardial damage.(1)

1. **Swynghedauw B.Are adult cardiocytes still able to proliferate?Arch Mal Coeur Vaiss. 2003;96:1225-30.**

Although cellular cardiomyoplasty shows great early clinical promise, its future as a new frontier in the treatment for cardiovascular disease will rest heavily on how we move forward in the next few years. Its success will heavily depend upon conducting carefully controlled, randomized double-blind clinical trials with appropriate endpoints, in the right patients. Choice of cell type, and mode of cell delivery, will also have to be considered, and may have to be matched to the patient. Irrespective of cell type, we can also be assured that cells offer both an opportunity for tissue repair and the potential for not yet understood outcomes. As with any frontier, there will be pitfalls and consequences to be considered that may surpass those of previous endeavors. But so too is the potential for previously unimagined success at treating the leading cause of death in the western world. In short, the promise for cardiovascular cell therapy is too great to be spoiled by ill-designed attempts that forget to account for both the natural propensities of cells and of the myocardium.(1) Human mesenchymal stem cells (hMSC) have proven beneficial in the repair and preservation of infarcted myocardium., the use of hES-MC provides similar efficacy for cellular cardiomyoplasty as compared to hMSC and may be considered a suitable alternative for cell therapy.(2)

1. **Taylor DA.Cell-based myocardial repair: how should we proceed? Int J Cardiol. 2004; 95:S8-12.**
2. **Simpson DL, Boyd NL, Kaushal S, et al. Use of human embryonic stem** cell **derived-mesenchymal** cells **for cardiac repair. Biotechnol Bioeng. 2011 Aug 11. doi: 10.1002/bit.23301. [Epub ahead of print**