Effort-induced syncopal episodes in a child with family history of sudden death

English: Case report

IGS, male, 11-year-old patient, student, born and living in Ubajara, Ceará, Brazil.
Reason for the visit: fainting.

History of current disease:

- Report of 2 episodes of sudden loss of consciousness while doing physical exercise, with no prodromes. He recovers conscious after some minutes, with no complaints after the event.
- He was referred by the neurologist after the second episode of syncope.
- Referred to cardiological evaluation after normal neurological tests.
- The first episode was 2 years ago when he was playing soccer and the second 8 months ago, riding a bicycle.

Personal history:

- Previously healthy.
- He mentioned 2 previous episodes of passing out during physical activity.
- He denies using medication regularly
- He was born through C-section, in term, without problems during pregnancy.

Family history:

- His brother died at the age of 8, while doing physical exercise.

Lab tests: normal.

Two-dimensional transthoracic echocardiography color Doppler: normal

Electrophysiological study (EPS)

- It was not able to induce ventricular tachyarrhythmia after stimulation of the right ventricle.
- Triggered episode of polymorphic ventricular tachycardia with isoproterenol infusion.

Questions:

1. Which is the clinical diagnosis? And why?
2. Which are the electrocardiographic diagnose during treadmill stress testing and isoproterenol infusion?

Raimundo & Andrés

Portuguese: Relato de caso

IGS, masculino, 11 anos, estudante, natural e procedente de Ubajara, Ceará, Brasil.

Queixa principal: desmaios

História da doença atual:

- Relato de 2 episódios de perda súbita da consciência enquanto fazia esforço físico, sem pródromos. Recupera a consciência após alguns minutos, sem queixas após o evento.
- Encaminhado por neurologista após o segundo episódio de síncope.
- Encaminhado para avaliação do cardiologista, após exames neurológicos inalterados.
- O primeiro episódio há 2 anos quando jogava futebol e o segundo há 8meses, andando de bicicleta.

Antecedentes pessoais:

- Previamente hígido
- Relata de 2 episódios prévios de desmaios durante atividade física.
- Nega uso de medicação regular
- Nasceu de parto cesariano, termo, sem intercorrência na gestação.

Antecedentes familiares:

- Irmão faleceu aos 8 anos, quando fazia esforço físico.

Exames laboratoriais: normais

Ecocardiograma transtorácico bidimensional color Doppler: normal

Estudo eletrofisiológico (EEF)

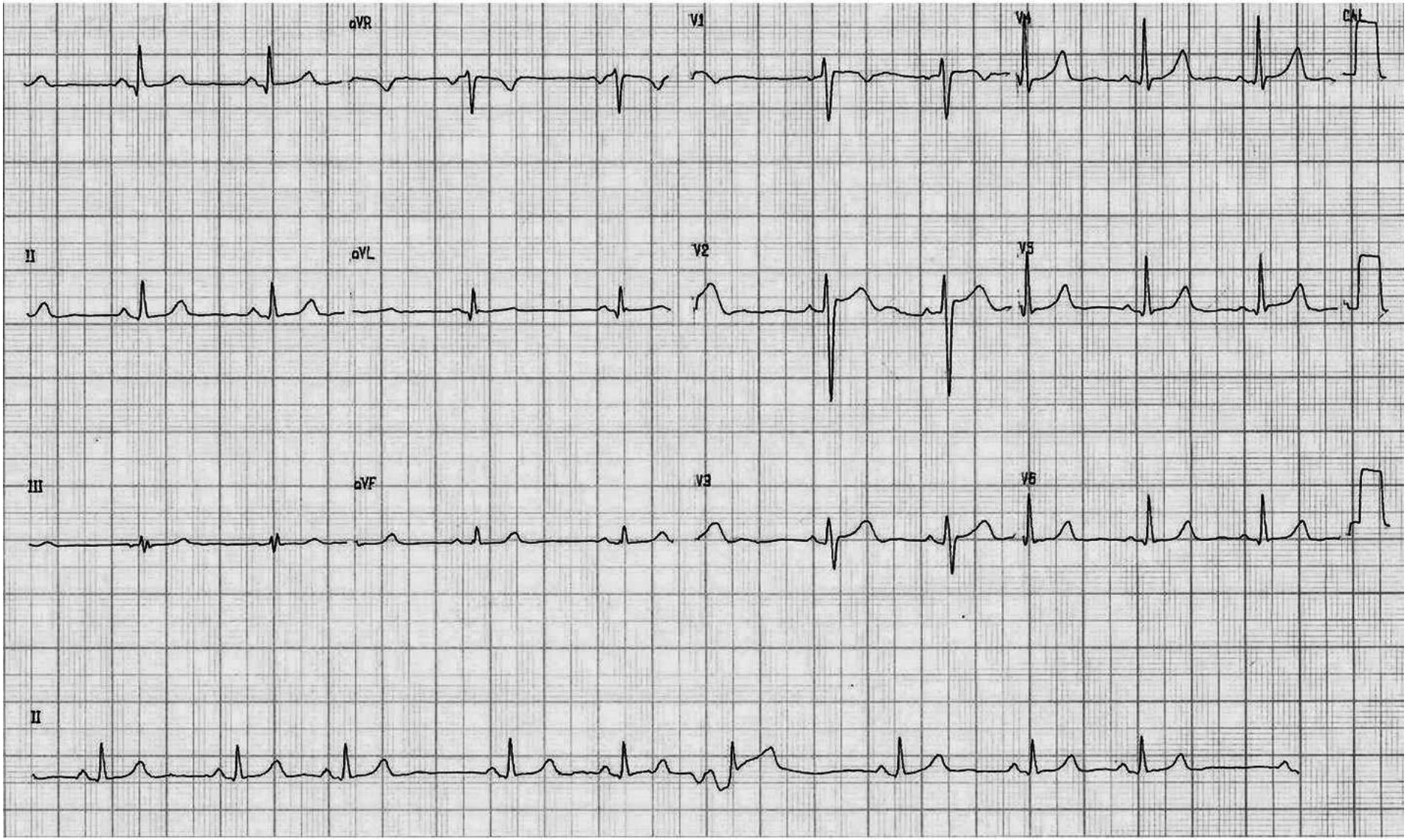
- Não se conseguiu induzir taquiarritmia ventricular após estimulação do ventrículo direito.
- Desencadeado episódio de taquicardia ventricular polimórfica com infusão de isoproterenol.

Perguntas:

1. Qual o diagnóstico clínico? E por quê?
2. Quais os diagnósticos eletrocardiográficos durante o teste ergométrico e durante a infusão do isoproterenol?

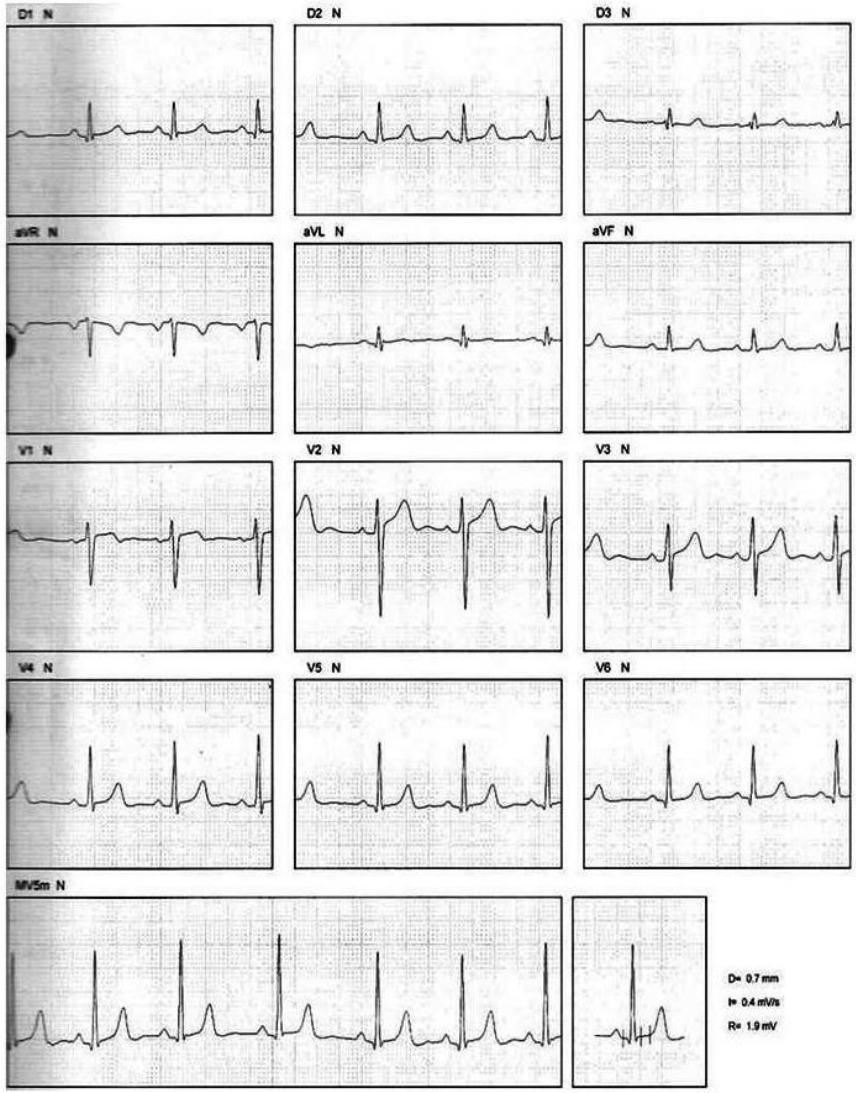
Raimundo & Andrés

ECG at admission

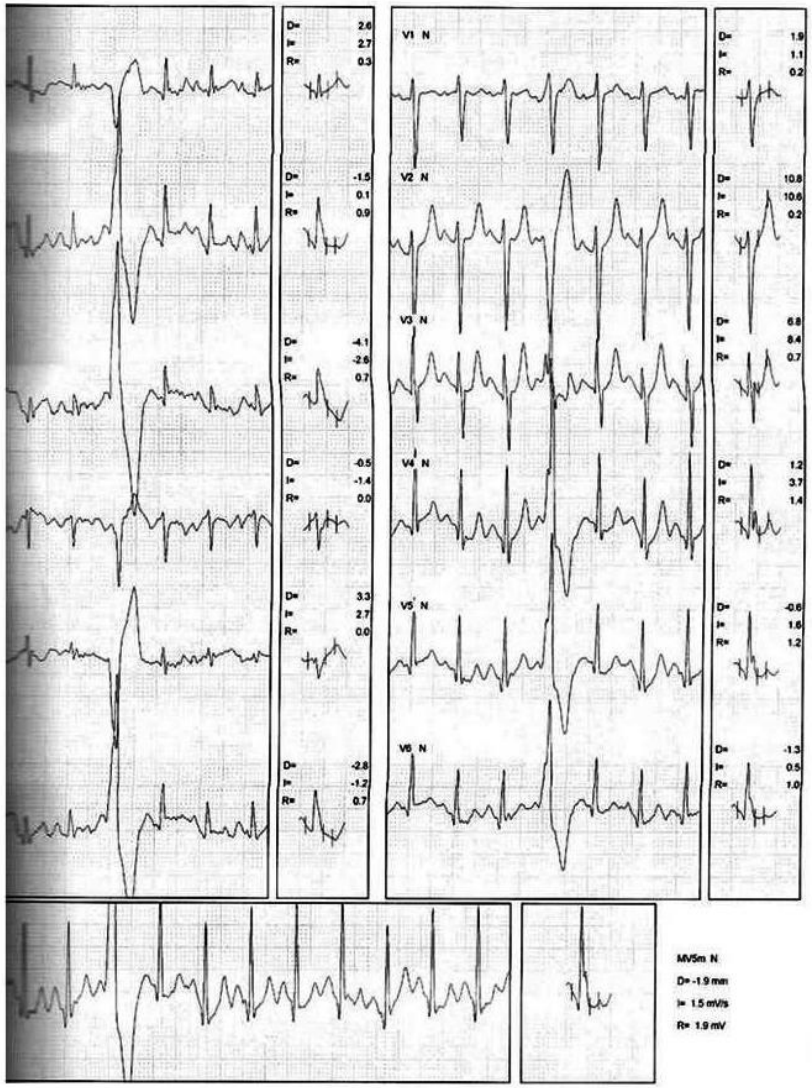


Treadmill Stress Testing

ECG at rest

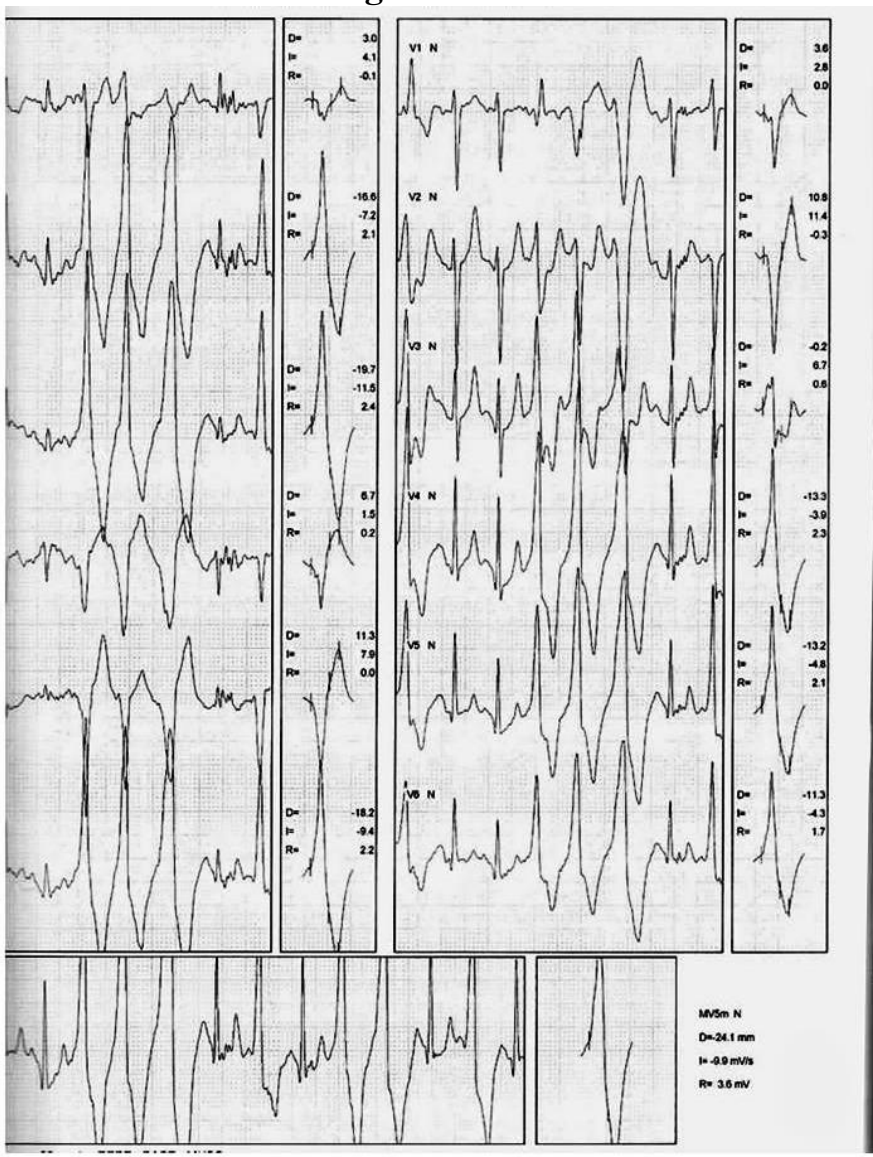


During initial effort

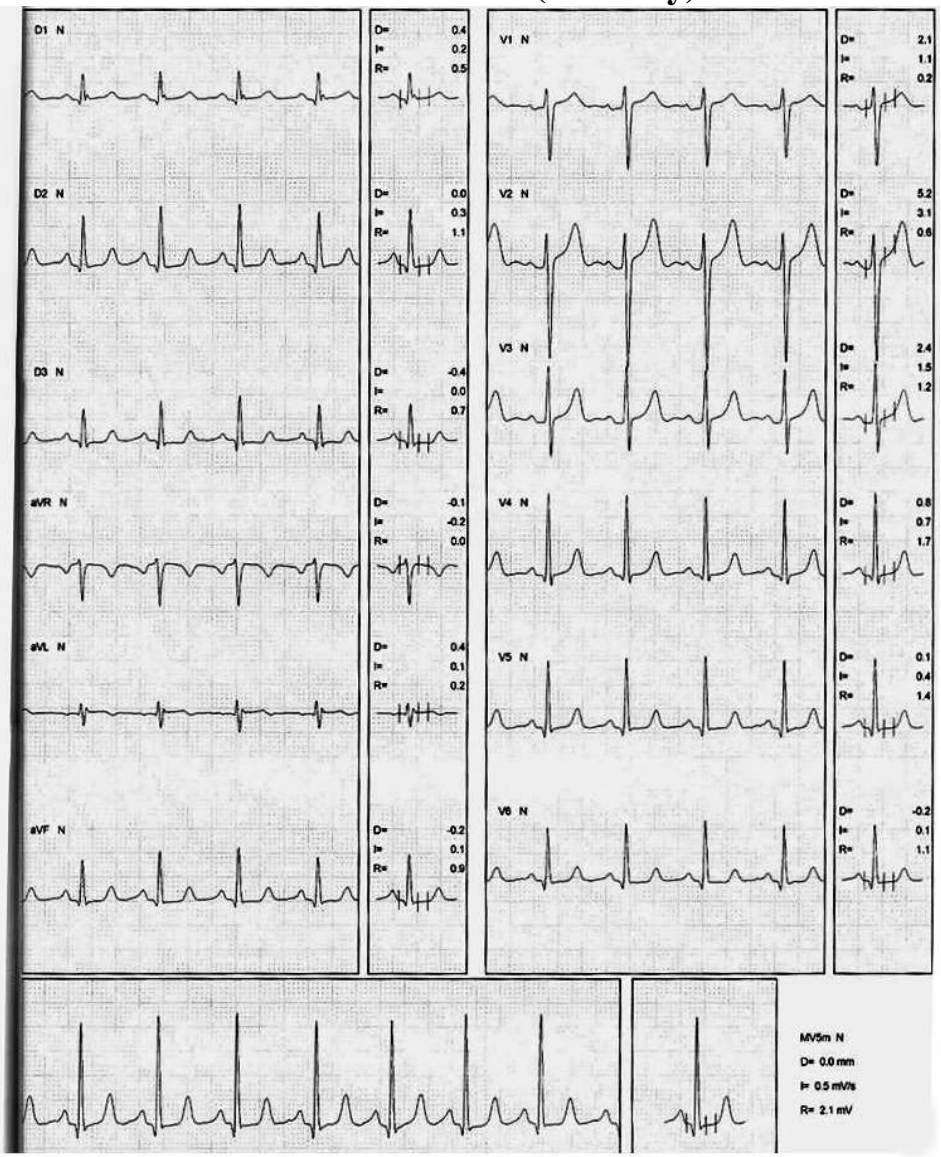


Treadmill Stress Testing

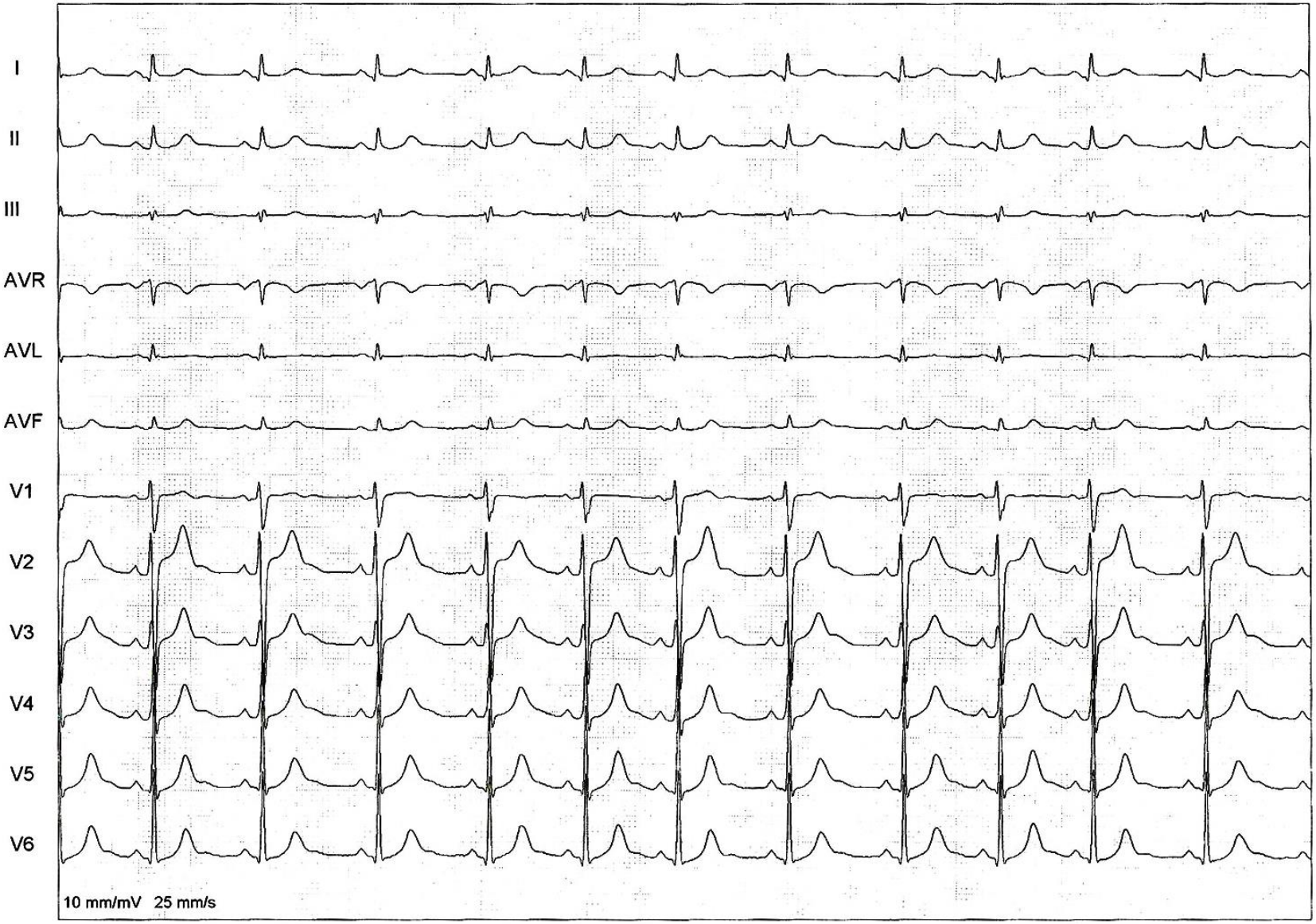
During maximal effort

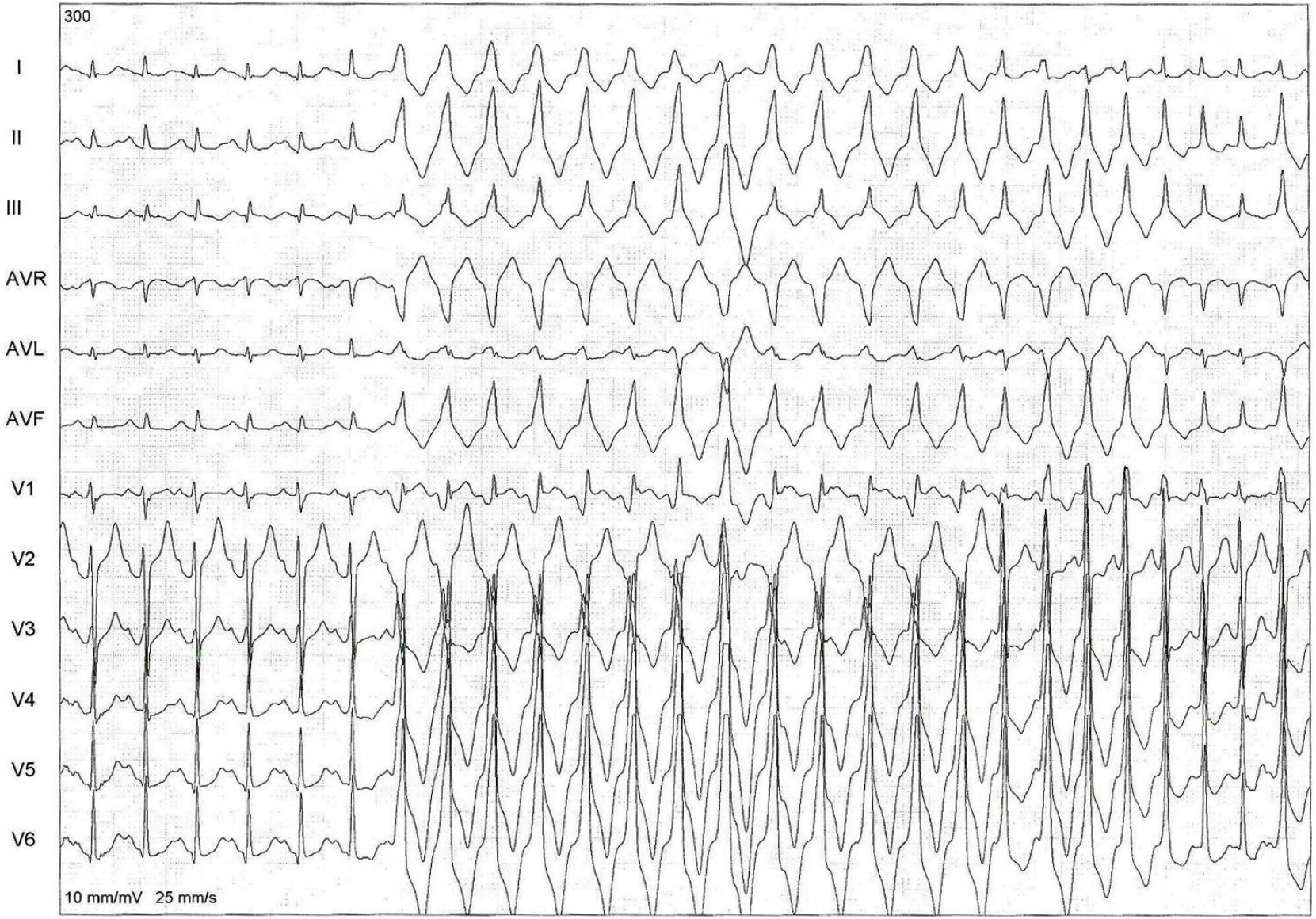


After effort (recovery)



ECG during invasive evaluation with infusion of isoproterenol




300
I
II
III
AVR
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V1
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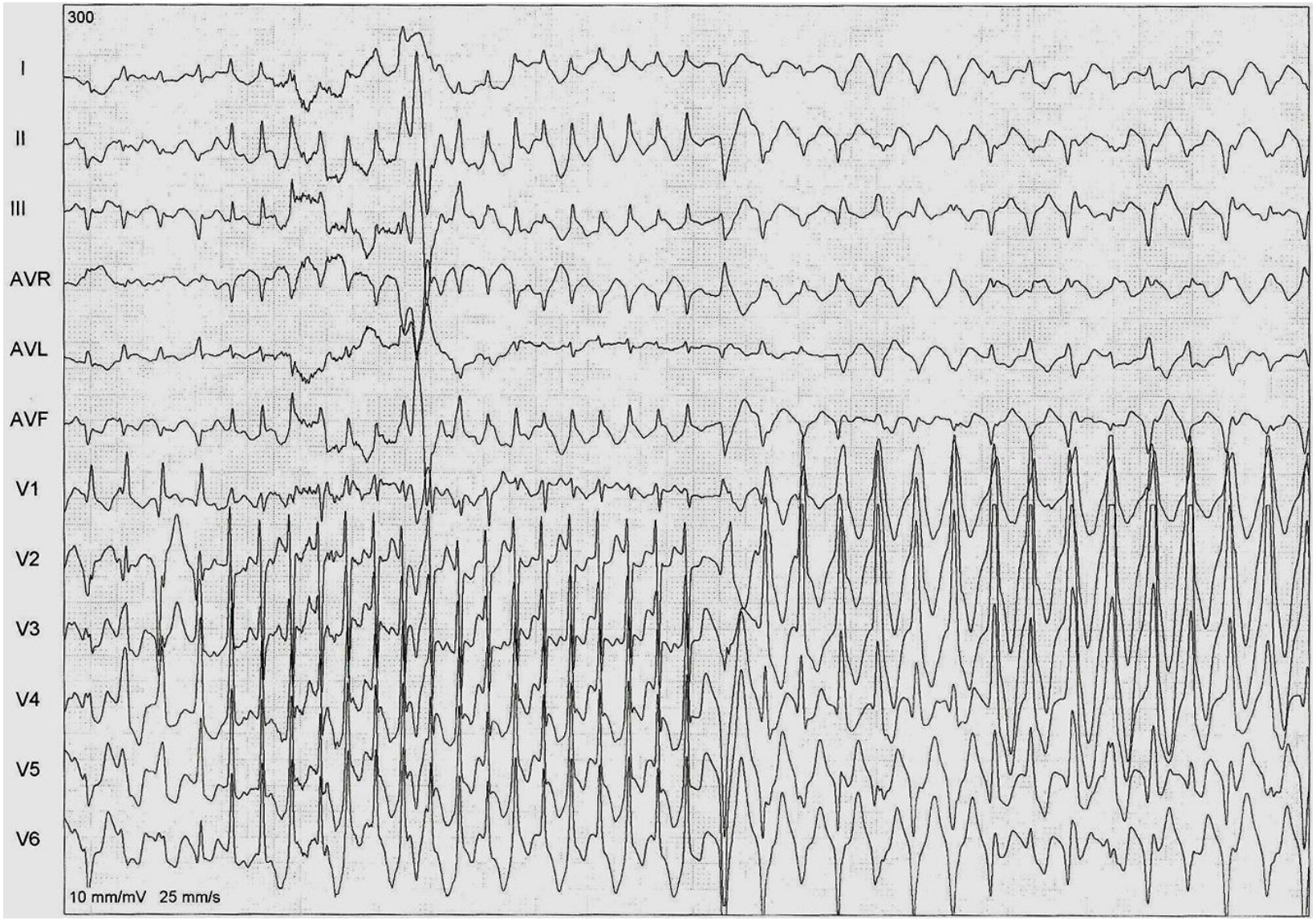
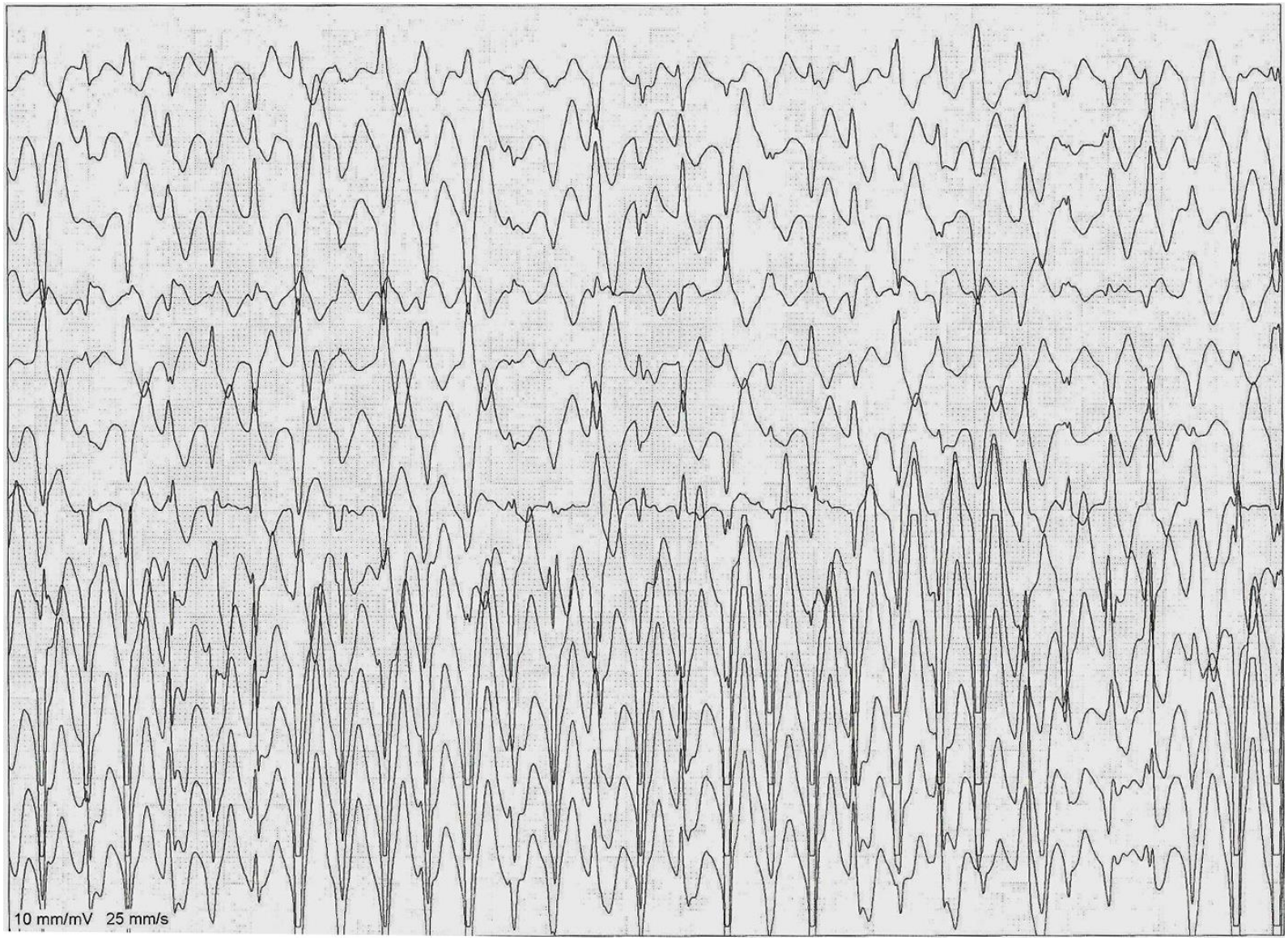
V3
V4
V5
V6
10 mm/mV 25 mm/s

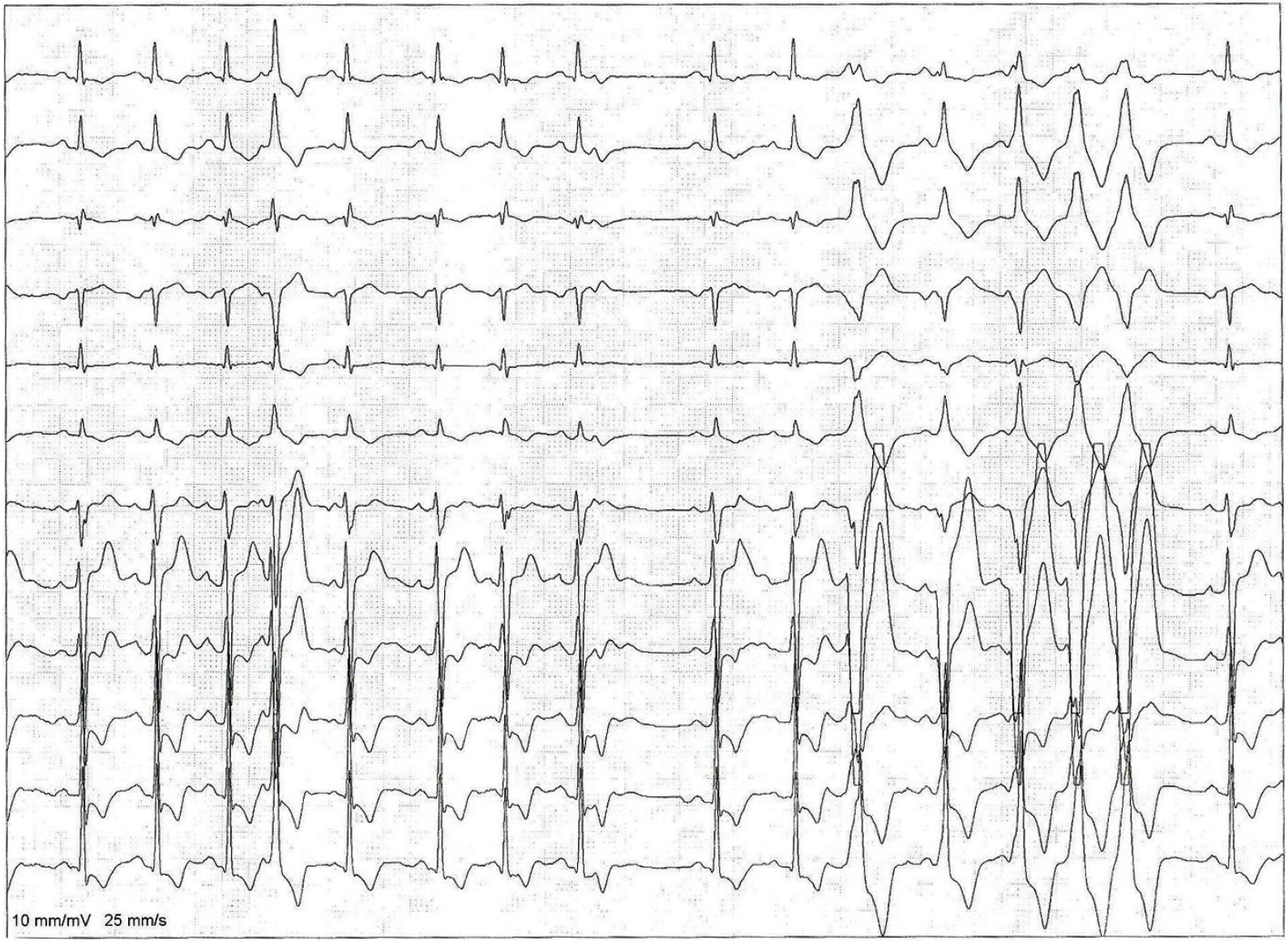
Isoproterenol infusion



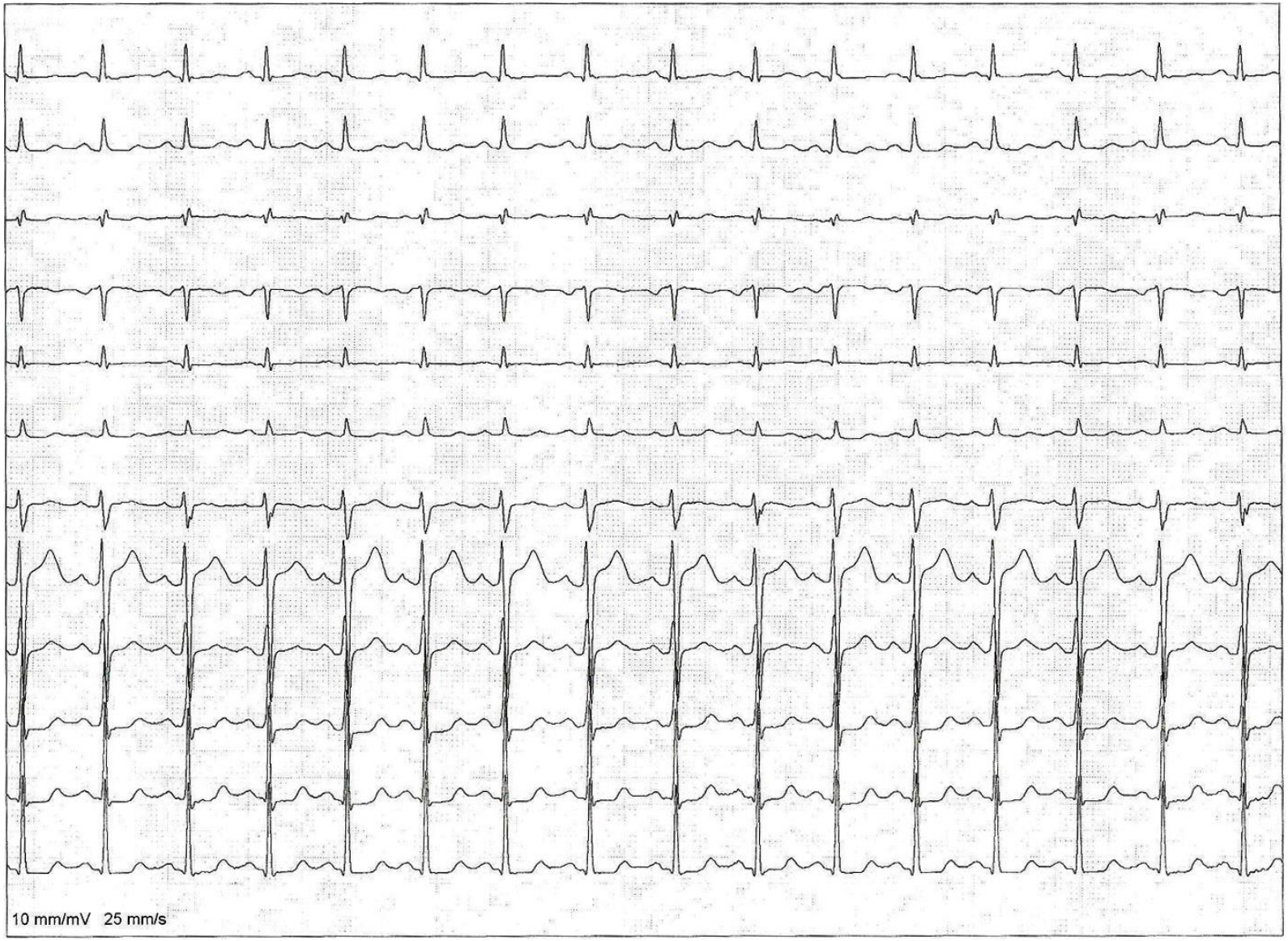
Isoproterenol infusion



Immediately after isoproterenol infusion



After ending isoproterenol infusion effect



Colleagues opinions

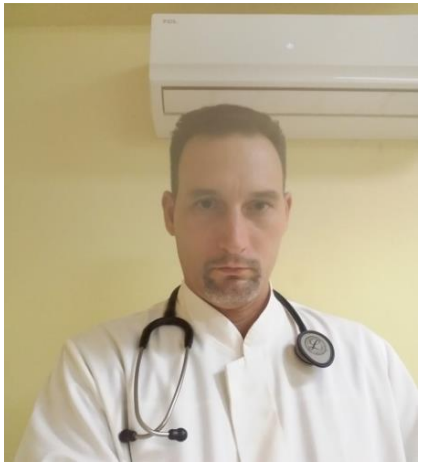
Spanish: Estimado Potro, en el electrocardiograma basal no presenta alteraciones. Los estudios cardiológicos descartan cardiopatía estructural. El diagnostico es el de una taquicardia ventricular (TV) polimórfica catecolaminérgica, que es una enfermedad genética (una canelopatia), que se caracteriza por síncope de esfuerzo y la arritmia característica es la TV bidireccional y TV polimórfica, similar a la desencadenada por la infusión de isoproterenol.
Presentan habitualmente buena respuesta al tratamiento con β bloqueantes.
Un cordial saludo
Martín Ibarrola

English: Dear Andrés, there are no alterations in the basal electrocardiogram. Cardiological tests rule out structural heart disease.
The clinical diagnosis is catecholaminergic polymorphic ventricular tachycardia (CPVT), that is a genetic disease (a channelopathy), characterized by exertional syncope and the feature bidirectional tachycardia and polymorphic VT, similar to the one triggered by isoproterenol infusion.
Usually patients have a good response to the treatment with β-blockers.
A cordial greeting
Martin Ibarrola. MD Buenos Aires Argentina

Dear: Raimundo & Andrés
I've been checking the electrocardiogram at rest and during the exercise stress test. A ventricular tachycardia has appeared during the test and in the rest appeared sinusal arrest in some complexes.
But in my observation I don't have a good definition but in more than 4 measures the QT is long.
In my opinion with this family history and the history of syncope and the finding in the test and rest the first diagnosis which we should have is the Congenital QT Long syndrome
Regards

José Enrique. **Castellanos Heredia.** MD
Especialista de Primer Grado en Medicina Interna y Segundo Grado en Cardiología. Asistente. Investigador Agregado. Hospital Clínico Quirúrgico Lucía Íñiguez Landín. Universidad de Ciencias Médicas de Holguín. Holguín. Cuba.
jecheredia75@GMAIL.COM

Answer Exercise-related syncope is also typically found in the LQT1 variant of LQTS. Since incomplete penetrance is possible in LQT1, some individuals may have a normal QT interval and may therefore appear to have the typical CPVT clinical presentation (exercise-related syncope and normal ECG). However, individuals with LQT1 do not usually show any inducible arrhythmia during graded exercise (exercise stress test). The initial description of CPVT by Philippe Coumel included cases with borderline or mildly prolonged QT interval. For this reason it has been suggested that an overlap phenotype (LQTS-CPVT) is possible. This hypothesis has not been thoroughly investigated.
Andrés



Portuguese:
Caro Andrés: Taquicardia Ventricular em coração estruturalmente normal com ECG de base também normal de caráter genético.
Taquicardia não reentrante (não induzida por estudo eletrofisiológico) e adrenérgica dependente.
De inicio a taquicardia ventricular é monomórfica com algumas morfologias diferentes devido a batimentos de fusão ventricular porém é monofocal e com provável origem em via de saída ventricular.
Pensei no início em cardiomiopatia arritmogênica, porém, com o evoluir do evento nota-se na TV o padrão polimórfico bidirecional.
Conclusão: Trata- se de uma taquicardia ventricular polimórfica catecolaminérgica.

English

Dear Andrés: It is a ventricular tachycardia in a patient without structural heart disease, with positive familial background. The 12-lead ECG is normal. It is non-reentrant tachycardia (not induced by electrophysiological study) and adrenergic-dependent.
Initially, the ventricular tachycardia is monomorphic with a minimal morphology differences due to fusion or Dressler beats, but it is monofocal and with probable focus origin in the ventricular outflow tract.
I thought at the beginning in arrhythmogenic cardiomyopathy but with the evolution of the event the bidirectional VT pattern is noted.
Conclusion: it is a Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

Marcelo **Garcia-Leal MD** Cardiology Division assistant at the Hospital das Clinicas, Ribeirão Preto Medical School – USP
Coordinator of clinical arrhythmia service cardiology division of the Hospital das Clínicas de Ribeirão Preto.
Head of the Cardiology Service of Santa Casa of Ribeirão Preto. Ribeirao Preto São Paulo Brazil.

Spanish

Para mi, la relación entre las arritmias de el síndrome de QT largo y el “esfuerzo” es un enigma. Por un lado, estoy conciente que la literatura marca “ejercicio” (o effort en ingles) como un precipitante importante de arritmias en el síndrome de QT largo (Schwartz, P.J., et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89). Por otro lado, todo el que ha tratado a pacientes con sindromes de QT largo seguro sabe que uno les puede hacer todas las pruebas de esfuerzo que uno quiera….. y nunca (y digo NUNCA!) van a tener arritmias serias. Uno que otro tendrán arritmias ventriculares que probablemente no tengan que ver mucho con la enfermedad (Ackerman MJ. The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. Heart Rhythm. 2011;8(11):1698). Pienso que la literatura a confundido “ejercicio” con la emoción de la competencia. Claro, cuando uno ve la respuesta del QT al aceleramiento repentino (Viskin, S. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. J Am Coll Cardiol. 2010;55(18):1955) uno puede imaginar que le pasa al QT a la hora de correr un sprint. Pero….. hágales correr a los pacientes todo lo que quiera en el tredmil y comprobará que no pasa nada. Por eso, para mi, la historia del paciente, con hermano muerto durante ejercicio, No sugiere síndrome de QT largo.

El QT de este muchacho es normal. Contando cuadritos yo mido un QT de 400 y un QTc de 436 msec. No hay pacientes con sindrome de QT largo que tengan QTc de este tamano (Vincent, Long QT syndrome in children: the value of rate corrected QT interval and DNA analysis as screening tests in the general population. J Med Screen. 2001;8(4):173).

El diagnostico es taquicardia ventricular polimórfica catecolaminérgica (CPVT). La prueba de esfuerzo la sugiere, aunque no es diagnóstica. Claro, TV monomorfica originando de el tracto de salida del ventrículo izquierdo (que es lo que demuestra la prueba de esfuerzo) podría ser simplemente una TV idiopática (aunque en las TVs idiopáticas aparece al terminar el esfuerzo mas que durante… pero todo es posible). Sin embargo, ESTA taquicardia monomórfica con una historia de hermano muerto es CPVT hasta que se demuestre lo contrario. Interesantemente, este tipo de arritthmais se ven muy seguido en pacientes con CPVT parcialmente tratados con β-bloqueadores.

La respuesta al isoproterenol es fascinante: Primero fibrilación auricular y TV bastantemente monomórfica pero eventualmente taquicardia bidireccional.

El paciente tiene CPVT y hay que tratarlo con β-bloqueadores y flecainida.

Sami Viskin MD Israel

English: For me, the link between LQTS arrhythmias and “strain” is an enigma. On the one hand, I am aware that literature indicates “exercise” or effort/strain is a significant trigger of arrhythmias in LQTS (1) On the other hand, any of us who have treated patients with LQTS, I’m certain knows that we can make all the stress tests available…and patients will never (and I mean NEVER!) display severe arrhythmias. A few will present VTs that are probably unrelated to the disease (2). The way I see it, literature mixed up “exercise” with the excitement of competition. Of course, when we see the QT response to a sudden acceleration (3)) we can imagine what happens to QT when sprinting. But…make patients run as much as you want in the treadmill, and you will see that nothing happens. For this reason, for me, the history of the patient with a deceased brother during exercise, DOES NOT suggest LQTS. The QT of this boy is normal. By counting small squares I measure 400 and a QTc of 436 ms. There are no patients with LQTS with a QTc of this size (4). The diagnosis is CPVT. Stress test suggests it, but it is not diagnostic. Of course,MVT originating in the LVOT (which is shown by the stress test) could be just IVT (although in tachycardiopathic ones, VT appears at the end of strain rather than during…but anything is possible). However, This monomorphic VT with a history of a brother who died is CPVT until the contrary is proven. Interestingly, this type of arrhythmias are seen very often in patients with CPVT, partially treated with β-blockers. The response to isoproterenol is fascinating: First, AF and quite MVT, but later bidirectional tachycardia. The patient has CPVT and he has to be treated with β-blockers and flecainide.

1. **Schwartz, P.J., et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89.**
2. **Ackerman MJ. The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. HeartRhythm. 2011;8(11):1698**
3. **Viskin, S. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. J Am CollCardiol. 2010;55(18):1955**
4. **Vincent, Long QT syndrome in children: the value of rate corrected QT interval and DNA analysis as screening tests in the general population. J Med Screen. 2001;8(4):173.**

Sami **Viskin MD Israel** Director, Cardiac Hospitalization Unit, Tel-Aviv Medical Center, Israel. Associate Professor of Cardiology, Tel Aviv University. Editor: HEART RHYTHM. EDITORIAL CONSULTANT: THE LANCET.

Dear Sami,

First, let me tell the young and non-expert colleagues, that Dr. Sami is one of the most outstanding and well-respected researcher in the world, mainly in relation to LQTS, TdP mechanisms, idiopathic VF, and other channelopathies without structural heart disease. It is a luxury to have his invaluable opinion. Nevertheless, let me tell you that this boy continued presenting ventricular arrhythmia, even with high doses of β-blockers. On the other hand, he is symptomatic. In spite of being very promising, and being approved both clinically (1;2;3) and experimentally (4;5), flecainide is still considered a therapy being investigated. ICD has class IIa indication in patients that remain with syncope or sustained VT in spite of using β-blockers. Sami, if you were the boy's dad, would you feel comfortable just with the pharmacological therapy? I agree with you on the association of flecainide, but only after making a stress test, before and after the introduction of flecainamide. The typical symptoms are the appearance of arrhythmias during exercise, more often when HR reaches 120-130 bpm, starting with isolated PVCs, progressing into non-sustained and sustained ventricular tachycardia episodes, and if the strain is maintained, bidirectional tachycardia may appear. Using β-blockers is very efficient when reducing symptoms, and it is class I indication for patients with clinical symptoms. Using ICD is a class I indication in patients who recovered from sudden cardiac death and class IIa in patients that remain with syncope or sustained VT in spite of using β-blockers. I would indicate ICD+drugs so that the device may not apply useless shocks. A treatment with left cardiac denervation has been suggested as a therapeutic alternative for patients that may not use β-blockers (e.g., asthmatic). Or maybe, flecainide is of choice in these cases. It is the first addition to β-blockers. When ventricular arrhythmia suppression is incomplete, consensuses guidelines by current experts state a class IIa recommendation to use flecainide in patients with CPVT. Moreover, flecainide is considered an "emerging recommendation" according to the 2015 European Society of Cardiology. Flecainide should not be considered in patients who still suffer ventricular arrhythmias and/or symptoms in spite of the maximum tolerated dose of β-blockers, with or without ICD. The dose-response effect has been observed in previous studies on flecainide; and the optimal dose for arrhythmia suppression is approximately 150-300 mg/day; while doses below 100 mg/day have been associated to a lack of response in most cases; and treatment failure has been associated to this date, to a low flecainide dose and/or non-compliance. Currently, the only efficacy measure for flecainide is the so-called **ventricular arrhythmic load in the stress test before and after the introduction of the drug**. There were cases in which the ventricular arrhythmic load in the stress test was not a reliable predictor of events (i.e., events were experienced before and after the drug in the stress test). It is unknown whether the administration once or twice a day is beneficial, but a slow-release drug is preferred, to prevent non-compliance. In general, the reported secondary effects of flecainide are mild, and have caused an interruption only in a small percentage of patients. Thank you Sami for always enriching our Pablo Chiale Forum.

References in the next slide.

References

1. van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: important messages from case reports.Europace. 2011;13(1):11-3.
2. van der Werf C, Kannankeril PJ, Sacher F, et al.Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia.J Am Coll Cardiol. 2011;57(22):2244-54.
3. van der Werf C, Zwinderman AH, Wilde AA.Therapeutic approach for patients with catecholaminergic polymorphic ventricular tachycardia: state of the art and future developments. Europace. 2012;14(2):175-83.
4. Liu N, Colombi B, Memmi M, et al.Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia: insights from a RyR2 R4496C knock-in mouse model.Circ Res. 2006;99(3):292-8.
5. Liu Y, Kimlicka L, Hiess F, et al.The CPVT-associated RyR2 mutation G230C enhances store overload-induced Ca2+ release and destabilizes the N-terminal domains.Biochem J. 2013;454(1):123-31.

Andrés

Spanish: Estimado Sami: primeramente debo comentar a los jóvenes y no expertos que el Dr Sami es uno de los investigadores mas destacados y respetados alrededor del mudo principalmente en relación a LQTS, TdP mechanism, idiopatic VF y otras canalopatias without structural heart disease. Es un lujo tener su valiosísima opinión. No obstante, permítame comentar que este niño mostró continuar con los eventos de arrtimia ventricular mismo impregnado de alta dosis de β-bloqueador. Por otra parte es sintomático. Apesar de muy promisora y aprobada tanto clínica (1;2;3) como experimentalmente (4;5) la flecainamida todavía es considerada una terapia en investigación promisora. El CDI tiene indicación clase IIa en pacientes que permanecen con síncope o TV sostenida a pesar del uso de β-bloqueadores. Sami si usted fuera el papá de este niño se quedaría tranquilo apenas con los fármacos? Comparto su idea de asociar flecainamida pero solo después de realizar una prueba de esfuerzo antes y después de la introducción de la flecainamida. La manifestación típica es la aparición de arritmias durante el ejercicio, más a menudo cuando la FC alcanza los 120-130 lpm, comenzando con extrasístoles ventriculares aisladas, progresando a episodios de taquicardia ventricular no sostenida y sostenida, si el esfuerzo se mantiene puede aparecer taquicardia bidireccional. El uso de β-bloqueadores es muy eficaz en la reducción de los síntomas, e indicación clase I para pacientes con manifestaciones clínicas, El uso del CDI es una indicación de clase I en quien fue recuperado de la muerte súbita y clase IIa en pacientes que permanecen con síncope o TV sostenida a pesar del uso de β-bloqueantes. Le indicaría un CDI + fármacos para que el aparto nao de descargas inútiles. Se ha sugerido el tratamiento con denervación cardíaca izquierda como una alternativa terapéutica para los pacientes que no pueden hacer uso de los β-bloqueantes (ejemplo asmáticos) O talvez la fleca sea de elección en estos casos . La flecainida es la primera adición a los β-bloqueantes Cuando la supresión de la arritmia ventricular es incompleta. directrices de consenso de expertos actuales han dado una recomendación de clase IIa para el uso de flecainida en pacientes con CPVT. Además, flecainida se considera una “recomendación emergente" de acuerdo con la 2015 Sociedad Europea de Cardiología VT guideline. con β-bloqueantes y flecainida añadido a los β-bloqueadores en el paciente CPVT. Flecainida no debería ser considerada en pacientes que sigue teniendo arritmias y / o síntomas ventriculares pesar dosis tolerada máxima β-bloqueantes en pacientes con o sin un CDI. El efecto dosis-respuesta se ha observado en estudios previos sobre la flecainida y la dosificación óptima para la supresión de la arritmia en los adultos es de aproximadamente 150-300 mg / día, mientras que las dosis inferiores a 100 mg / día se han asociado con la falta de respuesta en la mayoría de los casos, el fracaso del tratamiento hasta el momento se ha asociado con una baja dosis de flecainida y / o no -Conformidad. En la actualidad, la única medida de la eficacia de la flecainida es la llamada **carga ventricular arrítmica en la prueba de esfuerzo antes y después de la introducción del fármaco.** En los casos en los que la carga de arritmia ventricular en la prueba de ejercicio no fue un predictor fiable de eventos (es decir, que experimentó eventos antes y después del fármaco en la prueba de esfuerzo) Se desconoce si la administración una vez o dos veces al día es beneficioso, pero se prefiere un fármaco de liberación lenta para evitar el incumplimiento. En general, los efectos secundarios reportados de flecainida son leves y han dado lugar a la interrupción sólo en una pequeña proporción de pacientes. Gracias Sami por siempre abrillantar nuestro Pablo Chiale fórum. Andrés

Referencias,

1. van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: important messages from case reports.Europace. 2011;13(1):11-3.
2. van der Werf C, Kannankeril PJ, Sacher F, et al.Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia.J Am Coll Cardiol. 2011;57(22):2244-54.
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Spanish: La combinación de flecainida y β-bloqueadores hace milagros en CPVT.
El que quiera ademas ponerle un desfibrillador automático (CDI) que tenga cuidado: Es muy important programar duraciones de detección LARGAS. La tachycardia ventricular polymorfica de CPVT es de tipo "trigger activity." El shock del desfibrilador NO la va a terminar! Unicamente le va a producir susto y dolor al paciente y le provocara mas arritmias. Hay bastantes reported de pacientes con CPVT que murieron a causa del defibrilador. Por eso es que el desfibrillador en CPVT siempre es usado como ultimo recurso a los que han tenido síntomas y siguen teniendo arritmias en prueba de esfuerzo a pesar de β-bloqueadores y flecainida. Si se implanta, hay que programarlo para que una vez detectada la tachycardia, el desbifrilador espere hasta que la tachycardia polymorphica se convierta en fibrillacion ventricular. Mis pacientes lo tiene programado con detección a >220 que dure mas de TREINTA segundos.
Para el paciente que no tolere las medicinas, el siguiente paso es la denervacion
Sami Viskin

English: Andrés,
The combination of flecainide and β-blockers works wonders in CPVT.
Whoever also wants to add an implantable cardioverter defibrillator (ICD) should be careful: it is very important to program LONG detection durations. The polymorphic ventricular tachycardia of CPVT is of the “activity-triggered” type. The defibrillator shock will NOT end it! It will only scare and cause pain to the patient, and will cause further arrhythmias. There are quite a number of patients with CPVT who died because of the defibrillator. For this reason, defibrillators in CPVT are always used as a last resource in those who have suffered symptoms and continue having arrhythmias in the stress test, in spite of β-blockers and flecainide. If implanted, it has to be programmed so that once the tachycardia is detected, the defibrillator waits until the polymorphic tachycardia becomes ventricular fibrillation. My patients have it programmed with a detection at >220 that lasts more than THIRTY seconds.
For patients that do not tolerate medicines, the next step is denervation.
Sami Viskin

Spanish: Estoy de acuerdo!

He visto casos horribles de CPVT a los que se le implanto un desfibrilador sin saber la causa de la arritmia. Cada choque genera más stress en el paciente lo que exacerba las arritmias y esto induce más choques (tormenta eléctrica).

Saludos,

Mario D. González

English: I agree!

I have seen horrible cases of CPVT in whom a defibrillator was implanted not knowing the case of the arrhythmia. Every shock generates more stress in the patient, exacerbating the arrhythmias and thus more shocks are induced (electrical storm).

Regards,

Mario D. González

According to what I understood from my colleague in Israel, Professor Sami Viskin, the child suffered ventricular tachycardia polymorphic episodes as well as bidirectional tachycardia.
One suspects that this child has a calcium metabolism dysfunction, very probably a mutation of an amino acid in the ryanodine receptor. Only this mutation induces these two dramatic arrhythmias.
Biologically there must be two factors of adrenaline and receptor mutation, which releases calcium to the intercellular space. It would seem that the adrenergic substances are not an important factor, as they filled the young boy with β-blockers yet it did not help……
The only remedy is to give verapamil, which has the ability to close the calcium receptors.
This medicine will depress all complicated ventricular arrhythmias.
I cannot be quiet knowing that this child might suffer pointlessly.
I recommend the forum not send me anymore mail because I'm not the kind of person who can keep silent before such a dramatic case and when I believe that I can help save the child.
The verapamil will have no side effects other than slight constipation.
Please use this drug it gives the child a great chance to be saved.

Respectfully yours,

Samuel Sclarovsky MD Israel

Answer to Dr Samuel from Andrés: Additional pharmacologic treatment has been proposed for CPVT, but in the past failures with sodium channel blockers (**Leenhardt 1995, Sumitomo 2003**) and amiodarone (**Leenhardt et al 1995**) have been reported. Other authors have reported partial effectiveness with verapamil (**Sumitomo 2003; Swan 2005**). However, these reports remain anecdotal and have not been independently confirmed. Furthermore, the effect of chronic treatment with high doses of β-blockers and calcium antagonists on cardiac contractility in children is not known. At present, calcium antagonists cannot be considered an alternative for persons unresponsive to ICDs.

What a superb case in a young 11-year-old child with a history of familial sudden death (brother at age 8 died during physical exercise) !!.

Which is the clinical diagnosis? Everybody will easily recognize in this patient the typical features of CPVT (catecholaminergic polymorphic ventricular tachycardia): familial occurrence, apparently normal heart with normal echocardiogram and lack of obvious ECG signs of myocardial ischemia before occurrence of the tachyarrhythmias during exercise, subnormal ECG (mild ST-T elevation in V1-V3) with normal QTc; occurrence of various tachyarrhythmias during exercise and isoproterenol infusion; return to normal upon discontinuation of exercise and isoproterenol.

Which are the electrocardiographic diagnose during treadmill stress testing and isoproterenol infusion?

- **IPNA infusion:** the arrhythmia started with a monomorphic slightly irregular VT originating from the outflow tract (either the posterior RVOT, or maybe the right coronary cusp that is anatomically close); the VT rate accelerated quickly while at the end of the tracing a narrower, faster tachycardia appeared that suggests the simultaneous occurrence of an atrial tachyarrhythmia (with resulting fusion beats) (also called "bitachycardia"). In the next slide multiple types of QRS complexes are present apparently associated that atrial tachyarrhythmia with a different morphologic type of VT (having a RBBB pattern left QRS axis contrasting with the early one exhibiting a LBBB pattern and right QRS axis). The next slide show various VPC's with major different alternant morphologies.
- **Treadmill test testing:** there are only few beats that can be discussed. I think that there is some bitachycardia with an outflow tract ventricular arrhythmia.

You do not ask me about patient's management but I will give my opinion in a few words: we should do our best in these patients to avoid implantation of ICD. β-blockers, verapamil, flecainide alone or in combination and even sympathectomy should be tried first based on usual ability to reproduce the arrhythmia with EET.

Recommendations: genetic testing + familial screening.

Bernard **Belhassen ("BB")** MD PhD Israel.
Cardiologist. Director, Cardiac Electrophysiology Laboratory Professor of Cardiology,
Sackler School of Medicine, Tel-Aviv University.

CPVT author references of BB in the next slide

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Brief CV Professor Bernard Belhassen ("BB") from Andrés BB is a Tunisian cardiologist, educator. He is Doctor of Medicine (Paris University 1973). Career: Cardiologist Fernand Widal Hospital, Paris, 1976-1978. During 1983-1984 completed the fellowship programs as a Visiting Professor of Cardiology, Hahnemann University, Philadelphia, USA and in 1988 as a Visiting Professor of Cardiology, Department of Cardiology, Hospital Broussais, Paris, France. Director cardiac laboratory Tel Aviv Medical Center, since 1978. Associate professor cardiology Tel Aviv University, 1989-2000, full professor cardiology, since 2000. Awards: William Fulbright grant, 1983, 1984 - Israel Medical Association Award; Henri Neufeld award, 1987, 88. 1990 - The Israeli-German Symposium on Clinical Cardiology Award; 1997 - The First Michel Mirowski Prize; 1998 - Henry Neufeld Award, First Prize. He is Fellow of American College Cardiology, North America Society Pacing and Electrophysiology, Israel Heart Society (general secretary 1989-1991). He is an author of over 200 medical publications in leading medical journals and over 230 lectures. BB was born on June 15, 1948 in Tunis, Tunisia. Arrived in Israel, 1978. Son of Maurice and Arlette (Bellaiche) Belhassen. Married Michele Hanna Azoulay. He has five children: Gilla, Yehonathan, Lior, Elinor, and Yael.

I would like to just contribute with the experience of a first patient with almost 15 years of follow-up. Quite a problem. ICD implanted because of VT with syncope, refractory to β-blockers at age 14. As Sami Viskin says, PVT was treated unsuccessfully by frequent shocks (proper but ineffective therapies). The electrophysiology study with high doses of isoproterenol showed the same result: polymorphic VT refractory to external defibrillation. The induced VF was successfully reverted by external defibrillation. In spite of being a boy weighing only 46 Kg, the solution to reduce the shocks was to combine high doses of β-blockers: nadolol 240 mg/day + carvedilol 50 mg/day, that were well tolerated, and programming therapies only in the range of VF with prolonged detection at the maximum allowed rate (250 bpm). For years after the implant, and after a long period with no shocks but with polymorphic VT episodes in the range of monitor VT (there was no way to stop him from play soccer for instance, which is understandable with him being a teenager), he had his first proper and successful shock due to VF at age 18, induced by emotional stress (first arrhythmic event induced by non-physical stress).Regards,
Roberto Keegan MD

Spanish
Solo para aportar con la experiencia de un primer paciente con casi 15 años de seguimiento. Un gran dolor de cabeza. CDI implantado por TV sincopal refractaria a beta-bloqueantes a los 14 años. Como dice Sami Viskin, la TV polimorfa fue tratada sin éxito con choques frecuentes (terapias apropiadas no efectivas). El estudio electrofisiológico con altas dosis de isoproterenol mostró igual resultado: TV polimorfa refractaria a desfibrilacion externa. La FV inducida fue exitosamente revertida con desfibrilación externa. A pesar de ser un niño con solo 46 kg de peso, la solución para reducir choques fue combinar altas dosis de beta-bloqueantes: nadolol 240 mg/d+carvedilol 50 mg/d, bien toleradas, y programar terapias solo en zona de FV con detección prolongada a la frecuencia máxima permitida (250 lpm). Cuatro años después del implante, y luego de un largo periodo sin terapias pero con episodios de TV polimorfa en zona de TV monitor (no hubo manera de que dejara de jugar al fútbol por ej. creo entendible tratándose de un niño) tuvo su primer terapia apropiada exitosa por FV a los 18 años inducida por estrés emocional (primer evento arrítmico inducido por estrés no físico).

Saludos,
Roberto Keegan MD

Dear Roberto: What you tell us in fact, is that in spite of being painful, ICD saved the life of this young man at age 18. This indicates that using drugs in the long term, mainly in teenagers, may not be taken seriously and thus a regrettable early sudden cardiac death may occur. If that teenager had no ICD implanted, his life would have ended at 18. You yourself are stating that he could not be controlled in terms of recommendations to him. This is in favor of ICD, because it is the only thing that guarantees life. If I myself, being a physician, when I have to take an antibiotic for seven days due to an infection, I have to confess that I never take them for that long. The same thing happens with everyone. People become careless, they stop taking the medication or take less, or the medicine is not available, or it is too expensive, or they travel and do not take the medication with them, and if there is adrenaline release, an event occurs that could be fatal. So it is not so easy. I am not denying that the association of beta blockers + flecainide can be very efficient, or that ICD is free from trouble, but the only guarantee of life is ICD. ICD is not careless. ICD does not display the randomness of being careless. How often a young, diabetic patient falls into a coma by a mere distraction or by not taking insulin, or by carelessness. I see in my daily practice, hypertensive people that do not take the medicine due to numerous causes: financial, because of ignorance, lack of discipline, and suddenly there is a devastating stroke. I recently attended a man who had a hemorrhagic stroke due to a hypertensive crisis. When I asked him if he was taking his medication, his reply was: “Dr. the problem is I had a party in which I was going to drink alcohol. So I stopped taking the medication for 2 days.” The poor man was so ignorant that he thought that while ingesting alcohol he could not take his antihypertensive medication. In brief, I am not fully convinced that drugs in consensus cases are enough. It is not right to ignore consensuses rules just by a hunch. We may end up having a pyrrhic victory; i.e. we win a battle but lose the war.

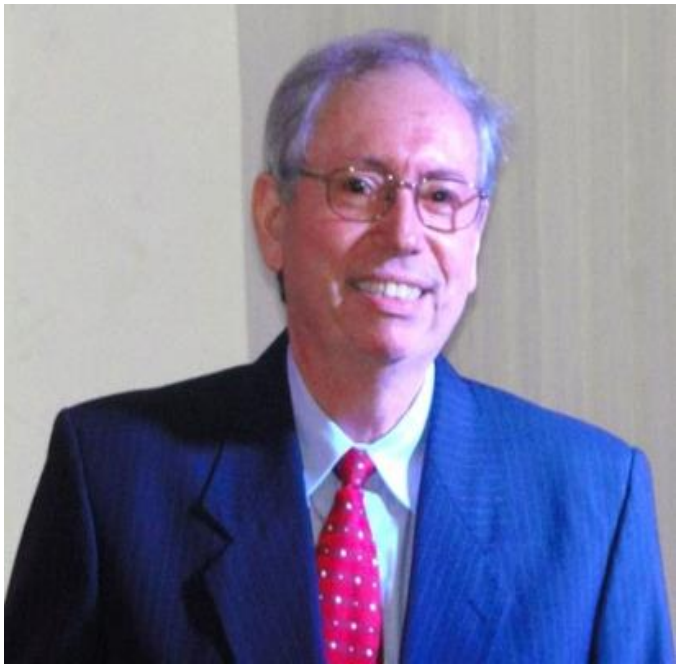
Andrés Ricardo Pérez-Riera

Spanish Querido Roberto lo que usted nos cuenta en realidad es que a pesar de doloroso el CDI le salvó la vida a ese joven a los 18 anos. Eso indica que el uso de fármacos de largo plazo principalmente en adolescentes puede no llevarse a serio y así ocurrir una lamentable muerte súbita precoz. Si ese adolescente no tuviera implantado un CDI su vida hubiera terminado a los 18 anos. Usted mismo esta diciendo que no se pudo controlar en las recomendaciones. Esto es en favor del CDI porque es la única garantía de vida. Si yo que soy médico cuando tengo que tomar un antibiótico por siete días por una infección confieso que jamás tomo los días indicados. Lo mismo ocurre con todo el mundo se descuida, deja de tomar o toma menos, o falta el remedio, o es muy caro, o viajé y no llevé los remedios, y si tengo una liberación de adrenalina ocurre el evento que puede ser fatal. Por lo tanto la cosa no es tan fácil. No niego que la asociación beta bloqueantes + fleca pueda ser muy eficaz ni que el CDI este libre de problemas mas la única garantía de vida es el CDI. Este no se descuida. Este no tiene el imponderable del descuido. Cuantas veces en un joven diabético juvenil entra en coma por mero descuido o por no tomar la insulina o por falta de cuidado. Yo veo en mi dia a dia personas hipertensas que no toman el remedio por numerosas causas: económicas, ignorancia, falta de celo, y súbitamente tienen un devastador AVC. Recientemente atendí un señor que tuvo AVC hemorrágico por crisis hipertensiva. Cuando le pregunto si estaba tomando la medicación me

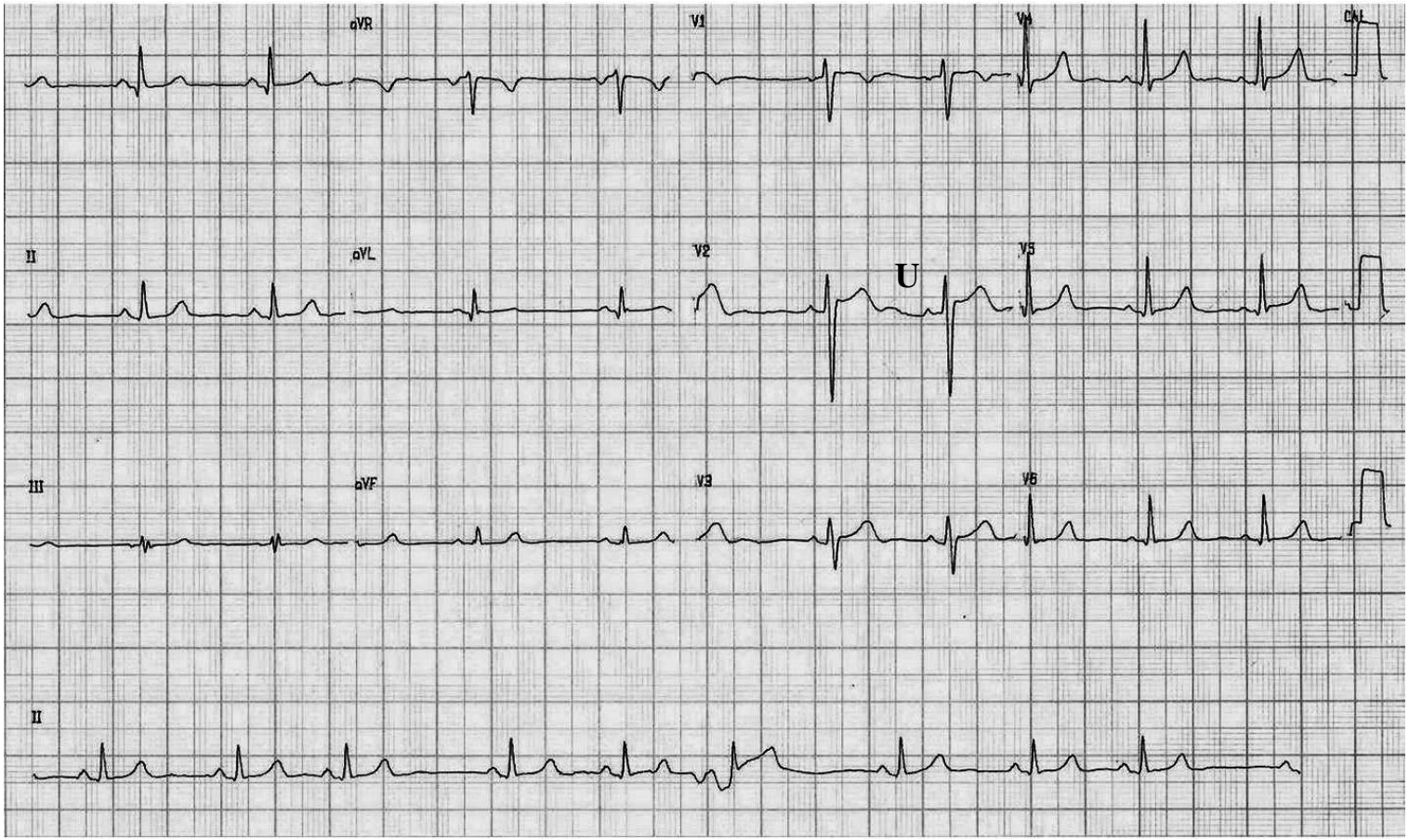
responde así: Dr ocurre que el fin de semana yo tenia una fiesta donde iría a tomar bebida alcohólica. Entonces paré 2 días la medicación. El pobre hombre era tan tan ignorante que pensaba que tomando alcohol jamás podría tomar su medicina para hipertensión. En resumen no estoy totalmente convencido que las drogas en los casos de consenso debamos hacer otra cosa. No es correcto salir de las reglas de un consenso apenas por feeling Porque podemos tener una victoria a lo Pirro es decir ganamos una batalla y perdemos la guerra.
Andrés Ricardo Pérez-Riera

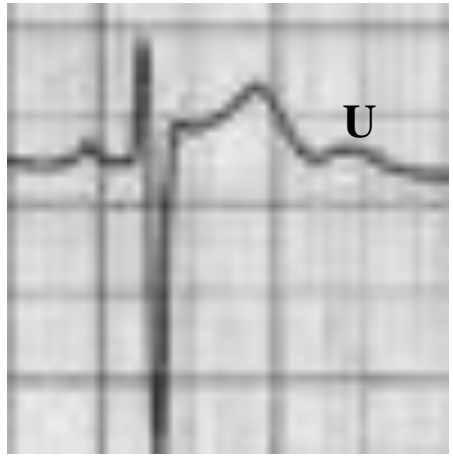
Final comments

Andrés Ricardo **Pérez-Riera, M.D. Ph.D.**
Design of Studies and Scientific Writing Laboratory in the ABC School of Medicine, Santo André, São Paulo, Brazil
https://ekgvcg.wordpress.com
Raimundo **Barbosa-Barros**, M.D. (nickname "Raymond, the Fox")
Chief of Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza, Ceará CE, Brazil
Luiz Carlos **de Abreu**, PhD
Visiting Scientist at Program in Molecular and Integrative Physiological Sciences (MIPS), Department of Environmental Health | Harvard T.H. Chan School of Public Health.



ECG at admission

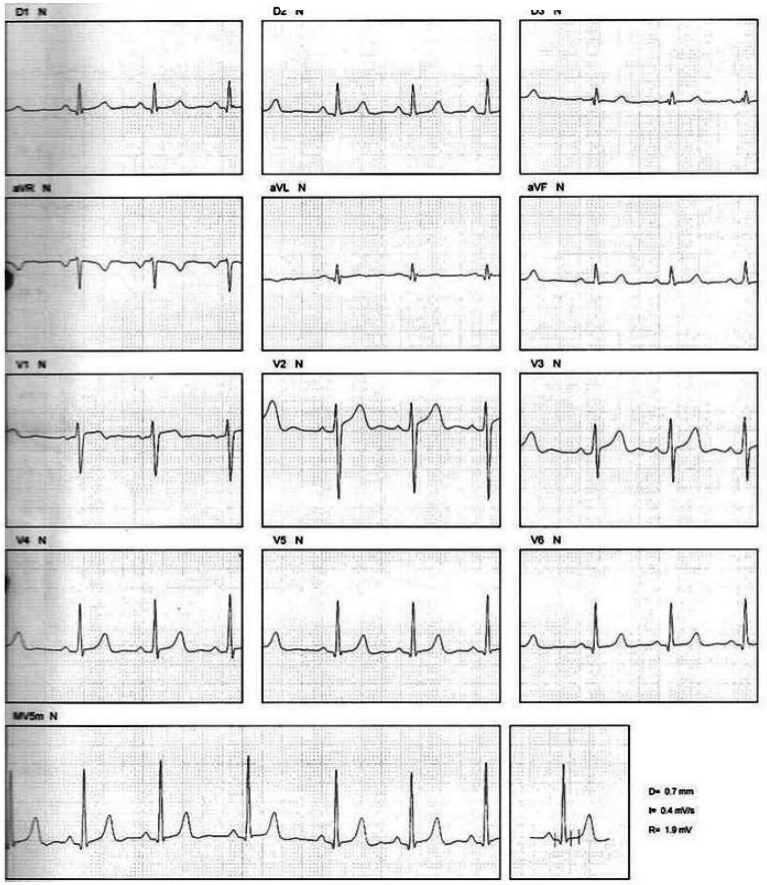




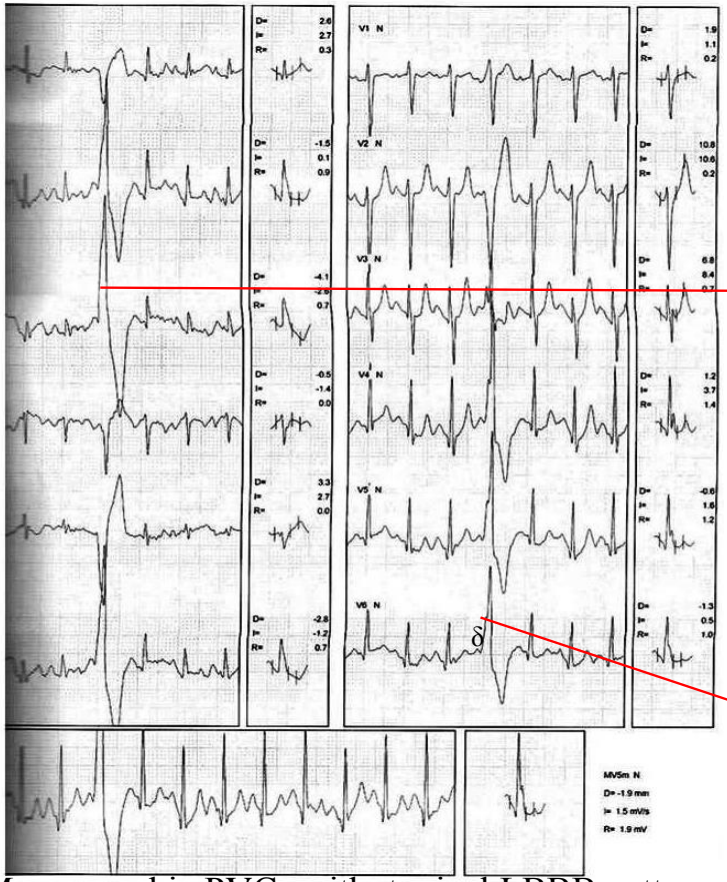
ECG diagnosis: Heart rate 60bpm. (from eight to sixteen years old the normal HR is equal to adults from 60 to 100bpm. Observation: baseline bradycardia tendency off drugs is observed in all carriers with CPVT (slow HR). Normal QT interval. Visible normal U wave in V2. U-wave alternans was observed in CPVT after ventricular pacing at 160 bpm; during the recovery phase after the exercise stress test, following a pause from sinus arrest and a change in T-wave was also noted. Precordial V_3-V_5 are the leads showing U alternans more clearly (**Aizawa 2006**).

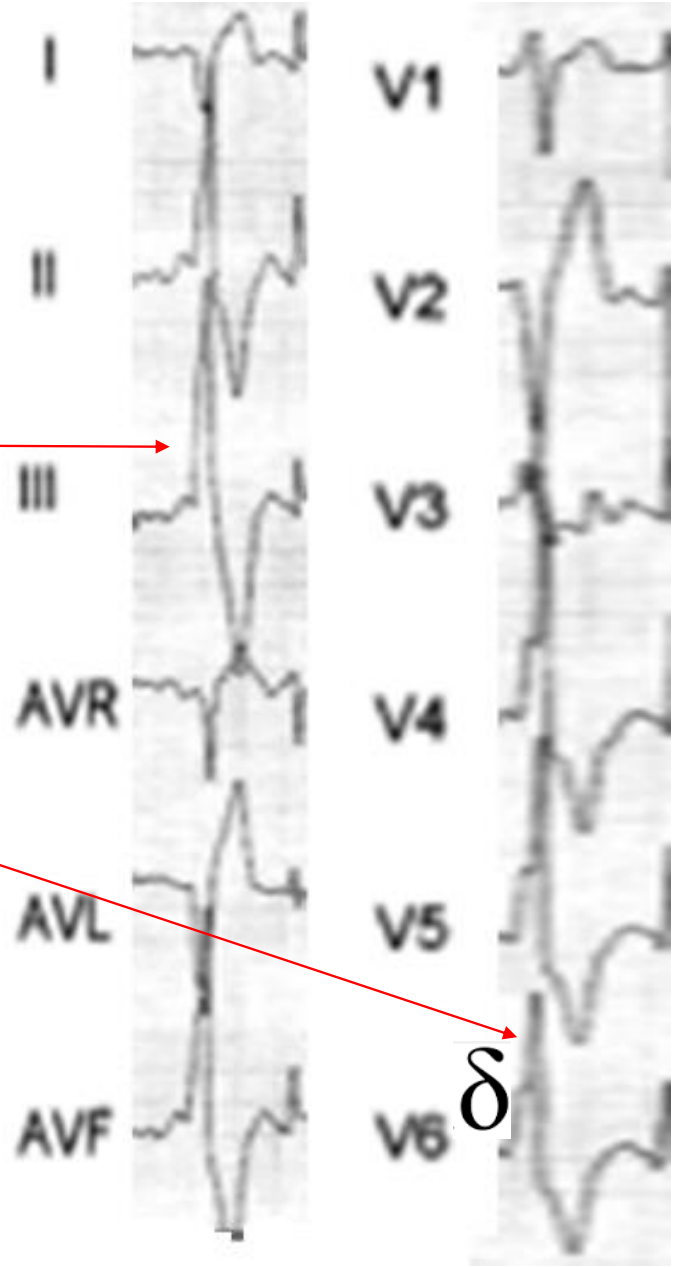
Treadmill Stress Testing

ECG at rest

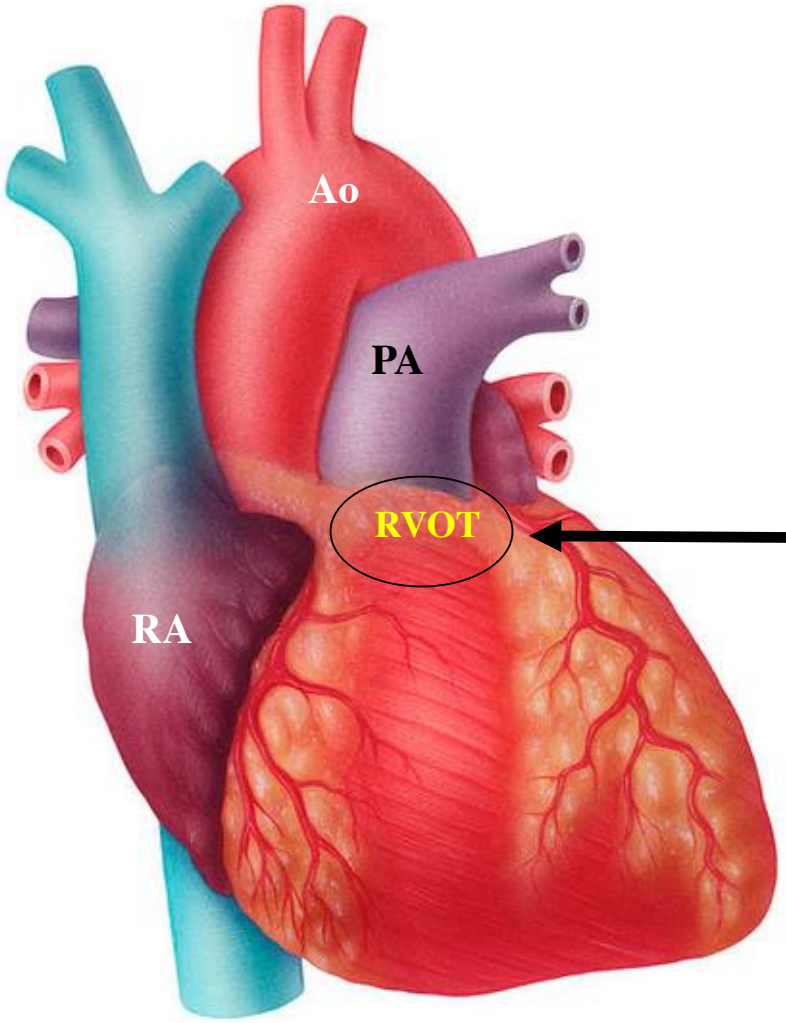


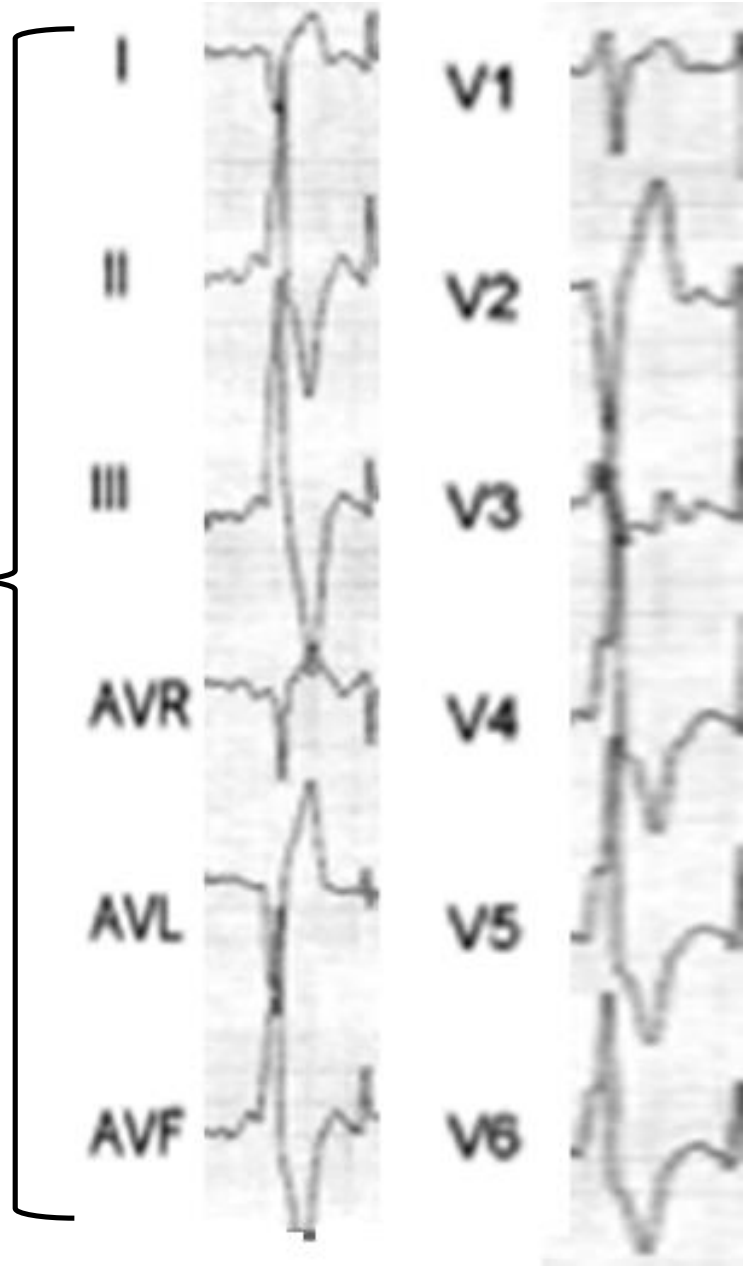
During initial effort





Monomorphic PVCs with typical LBBB pattern pseudo-delta (δ) waves (epicardial circuit) ≥34 ms), R-peak time ≥85 ms) (**Bazan 2006**) and inferior axis: Focus suggesting epicardial origin in posterior RVOT or right coronary cusp.

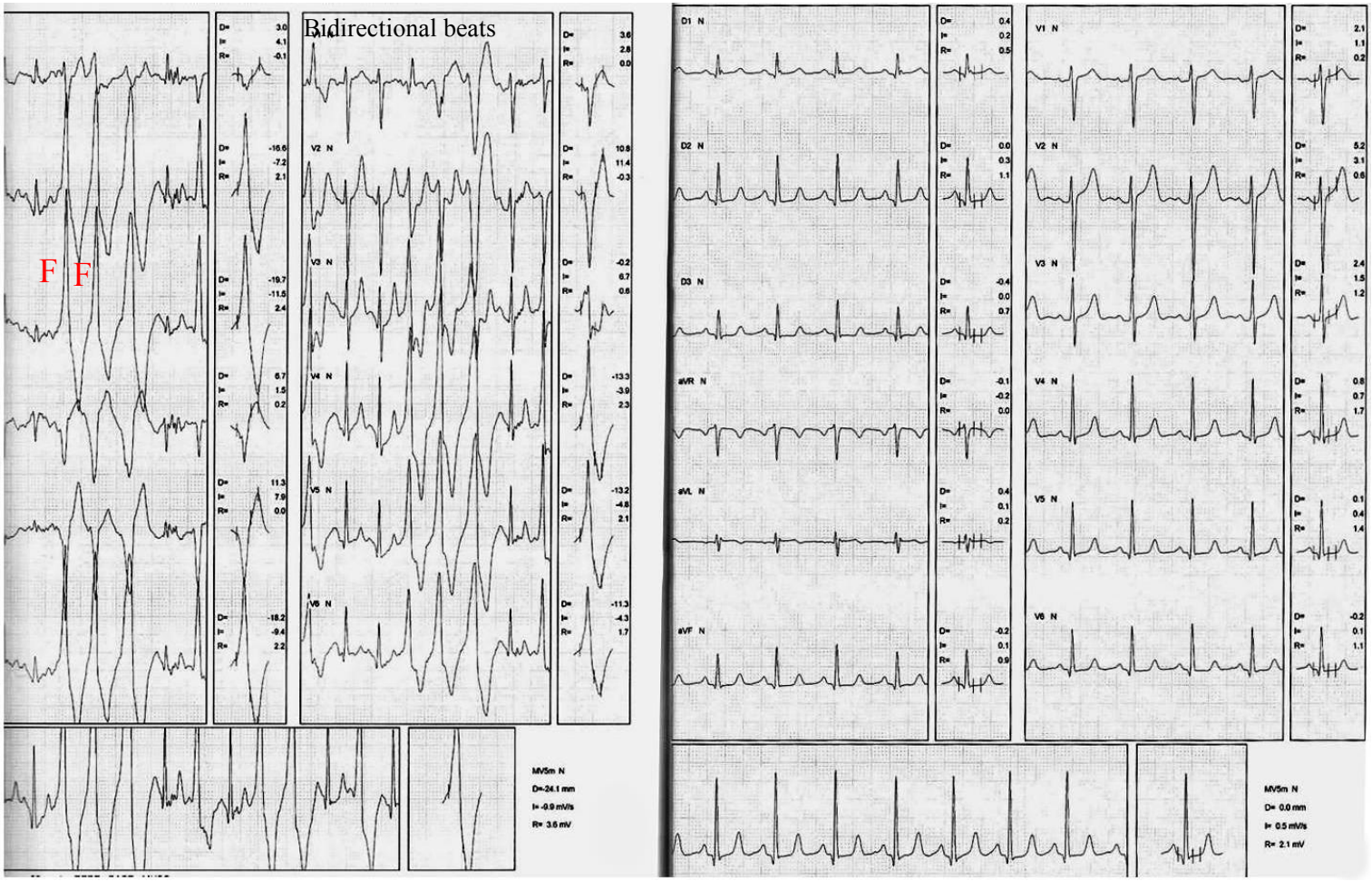




Monomorphic PVCs with morphology of CLBBB and inferior SÂQRS (positive QRS in II, III and aVF; and negative in aVR and aVL), which indicates that the focus of origin is in the RVOT (infundibulum). SÂQRS is to the right from > 90º.

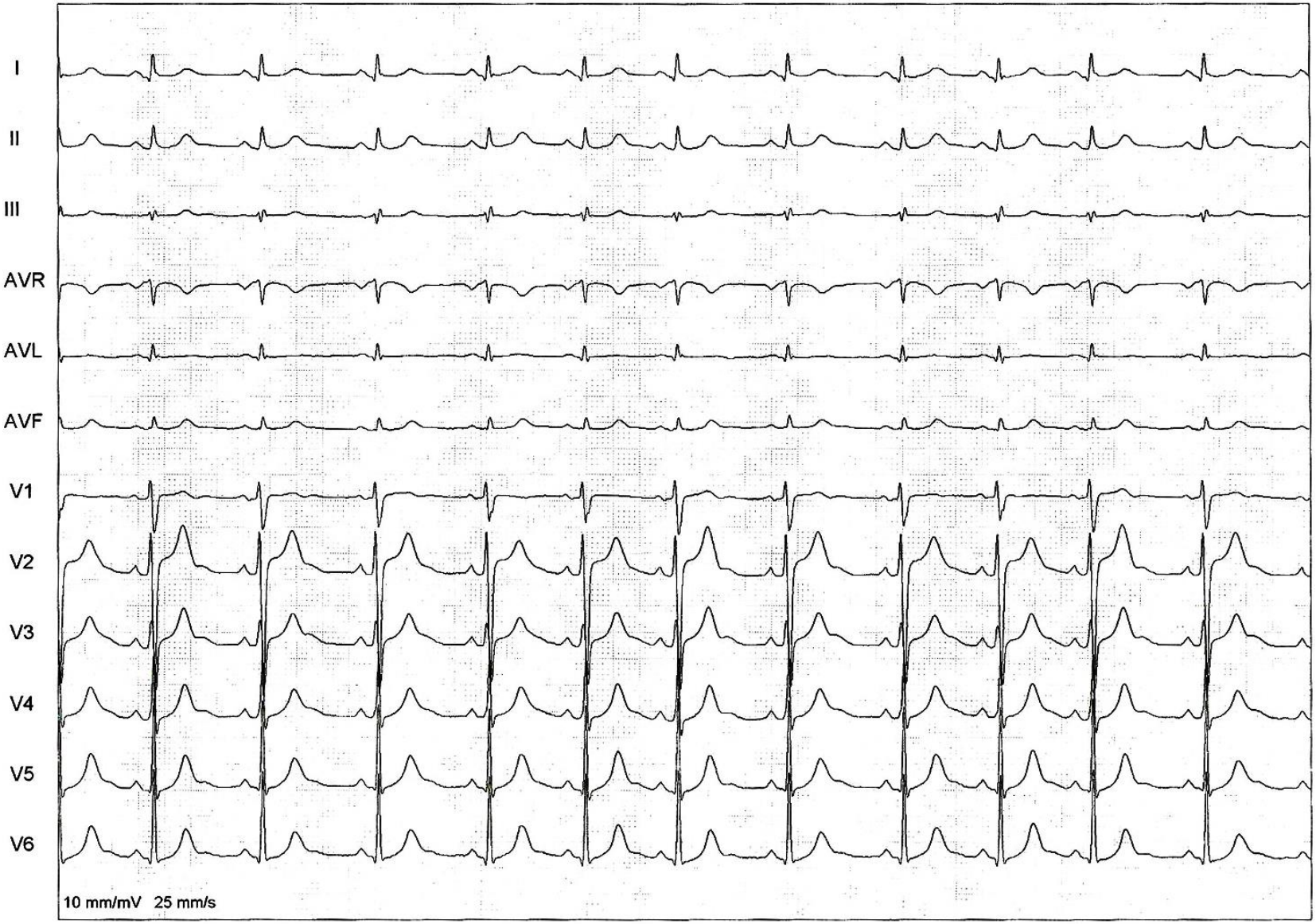
Treadmill Stress Testing

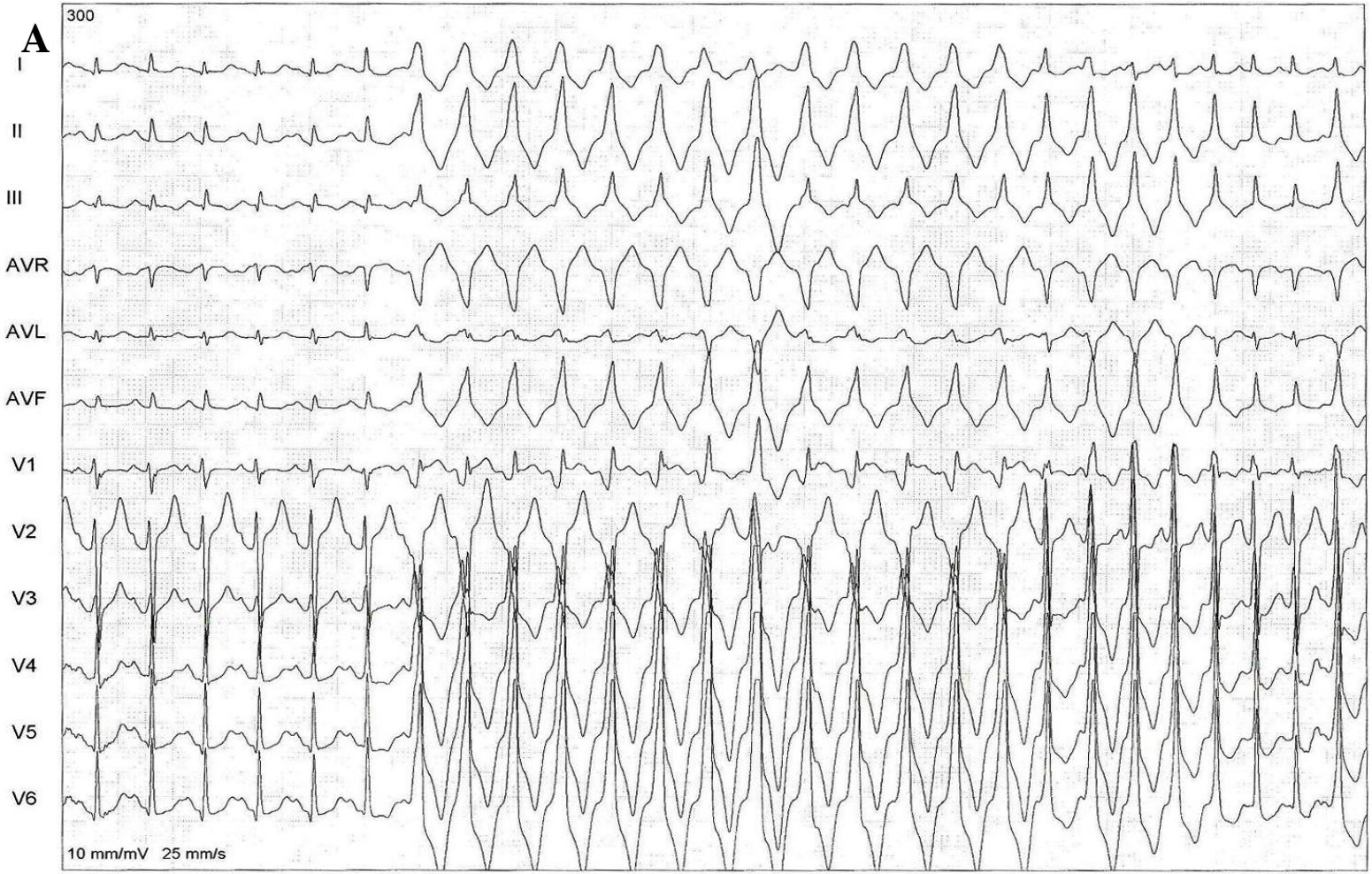
During maximal effort **After effort (recovery)**

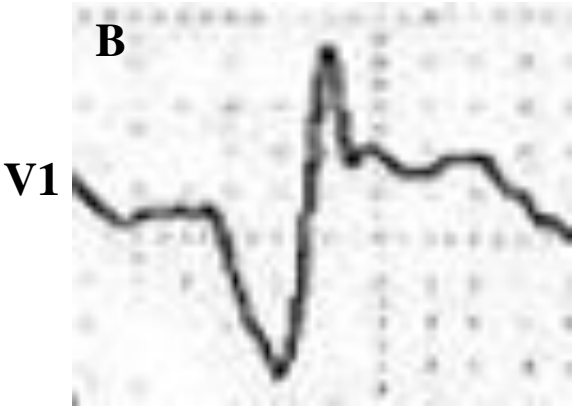


During maximal effort: Non-Sustained Monomorphic VT (≥3 consecutive ventricular depolarizations with a heart rate ≥ 100 bpm and with a duration < 30 seconds.) and LBBB pattern with inferior QRS axis. The first and second beats of VT are fusion beats (F). Normal ECG after effort. Also aleatory bidirectional beats.

ECG during invasive evaluation with infusion of isoproterenol

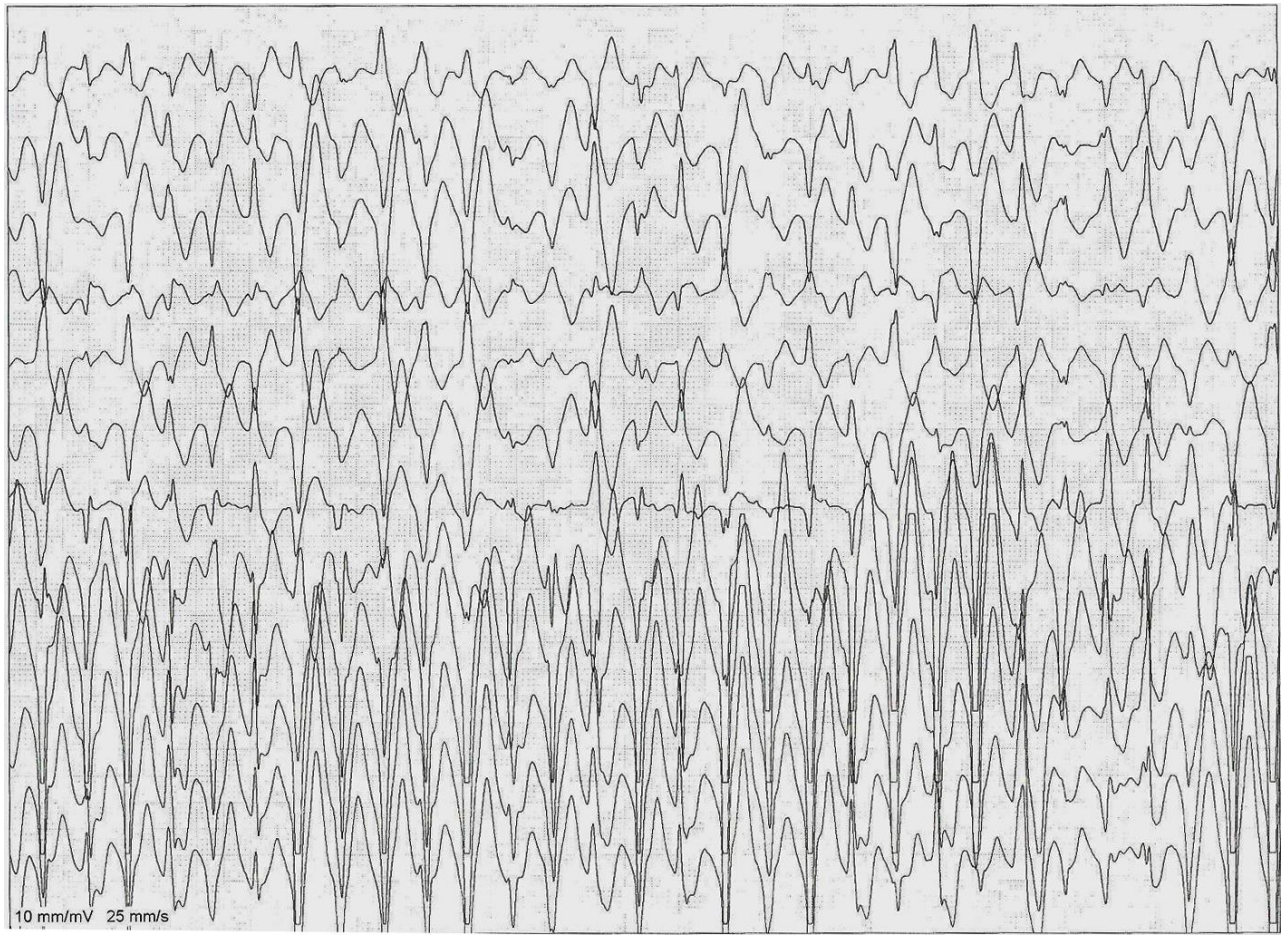






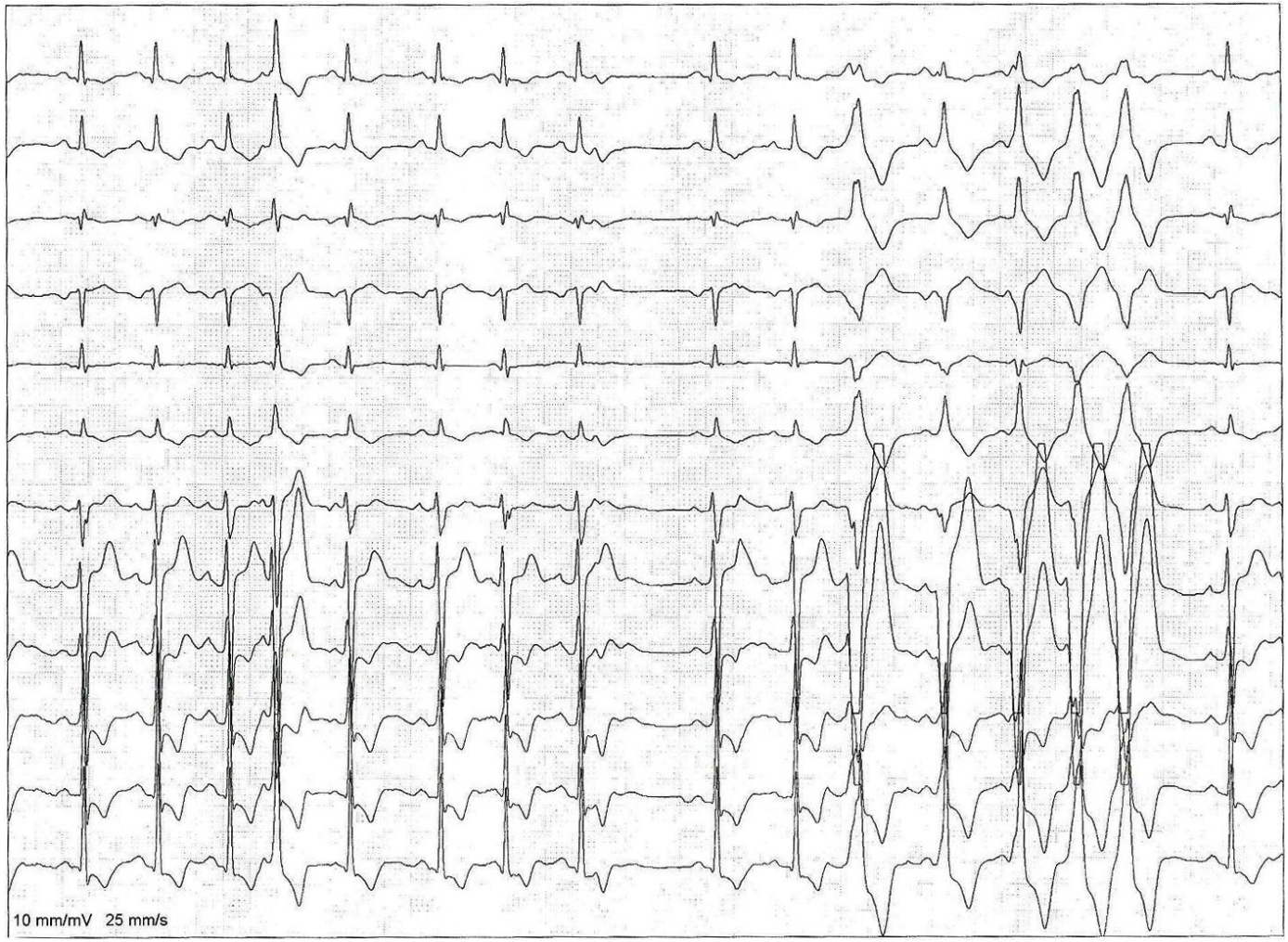
Sustained monomorphic VT with LBBB morphology and with inferior QRS axis (positive QRS in II, III and aVF). We observe several fusion beats. The focus is located on posterior RVOT, or in the right coronary cusp. Lead V1 is both a right-sided and anterior lead. Since the RVOT is anterior and leftward within the body, when the impulse begins in the RVOT and spreads away posteriorly and leftward, V1 should manifest a predominately negative complex. See the figure B.

Isoproterenol infusion



Typical bidirectional tachycardia: Sudden change of QRS morphology by changing of SÂQRS, successively from beat to beat. This suggested a single focus at the interventricular septum with two exit sites, depolarizing the right and left ventricle in an alternate fashion. Two sets of fairly constant and alternating VA intervals are recorded. This fact is consistent with two ventricular circuits used alternatively. It is postulated that the tachycardia is due to macro reentry involving the two fascicles of the left branch. Reentry may be a possible mechanism in some cases of bidirectional tachycardia.

Immediately after isoproterenol infusion



Runs of monomorphic non-sustained VT with frequent fusion beats with focus on RVOT (positive QRS complex in II, III and aVF).

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare clinically and genetically heterogeneous disease characterized by exercise, stress-induced or catecholamine infusion (adrenergically mediated ventricular tachyarryhtmia), with recurrent syncope of uncertain etiology after physical and emotional stress or sudden cardiac death (SCD), usually in the pediatric or juvenile age group. Sudden infant death syndrome and juvenile SCD exert a deep social impact, due to the young age of the victims and the unexpected occurrence of death (**Carturan 2007**). Despite its rare occurrence, CPVT is an important cause of stress and emotion induced syncope and SCD in children (**Massin 2003**). Familial occurrence has been noted in about 30% of cases. Inheritance may be autosomal dominant (AD) mutations of the cardiac Ryanodine receptor gene (RyR2). The causative genes have been mapped on chromosome 1 or recessive (AR) associated with homozygous mutations in the gene encoding the cardiac isoform of calsequestrin, CASQ2, calsequestrin gene CASQ2 mutations usually with high penetrance (**Laitinen 2004**). Due to its potential lethal outcome, exclusion or confirmation of CPVT in children with physical and emotional syncope is mandatory.

- The entity, together with Brugada syndrome (BrS), congenital long QT syndrome (LQTS), congenital short QT syndrome (SQTS) and familial atrial fibrillation (FAF) (**Roberts 2003**) are members of a group called electrical heart diseases, purely electrical heart diseases (**Farwell 2007**), primary electrical heart diseases (**Makita 2007**), primary electrical disorders (**Schulze-Bahr 2000**), ion channel diseases, channelopathies or "*sine material* sudden cardiac death (SCD) disease", because apparent structurally intact or normal hearts are observed.

Genetic analysis identifies two groups of patients:

1. **Sporadic or non-genotyped:** Patients with non-genotyped CPVT are predominantly women and become symptomatic later in life;
2. **With mutation:**
   - CPVT1**.** Cardiac RyR: Autonomic Dominant (AD) with locus on chromosome 1q42-43 60% of cases**.** Each child of an individual with autosomal dominant CPVT has a 50% chance of inheriting the pathogenic variant.
   - CPVT2. Calsequestrin, CASQ2, Autonomic Recessive (AR) (**Eldar 2003**) or AD (**Gray 2016**). CASQ2 mutations are more common than previously thought and produce a severe form of CPVT (**Postma 2002**). Locus on chromosome 1p11.13.3.
   - Miscellaneous
   - CPVT3: mutation on gene TRDN and with locus on chromosome 7p22-p14 and AD transmission
   - CPVT4: mutation on gene CALM1and with locus on chromosome 14q32.11 and AD transmission
   - CPVT1+CPVT3 in association Gomez-Hurtado et al discovered a novel CPVT mutation in the CALM3 gene that shares functional characteristics with CPVT-CALM1. A small proportion of A103V-CaM is sufficient to evoke arrhythmogenic Ca disturbances via ryanodine receptor 2 dysregulation, which explains the AD inheritance (**Gomez-Hurtado 2016**).

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Mutations in four genes – RYR2, CASQ2, TRDN, and CALM1 c are known to cause CPVT or related phenotypes of adrenergically induced life-threatening arrhythmias. The presence of other as-yet unidentified loci is postulated.

Cathecolamine- Dependent Polymorphic VT (CPVT)Catecholaminergic Polymorphic Ventricular Tachycardia				
Arrhythmia	Chromosome	Gene	Protein	Inheritance pattern
CPVT1 50-55%	1q42-43	RYR21	Cardiac RyR	AD
CPVT2 2-5%	1p11.13.3	CASQ2 Calsequestrin 2 gene	Calsequestrin	AR + AD (**Gray 2016**)
CPVT3<1%	7p22-p14; 6q22.31 (**Bhuiyan 2007**)	TRDN (**Roux-Buisson 2012**)	Triadin (**Rooryck 2015**)	AR
CPVT4 OMIM 61419	14q32.11 (**Nyegaard 2012**)	CALM1 camodulin		AD

AR: autosomal recessive inheritance; AD: autosomal dominant inheritance

AR -PVT: CASQ2- and TRDN-related CPVT are inherited in an AR manner. The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.

Minor abnormalities (rare and benign arrhythmias) have been reported in heterozygotes in anecdotal cases. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Prenatal testing for pregnancies at increased risk for some forms of CPVT is possible if the family-specific pathogenic variant(s) are known.

Catecholaminergic Polymorphic Ventricular Tachycardia Related Phenotypes

Evidence for further locus heterogeneity: Because causative allelic variants are identified in only approximately 55-65% of individuals with CPVT (**Tester 2011**), it is likely that other genes contribute to disease pathogenesis. A CPVT-like locus has been identified on chromosome 7p14-p22 but screening of candidate genes in the region has not revealed a disease-associated gene (**Bhuiyan 2007**).

"Ankirin B disease"ANKB. LQT4: In a single family presenting with mild QTc prolongation associated with atrial fibrillation, sinus bradycardia, sinus node dysfunction and polyphasic U waves a mutation in the ANK2 gene which codes for cardiac Ankyrin-B(Ank-B). It is a structural protein that anchors ion channels to the cell membrane, with pleiotropic effects on the cellular organization of the Na^+ pump, the sodium-calcium exchanger (often denoted Na^+/Ca^{2+} exchanger, NCX, or exchange protein). It is an antiporter membrane protein that removes calcium from cells. It uses the energy that is stored in the electrochemical gradient of Na^+ by allowing Na^+ to flow down its gradient across the sarcoplasmic membrane in exchange for the counter transport of Ca^{2+}. The NCX removes a single Ca^{2+} ion in exchange for the import of three Na^+ ions. The NCX is considered one of the most important cellular mechanisms for removing Ca^{2+}.The exchanger is usually found in the plasma membranes and the mitochondria and endoplasmic reticulum of excitable cells. ANK2 mutation had been diagnosed as having atypical or borderline LQTS.
A pathogenic variant in *ANKB*, the gene encoding ankyrin-B, was reported in a single individual with PVT similar to CPVT (**Mohler 2004**). The role of *ANKB* mutation in causing CPVT has yet to be elucidated. A group of patients characterized by a broad range of adrenergically mediated arrhythmias such as bidirectional VT were screened for ANK2, including patients who had CPVT without mutations on RYR2 or CASQ2.

KCNJ2 Disease: **Andersen Tawil syndrome (ATS)**
A possible phenotypic overlap may exist between CPVT and ATS. The latter defined as LQT7. Anderson-Tawil syndrome is a disorder that causes episodes of muscle weakness (periodic paralysis), changes in heart rhythm (arrhythmia), and developmental abnormalities. The most common changes affecting the heart are ventricular arrhythmia, and LQTS. Physical abnormalities associated with ATS typically affect the head, face, and limbs. These features often include a very small lower jaw (micrognathia), dental abnormalities, low-set ears, widely spaced eyes, and unusual curving of the fingers or toes (clinodactyly). Some affected people also have short stature and scoliosis. Two types of ATS are distinguished by their genetic causes. Type 1, which accounts for about 60% of all cases of the disorder, is caused by mutations in the *KCNJ2* gene. The remaining 40% of cases are designated as type 2; the cause of these cases is unknown. Some authors have claimed that *KCNJ2* variants responsible for ATS may also cause CPVT; however, ATS is a distinct disorder. A large genomic deletion in RYR2, which leads to extended clinical phenotypes (eg, SA node and AVN dysfunction, AF, atrial standstill, and DCM). These features have not previously been linked to RYR2 (**Bhuiyan 2007**).

Catecholaminergic Polymorphic Ventricular Tachycardia Related Phenotypes

Variant	Chromosomal Locus	Gene	Inheritance	Phenotype
LQT4	4q25-26	ANK2	AD	IVF, Atypical QT prolongation, stress induced bidirectional VT
ATS	17q23.1-q24-2	KCNJ2	AD	U waves, bidirectional VT, periodic paralysis, facial dimorphisms
CPVT-DCM	1q 42-43	RYR2	AD	Stress-induced VT, sinus node dysfunction, dilated cardiomyopathy

AR: autosomal recessive inheritance AD: autosomal dominant inheritance; ATS: Andersen Tawil Syndrome ; DCM: dilated cardiomyopathy ; IVF: idiopathic ventricular fibrillation; VT: ventricular tachycardia.

Clinical characteristics

CPVT is characterized by episodic syncope occurring during exercise or acute emotion in individuals without structural heart diseases. The onset of arrhythmias during exercise occurs at a heart rate threshold of 100-120bpm and the arrhythmias tend to worsen with increasing workload. Arrhythmias may be well tolerated, with only mild symptoms such as dizziness or lypothymia. The underlying cause of these episodes is the onset of fast bidirectional or polymorphic VT. Spontaneous recovery occurs when these arrhythmias self-terminate. VT may degenerate into VF and cause SCD if cardiopulmonary resuscitation is not readily available. SCD may be the first manifestation of the disease.

Two clinical studies (**Leenhardt 1995, Priori 2002**) have contributed to the understanding of the natural history of CPVT. The main clinical manifestation of CPVT is episodic syncope occurring during exercise or acute emotion. The underlying cause of these episodes is the onset of fast VT (bidirectional or polymorphic). Spontaneous recovery occurs when these arrhythmias self-terminate. In other instances, ventricular tachycardia may degenerate into VF and cause SCD if cardiopulmonary resuscitation is not readily available. SCD may be the first manifestation. As there is no structural abnormality of the myocardium, several individuals have tolerated the arrhythmias rather well, with only mild symptoms such as dizziness or lypothymia. If such symptoms reproducibly recur during exercise, further clinical investigations for CPVT may be indicated. CPVT is a cause of "idiopathic" VF in previously asymptomatic individuals (no history of syncope or dizziness) who die suddenly during exercise or while experiencing acute emotions. Growing evidence shows that sudden cardiac death can be the first manifestation of CPVT caused by mutation of *RYR2* (***Priori 2002, Krahn 2005***).

The mean age of onset of CPVT manifestations is between age 7 and 12 years (**Leenhardt 1995, Priori; 2002, Postma 2005**); onset as late as the fourth decade of life has been reported.

Instances of sudden infant death syndrome (SIDS) have been associated with mutation of *RYR2* (**Tester et al 2007**).

CPVT1 and strategic genotyping of RyR2 should be considered when LQT1 is excluded in the pathogenesis of a swimming-triggered arrhythmia syndrome (**Choi 2004**). Family history of SCD in relatives < 40 years is present in ≈ 30% of probands with CPVT (**Priori 2002**).

Genotype-Phenotype Correlations

Available evidence suggests that the clinical features of *CASQ2*- and *RYR2*-related CPVT are virtually identical. (**Lahat 2001**) reported a mild QT interval prolongation; however, this was not confirmed in subsequent reports (**Postma 2002**). *CASQ2* pathogenic variants appear more severe and more resistant to β-blockers At present no data support a role for genotype in risk stratification and management.

Individuals with polymorphic VT without a "stable" QRS vector alternans are more likely to have pathogenic variants in *CASQ2*.

(**Priori 2002; Lehnart 2004**) reported genotype-phenotype correlations by comparing the clinical characteristics of affected individuals with and without *RYR2* pathogenic variants. These data show the following:

The natural history of the disease does not appear to differ when affected individuals with and without *RYR2*pathogenic variants are compared. The average age of onset of the disease in both study groups (i.e., age of the first syncope) is 7 to 12 years

The mutation-specific clinical course of CPVT was analyzed by (**Lehnart 2004**), who did not find a significant difference in mortality rates or pattern of arrhythmias among a small cohort of individuals with the *RYR2* pathogenic variants p.Pro2328Ser, p.Gln4201Arg, and p.Val4653Phe.

Only two *CALM1* pathogenic variants have been described: in a large family with stress-induced SCD and arrhythmias and in a simplex case with suspected CPVT, arrhythmias, and *RYR2* screening that did not identify a pathogenic variant (**Nyegaard 2012**). No clear bi-directional pattern of ventricular arrhythmias as described in typical CPVT (**Leenhardt 1995**) was shown; thus, the clinical phenotype of individuals with *CALM1* pathogenic variants may be slightly different from that of typical CPVT. This observation awaits confirmation.

Penetrance

The mean penetrance of *RYR2* pathogenic variants is≈ 83%. Therefore, asymptomatic individuals with *RYR2*-related CPVT are a minority.

Anticipation

Anticipation has not been reported.

Prevalence

The true prevalence of CPVT has an estimated prevalence of 1:10,000 (**Paludan-Müller 2016**).

The high prevalence of simplex cases (i.e., single occurrences in a family) and lethality at a young age suggest that the overall prevalence of CPVT is significantly lower than that of other inherited arrhythmogenic disorders such as LQTS (1:7,000-1:5,000).

Genetically Related (Allelic) Disorders

Although some have suggested that ARVD/C may be caused by *RYR2* mutation in a few cases (designated ARVC2) that present with mild or "concealed" right ventricular myocardium abnormalities (**Tiso 2001**), these observations have not been confirmed by others. However, some *RYR2* pathogenic allelic variants have been associated with cardiomyopathy's and left ventricular non-compaction (LVNC) and appear to have different pathophysiologic mechanisms (**Tang2012; Ohno 2014; Roston2016**). These authors identifies a potentially lethal overlapping syndrome of LVNC and atypical CPVT related to a novel RYR2 variant. Structural and functional studies suggest that this is a loss-of-function mutation, which exerts a dominant-negative effect on wild type RyR2. The lack of systematic assessments in large populations makes it difficult to quantify the clinical relevance of these findings. No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *TRDN* or *CASQ2*.

CALM1

- *CALM1* promoter variants have been associated with osteoarthritis in the Japanese population (**Mototani 2005**).
- A *CALM1* pathogenic variant was also reported in a case of ventricular arrhythmias associated with QT prolongation, epilepsy, and neurodevelopmental disorders (**Crotti 2013**). This phenotype is compatible with the wide expression pattern of *CALM1* and the finding suggests that mutation of *CALM1* causes an atypical form of CPVT.

Differential Diagnosis

Given the absence of structural cardiac abnormalities, individuals presenting with cardiac arrest could be misclassified as having "idiopathic VF" (**Priori 2001**). Therefore, if a careful analysis of the factors triggering VF in an otherwise healthy individual indicates a possible causative role for adrenergic stimuli (e.g., cardiac arrest occurring in the setting of acute stresses such as fear or anger), CPVT should be considered in the differential diagnosis. Cardiac evaluation (including an exercise stress test to unmask CPVT arrhythmias) of relatives of persons dying a SCD may reveal the underlying disease and identify asymptomatic family members at risk for cardiac events (**Tan 2005**). The yield of genetic testing in relatives is yet to be established. However, it is justified to consider the diagnosis of CPVT (and to consider genetic testing) in cases of SCD or aborted cardiac arrest occurring during acute stress. The presence/absence of structural abnormalities of the right ventricle (right ventricle enlargement, fibro-fatty infiltrations) must be evaluated in all individuals with *RYR2* pathogenic variants in order to exclude the presence of a rare variant and “atypical” form of ARVDC2 allelic to*RYR2*-related CPVT. ARVC presents with structural abnormalities (dilatation, increased fibrosis/fat, micro-aneurysms) of the RV. Typical ARVC is caused by mutation of genes that code for desmosomal proteins. *RYR2* pathogenic variants have been found in few (<5) families labeled as ARVC. However, in all cases the structural abnormalities were atypical and very mild.

This raises the unresolved question of whether *RYR2*-ARVC is a real clinical entity or an incorrect classification of some families with CPVT who

have unspecific abnormalities of the RV. Short-coupled VT (SC-TdP) is a clinical entity presenting with life-threatening PVTs resembling in part the pattern of arrhythmias observed in individuals with CPVT. SC-TdP presents with PVT occurring without structural heart disease and in the absence of any overt baseline ECG abnormality. However, the onset of SC-TdP is not clearly related to adrenergic stimuli (exercise or emotion) and is not associated with the typical bidirectional pattern of CPVT-related tachycardia. Distinguishing between the two disorders is important as there is no known effective therapy for SC-TdP, whereas CPVT usually responds to β-blocking agents.

Exercise-related syncope is also typically found in the LQT1. Since incomplete penetrance is possible in LQT1, some individuals may have a normal QT interval and may therefore appear to have the typical CPVT clinical presentation (exercise-related syncope and normal ECG). However, individuals with LQT1 do not usually show any inducible arrhythmia during graded exercise (exercise stress test). The initial description of CPVT by Philippe Coumel included cases with borderline or mildly prolonged QT interval. For this reason it has been suggested that an overlap phenotype (LQTS-CPVT) is possible. This hypothesis has not been thoroughly investigated.

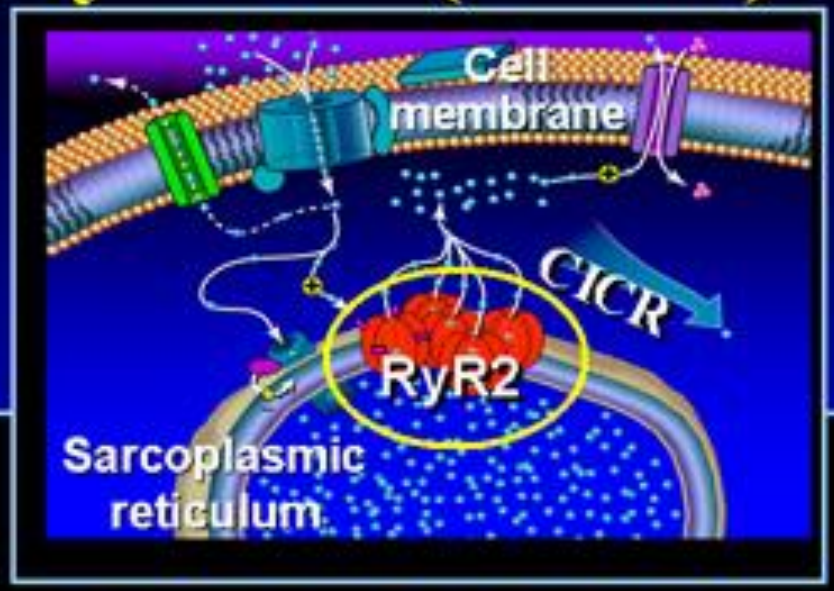
A possible parallelism between CPVT and Andersen-Tawil syndrome (ATS), an inherited arrhythmogenic disorder caused by mutation of *KCNJ2*, has been reported. ATS is characterized by cardiac (QT prolongation, prominent U waves) and extra-cardiac features (distinctive facial features, periodic paralysis). The present authors and others (**Postma 2006; Tester 2006**) have observed that some individuals with ATS may develop bidirectional VT similar to that of CPVT. However, ATS (LQT7) is to be considered as a distinct disorder with manifestations that may overlap with CVPT in rare instances. In ATS the presence of extracardiac manifestations, the low or absent risk of SCD, and the lack of a direct relationship of arrhythmias to adrenergic activation distinguish it from CPVT.

Ryanodine receptor (RyR) is the Ca^{2+} -induced Ca^{2+} release channel in cells. RyR1 and RyR2 are its isoforms expressed in the skeletal and cardiac muscles, respectively. Their missense mutations, which are clustered in three regions that correspond to each other, cause hereditary disorders such as malignant hyperthermia and central core disease in the skeletal muscle and CPVT, a form of ARVC (ARVD2), DCM, SA node and AV node dysfunction, AF, and atrial standstill in the cardiac muscle (**Bhuiyan 2007; Ogawa 2007**), usually with high penetrance.

The R176Q mutation in RyR2 predisposes the heart to catecholamine-induced oscillatory calcium-release events that trigger a calcium-dependent VT (**Kannankeril 2006**). Research points out that patients carriers of familial CPVT with AD inheritance pattern present a missense mutation of the SR in the CRC channel in type 2 ryanodine receptor (RyR2) where three mutations were verified: (P2328S, Q4201R, V4653F). This entity of early clinical onset and mean mortality rate of 30% up to 30 years old, is characterized by bursts of bidirectional VT and/or PVT related to exercise (catecholamine-dependent), with no evidence of structural heart disease.

Catecholaminergic idiopathic ventricular fibrillation (IVF) is occasionally observed.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

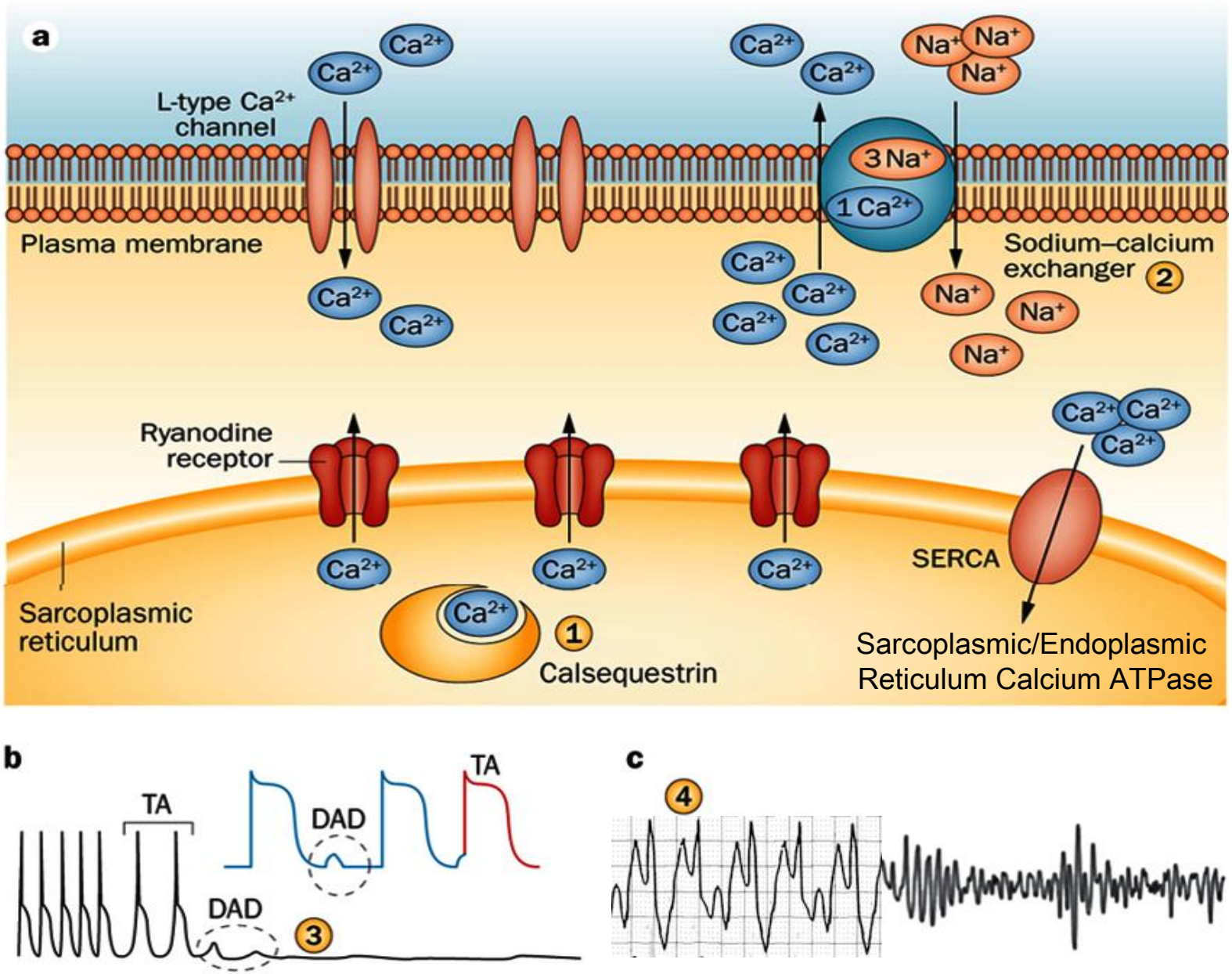


Molecular

RyR2 (CPVT1, Ch 1q42.1-q43)

Mutations in *RyR2* cause 2/3 of CPVT

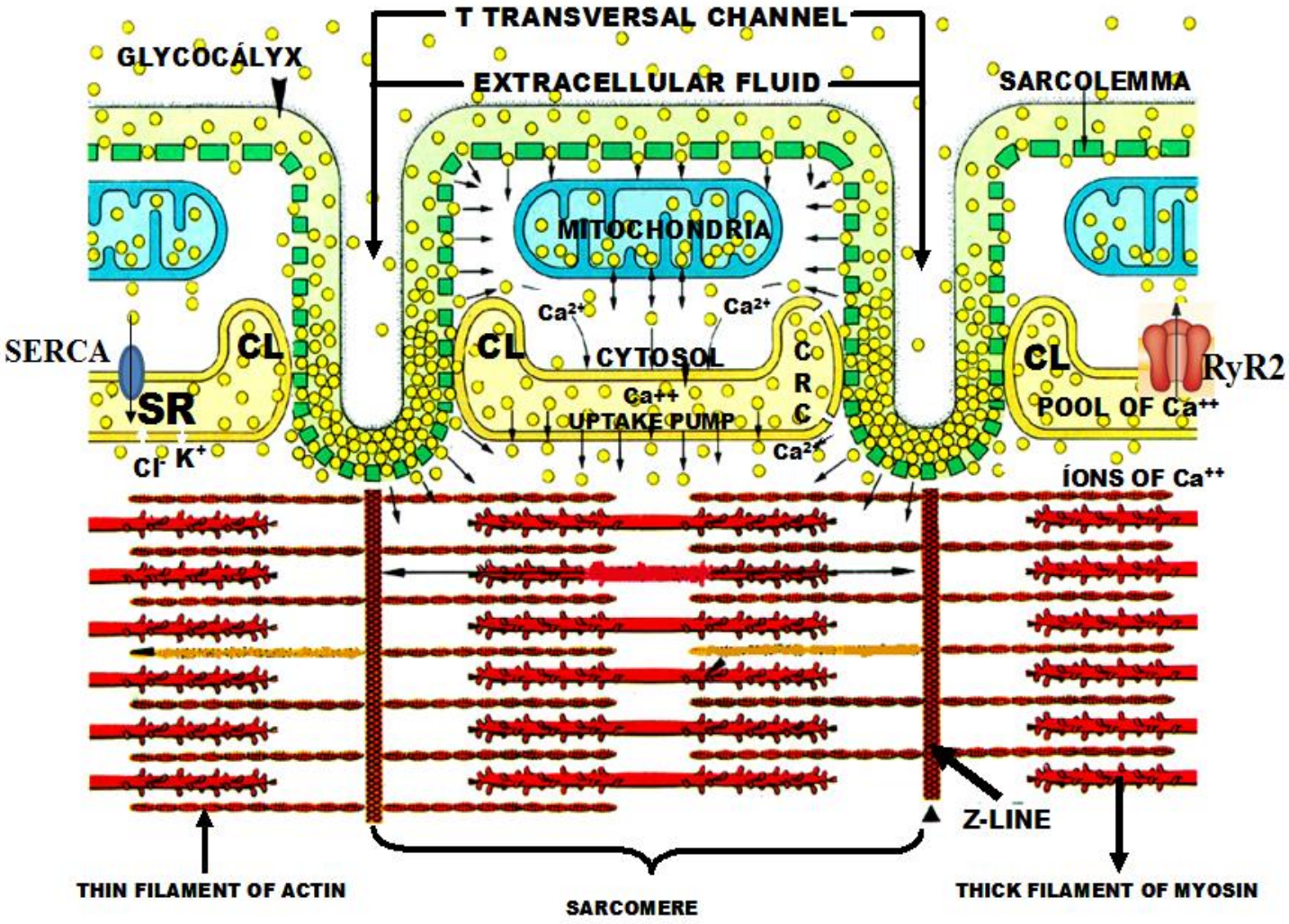
Priori et al. *Circulation* 2002;106(1):1479-1487



a It is a calcium-binding protein of the sarcoplasmic reticulum. The protein helps hold calcium in the cisterna of the sarcoplasmic reticulum after a muscle contraction, even though the concentration of Ca^{2+} in the sarcoplasmic reticulum is much higher than in the cytosol A mutation in calsequestrin (1) causes a reduced threshold for calcium release and store overload-induced Ca^{2+} release (SOICR), which leads to calcium overload in the cytosol. Activation of the Na^{+}/Ca^{2+} exchanger, NCX (2) generates delayed after depolarization (DADs) (3).

b A schematic representation and an actual recording from a cardiac cell isolated from a Casq2 knock-out mouse. DADs (blue) and triggered activity TA (red) are elicited by isoproterenol infusion.

c These cellular abnormalities are the cause of the bidirectional VT and polymorphic VT observed in thethe CPVT(4).



SR Sarcoplasmic reticulum ; **RyR2** (**RyRs**) Rianodine Receptor ;
SERCA Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase

RyR2 (**RyRs**) Ryanodine receptors mediate the release of calcium ions from the sarcoplasmic reticulum an essential step in muscle contraction. Ryanodine receptors are very close to mitochondria and Ca^{2+} release from RyR has been shown to regulate ATP production in heart. stimulated to transport Ca^{2+} into the cytosol by recognizing Ca^{2+} on its *cytosolic side*, thus establishing a positive feedback mechanism; a small amount of Ca^{2+} in the cytosol near the receptor will cause it to release even more Ca^{2+} (calcium-induced calcium release/CICR).

SERCA(Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase**s**) transfers Ca^{2+} from the cytosol of the cell to the lumen of the sarcoplasmatic reticulum
(SR) at the expense of ATP hydrolysis during muscle relaxation.

Calsequestrin is a calcium-binding protein of the **SR**. The protein helps hold calcium in the cisterna of the **SR** after a muscle contraction, even though the concentration of Ca^{2+} in the **SR** is much higher than in the cytosol. It also helps the **SR** store an extraordinarily high amount of Ca^{2+}. Each molecule of calsequestrin can bind 18 to 50 Ca^{2+} ions.

Intracellular calcium channels of the Sarcoplasmic Reticulum (SR)

I. Ca^{2+} release channel, Ryanodine receptor, hyperphosphorylated by protein kinase A (PKA) from the intracellular sarcoplasmic reticulum or CRC "Calcium Release Channel".

II. Ca^{2+}-ATPase uptake pump or Ca^{2+} Mg^{2+} ATPase (Sarcoplasmic Ca^{2+} (ATPase) reticulum SERCA).

III. IP3 receptor, Inositol triphosphate or IP3: inositol 1,4,5-trisphosphate (IP3) receptor channel.

The SR is an intracellular structure that holds a key role in muscular contraction and relaxation by its capacity of fast release and uptake of myoplasm from the Ca^{2+} ion, by having only in the junctions with the T system of the plasmatic membrane, the so-called Ca^{2+} release channel, Calcium Release Channel (CRC) or Ryanodine receptor. This channel, intracytoplasmatically located in the SR membrane, is very close to the sarcolemmal channels $I_{Ca\text{-}L}$ type, and like this, is voltage and time-dependent. Each $I_{Ca\text{-}L}$ type channel controls a group between 4 and 10 ryanodine receptor channels.

Each channel is a large and complex protein of 30 S, formed by four polypeptidic subunits in firm association of Mr ~560.000 with quatrefoil or tetrameric morphology that contours a single hydrophilic, cation-selective pore, with conductance for divalent cations from 100 to 150 pS with 50 mM Ca^{2+} and for monovalent cations of ~750 pS with 250 mM K^{+} that is found in the SR membrane and plays its role by releasing the cation of the SR lumen into the cytosol (efflux). It may be blocked by Ryanodine, a toxin derived from an alkaloid plant with nanomolar affinity, and for this reason it is known as ryanodine receptor.

The substances that stimulate this channel improve contractility, and those that block, worsen it. It seems to be the most important channel in heart failure, since a dramatic increase has been observed in its phosphorylation (hyperphosphorylation) in patients with terminal heart failure, what would provide another basis for using β-blockers in this condition.

Electrocardiographic features in Catecholaminergic Polymorphic Ventricular Tachycardia

I. **Heart Rate (HR):** baseline bradycardia tendency off drugs is observed in all carriers (slow HR);

II. **Rhythm:** Sinus rhythm is the rule. Abnormalities in sinoatrial node function, as well as atrioventricular nodal function, could produce atrial fibrillation, atrial flutter and atrial standstill (sick sinus syndrome).

III. **QTc interval:** normal at resting ECG (**Postma 2005**). See proposed algorithm diagnostic scheme for PVT or VF in structurally normal hearts based initially in QT interval duration.

IV. **U-wave alternans:** U-wave alternans was observed in the following clinical circumstances: After ventricular pacing at 160 bpm; during the recovery phase after the exercise stress test, following a pause from sinus arrest and a change in T-wave was also noted. Precordial V_3-V_5 are the leads showing alternans more clearly (**Aizawa 2006**).

V. **Arrhythmias**

A. **Supraventricular arrhythmias** The atrium could be affected by the channelopaties, and arrhythmias in these chambers may cause syncope. Atrial fibrillation, atrial flutter, atrial standstill, and sick sinus syndrome are occasionally present (**Fazelifar 2007**).

B. **Ventricular arrhythmias;** Ventricular arrhythmias elicited exclusively by exercise or adrenergic stress. Typically induced by isoproterenol infusion.

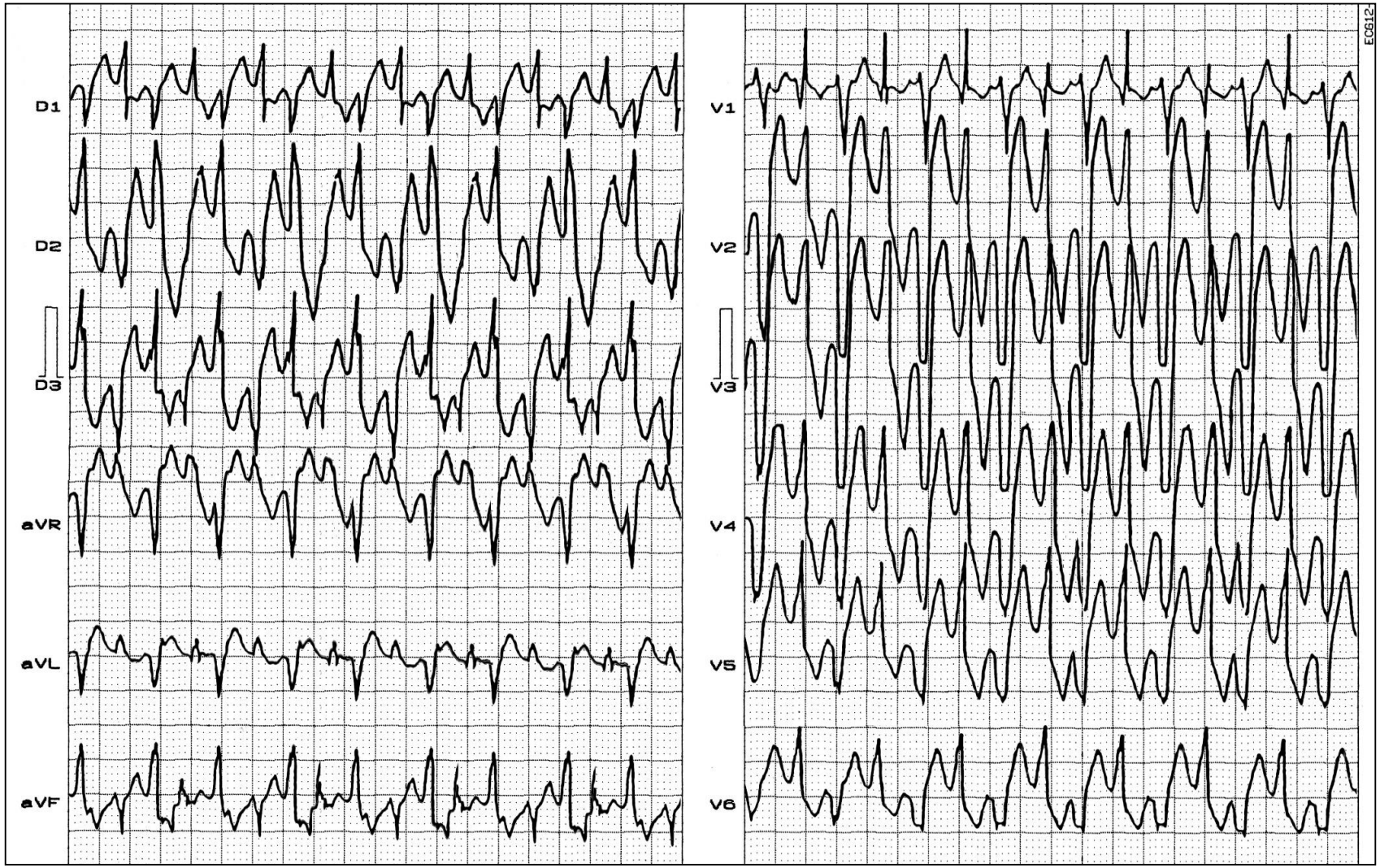
- **Premature Ventricular Contractions (PVCs):** Calcium channel antagonist, verapamil, can suppress PVCs and non-sustained VT salvoes in CPVT caused by RyR2 mutations. Modifying the abnormal calcium handling by calcium antagonists might have therapeutic value (**Swan 2005**). Calcium antagonists partially suppressed CPVT in AD cases.
- **Polymorphic ventricular tachycardia (PVT)** occurs during physical exercise or emotional stress. Mean heart rate during CPVT was 192 (30) beats/min. Most cases are non-sustained VT (72%), but 21% are sustained VT and 7% are associated with VF.
- PVT and bidirectional VT in association are observed in 21% of cases in the pediatric group. There is 100% inducement of CPVT by exercise, 75% by catecholamine infusion, and none by EPS. No late potentials is recorded. Onset is in the RVOT in more than 50% of the cases (**Sumitomo 2003**). The His-Purkinje system is an important source of focal arrhythmias in CPVT (**Cerrone 2007**).
- **Bidirectional ventricular tachycardia** is a more typical feature Bidirectional VT is regular VT with pattern of CRBBB, alternating QRS axis, determining the presence of two morphologies of QRS, secondary to change in axis (SÂQRS) in the frontal plane, from beat to beat, with differences of approximately 180º. One beat presents SÂQRS between –60º and –90º and the following, approximately +120 to +130º. The event may be both ventricular and supraventricular. The help of the His bundle electrogram is necessary to determine this.

Electrocardiographic characterization of bidirectional ventricular tachycardia

- Regular VT
- Heart Rate between 140 bpm and 200 bpm
- CRBBB Pattern
- Sudden change of QRS morphology by changing of SÂQRS, successively from beat to beat
- SÂQRS in the frontal plane with differences close to 180º: one beat presents ÂQRS between –60º and -90º (CRBBB + LAFB) and the following between +120º to +130º (CRBBB + LPFB).
- Occasionally alternating RBBB and LBBB morphologies. The origin of the tachycardia is located near the His bundle bifurcation. This suggested a single focus at the interventricular septum with two exit sites, depolarizing the right and left ventricle in an alternate fashion (**Dorfman 2006**). Two sets of fairly constant and alternating VA intervals are recorded. This fact is consistent with two ventricular circuits used alternatively. It is postulated that the tachycardia is due to macroreentry involving the two fascicles of the left bundle branch. Reentry may be a possible mechanism in some cases of bidirectional VT.

Possible etiologies: low prevalence (rare). Acquired forms are mainly observed in elderly patients. The clinical setting may be:

- Digitalis toxicity or digitalis poisoning: it is the main clinical cause (**Kummer 2006**);
- Digoxin and amiodarone treatment for rapid AF (**Lien 2004**);
- Herbal aconite poisoning (**Smith 2005**). Aconitine and its related alkaloids are known cardiotoxins with no therapeutic role in modern western medicine. The rootstocks of Aconitum plants, which contain aconite alkaloids, have been common components of Chinese herbal recipes. All patients developed symptoms of aconite toxicity within 2 h of herb ingestion. Most developed tachyarrhythmias, including VT and VF. A strict surveillance of herbal substances with low safety margins is necessary.
- Severe myocardial disease (advanced cardiomyopathy)
- Cardiac metastasis (**Dorfman 2006**).
- Without structural heart diseases:
  - ✓ CPVT
  - ✓ ATS mutations in KCNJ2, which encodes the α subunit of the potassium channel Kir2.1. The mutation is present in ≈60% of cases.



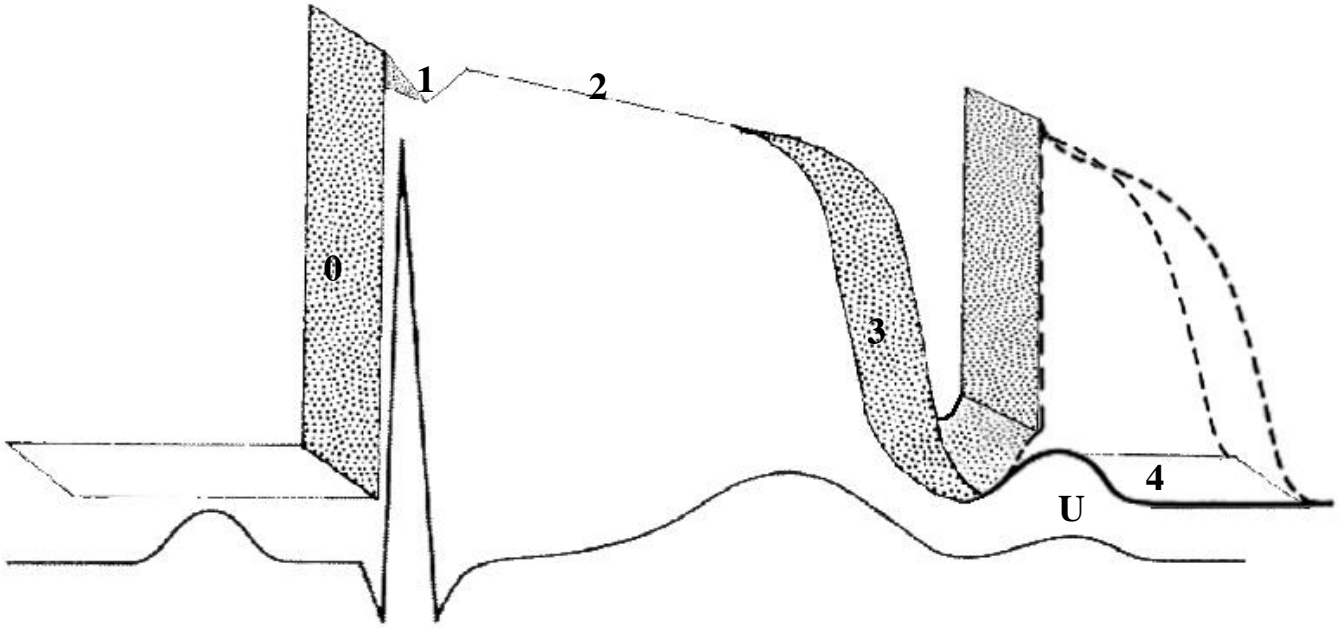
Female, white, 20-year-old patient; recurrent syncope of uncertain etiology after physical and emotional stress; carrier of familial catecholaminergic cardiomyopathy. QRS complexes alternans are observed with alternating right and left bundle branch block morphology. The QRS axis shifts from –60 to +120º.

Clue for electrocardiographic diagnosis of CPVT: association in ECG of sinus bradycardia + normal QTc interval + stress-related, bidirectional VT or PVT in the absence of apparent structural heart disease (Sumitomo 2003; Priori 2002; Liu 2007)

Electrophysiological mechanism in cases of CPVT

They are initiated by delayed afterdepolarizations (DADs) and triggered activity (**Mohamed 2007**), with focus the origin of which is in the proximal region of the right bundle, triggering activity and alternating activation of the LV by the left anterior and posteroinferior left fascicles of the left bundle branch. The events are caused by derangements of the control of intracellular calcium.

Delayed After Depolarization



DAD: they are oscillations of the membrane potential that occur after having completed phase 3 of AP or in phase 4. When they reach the limit, they trigger a new AP. They are observed in high rates (tachycardia-dependent). Their mechanism is caused by the opening of the INS. channel, sensitive to intracellular Ca^{2+} concentration. Causes: ischemia and reperfusion, digitalis intoxication: atrial, junctional, fascicular and VT, adrenergic stress (catecholamine-dependent VT), hypercalcemia, multifocal or chaotic atrial tachycardia: multiple foci with triggered automaticity by delayed after potentials in phase 4, originated by: increase of circulating catecholamines (CPVT), hypoxia, increase of CO2, hypopotassemia, hypomagnesemia, etc, idiopathic VT of the right and left ventricular outflow tract (RVOT / LVOT) and some idiopathic VT, and CPVT.

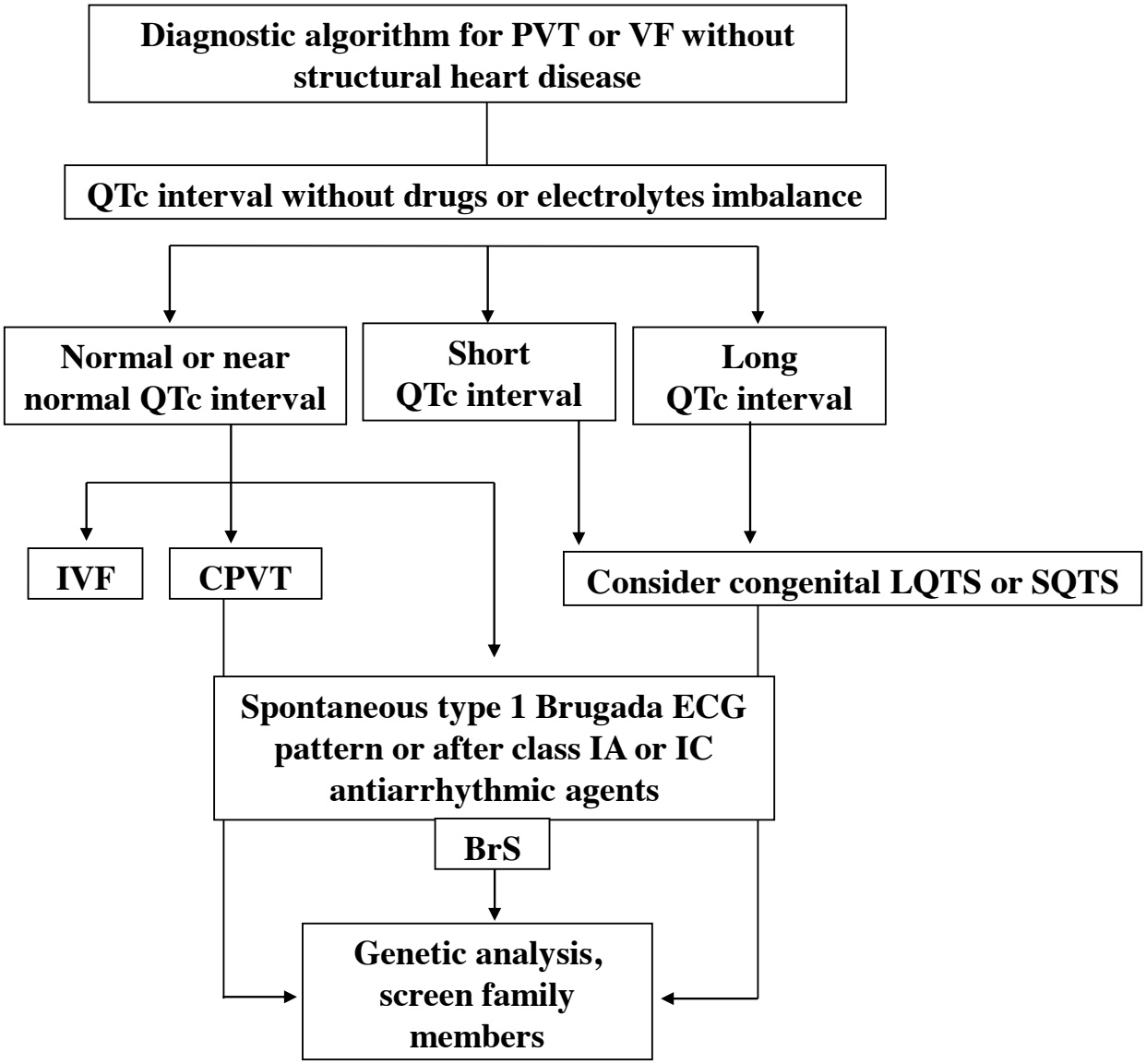
A gain-of-function mutation of the cardiac ryanodine receptor RyR2 gene is the cause of familial or CPVT. In an animal model of mutant RyR2 that is characterized by reduced FKBP binding to the RyR2 on β stimulation, the impaired coupled gating characteristic of these mutations was modeled by reducing cooperativity of the RyR2 activation. In current-clamp mode, the mutant RyR2 model exhibited increased diastolic RyR2 open probability that resulted in the formation of DADs (**Iyer 2007**).

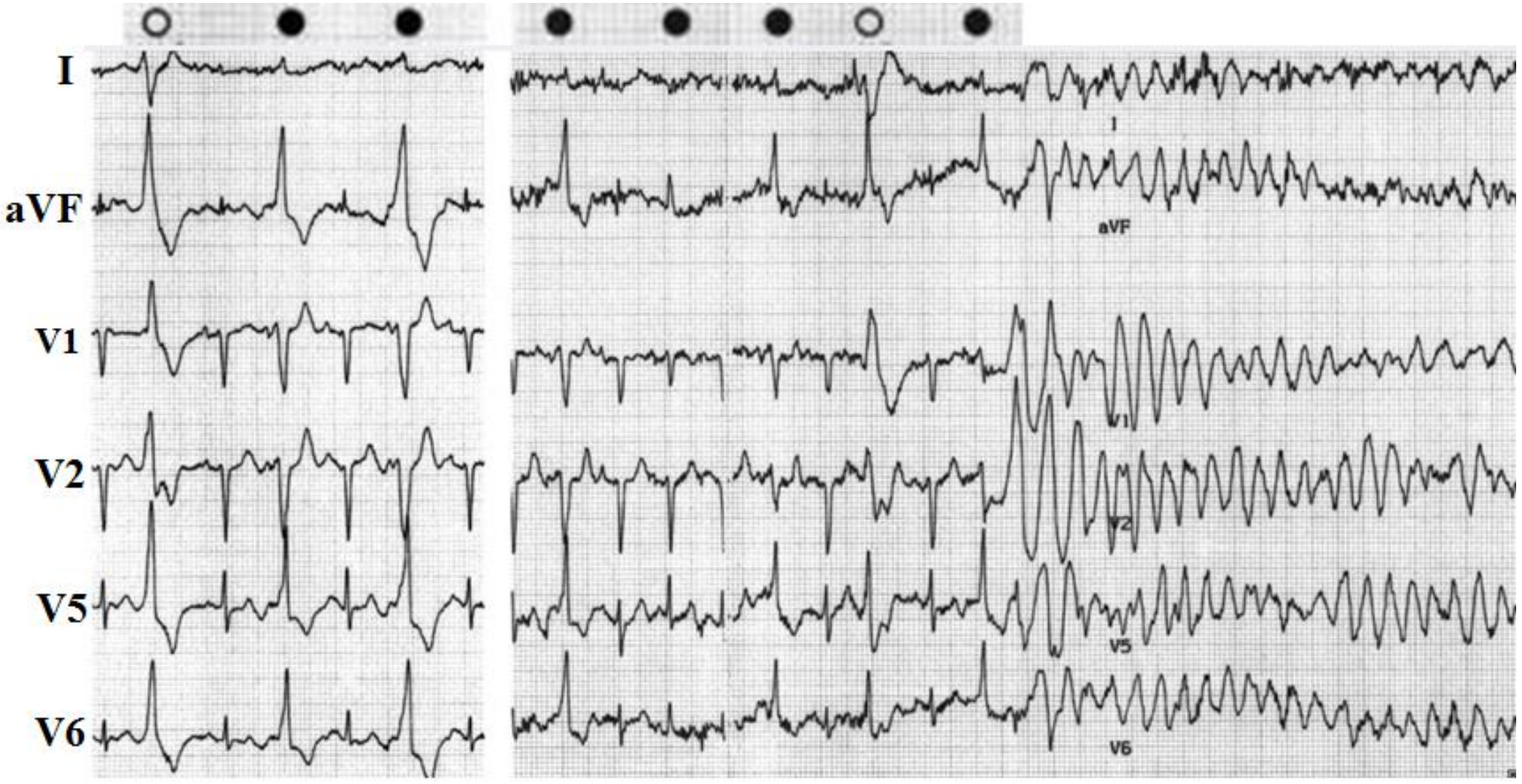
Calsequestrin is a high-capacity Ca^{2+}-binding protein expressed inside the SR, an intracellular Ca^{2+} release and storage organelle in the muscle. Patients with a missense mutation of the calsequestrin 2 gene (CASQ2) are at risk for CPVT. This mutation (CASQ2 (D307H)) results in decreased ability of CASQ2 to bind Ca^{2+} in the sarcoplasmic reticulum (SR). The CASQ2 (D307H) mutation manifests its pro-arrhythmic consequences due to store-overload-induced Ca^{2+} release and DADs formation due to excess free SR Ca^{2+} following rapid pacing and β--adrenergic stimulation (**Faber 2007**).

The arrhythmogenic CASQ2 (D307H) mutation impairs SR Ca^{2+} storing and release functions and destabilizes the Ca^{2+} -induced Ca^{2+} release mechanism by reducing the effective Ca^{2+} buffering inside the SR and/or by altering the responsiveness of the Ca^{2+} release channel complex to luminal C Ca^{2+}. These results establish at cellular level, the pathological link between CASQ2 mutations and the predisposition to adrenergically mediated arrhythmias observed in patients carrying the CASQ2 mutation (**Viatchenko-Karpinski 2004**).

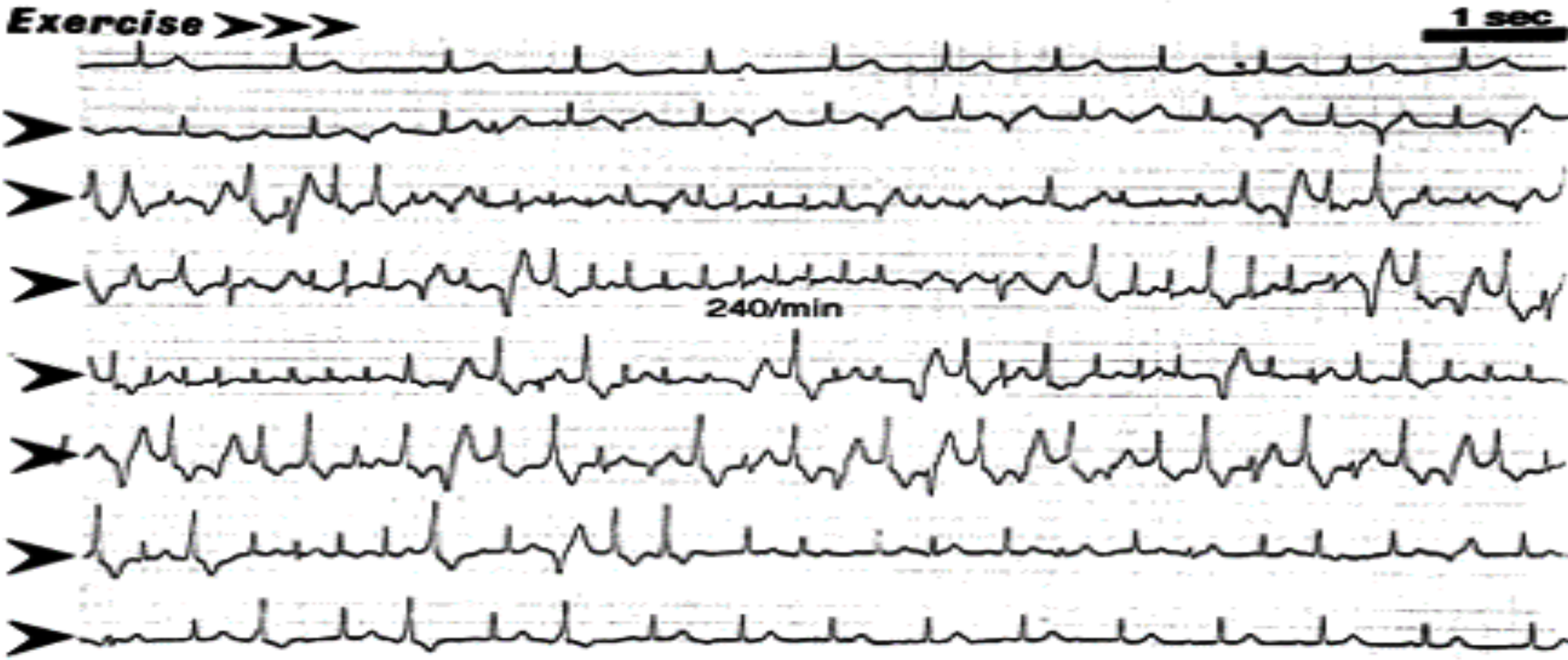
CSQ2 not only determines the Ca^{2+} storage capacity of the SR but also positively controls the amount of Ca^{2+} released from this organelle during excitation-contraction coupling. CSQ2 controls Ca^{2+} release by prolonging the duration of Ca^{2+} fluxes through the SR Ca^{2+}-release sites. In addition, the dynamics of functional restitution of Ca^{2+} -release sites after Ca^{2+} discharge is prolonged when CSQ2 levels are elevated and accelerated in the presence of lowered CSQ2 protein levels. Furthermore, profound disturbances in rhythmic Ca^{2+} transients in myocytes undergoing periodic electrical stimulation are observed when CSQ2 levels are reduced. CSQ2 is a key determinant of the functional size and stability of SR Ca^{2+} stores in cardiac muscle. CSQ2 appears to exert its effects by influencing the local luminal Ca^{2+} concentration-dependent gating of the Ca^{2+}-release channels and by acting as both a reservoir and a sink for Ca^{2+} in SR. The abnormal restitution of Ca^{2+}-release channels in the presence of reduced CSQ2 levels provides a plausible explanation for VT associated with mutations of CSQ2 (**Terentyev 2003**).

Diagnostic algorithm for PVT or VF without structural heart disease (Srivathsan 2005)





Exercise induced VF. This is an ECG of a 13 year old girl who had syncope while running. During a treadmill exercise test, bigeminy involving RBBB and rightward axis (empty circle) and LBBB, inferior axis type, PVCs (filled circles) were induced. VF was induced after LBBB type PVC. Several of the PVC morphologies appear somewhat different because of the fusion of the sinus beat.



ECG monitoring during a stress test (continuous strips). After an acceleration of the sinus rhythm, monomorphic ventricular premature beats appear with a bigeminy. Supraventricular tachycardia (atrial fibrillation and junctional tachycardia) with narrow QRS complexes are then recorded interfering with multiform ventricular premature beats and bidirectional ventricular tachycardia. At the end of the exercise, the arrhythmia disappears in the reverse order.

Prognosis: The mortality rate in untreated individuals is 30-50% by age 40.

Postmortem genetic testing: RyR2 should be considered as a part of the comprehensive medicolegal autopsy investigation of a sudden unexplained death case and that this potentially heritable and often elusive arrhythmia syndrome be scrutinized carefully in family members of those who experience sudden unexplained death (**Tester 2004**).

Treatment:

Management of CPVT is summarized in a recent consensus document from the Heart Rhythm Association (HRS) and the European Heart Rhythm Association (EHRA) (**Priori 2013b**). β-blockers are the most effective pharmacological approach, unfortunately 30% of patients have recurrences. β-blockers reduce arrhythmias, but in 30% of patients an ICD may be required (**Priori 2002**). ICD is necessary for prophylaxis of SCD because ≈30% of patients still experience VTs (**Liu 2007**) that may arise in certain specific areas but the prognosis is poor. The onset of CPVT may be an indication for an ICD.

Flecainide. Clinical (**van der Werf 2011a,b; 2012**) and experimental (**Liu 2011**) data show that to improve arrhythmia control, flecainide (100-300 mg/day) can be given along with β-blockers to persons who are not responsive to β-blockers alone (i.e., persons who have recurrence of syncope, asthmatic or complex arrhythmias during exercise). The evidence for effectiveness of flecainide is sufficient to indicate the use of this drug whenever β-blockers are not sufficient to control arrhythmias. β-blockers and flecainide are also indicated for affected individuals who have experienced a previous aborted SCD. An important development in this field has been the discovery of the RYR2 blocking properties of the Class 1c antiarrhythmic agent flecainide, which thereby can directly target 'the molecular defect' in CPVT (**Watanabe 2009; Hilliard 2010**). After promising results in in vitro and in vivo studies in (ventricular myocytes from) a CASQ2 knockout mouse model, flecainide was tested in two highly symptomatic CPVT patients (one RYR2 mutation and one CASQ2 mutation carrying patient). Flecainide dramatically reduced the VT burden during exercise testing in these patients. Next, the efficacy of flecainide was retrospectively evaluated in a relatively large multicenter study consisting of (**Rosso 2007**) mutation carrying CPVT patients (**van der Werf 2011**). Flecainide had been started in these patients because of persistent physical or emotional stress-induced VTs and/or persistent symptoms, while on β-blocker. However, clinical experience with flecainide is sufficient to allow for its use in a clinical setting. During a median follow-up of 20 months (range: 12–40) no arrhythmic events occurred, except for one patient who experienced ICD shocks for PVT, which was associated with very low flecainide levels. The study also included an RYR2 mutation carrier who presented with exercise-induced VT in 1981, and in whom flecainide has successfully suppressed exercise-induced VTs ever since. These findings were supported by a case of a female CPVT patient who did not tolerate β-blocker therapy and was successfully treated with flecainide (**Biernacka 2011**), and a case of a severely symptomatic RYR2 mutation carrying 11-year-old boy (**Pott 2011**). A concomitant advantage of treatment flecainide may be its efficacy in preventing supraventricular arrhythmias, which are associated with CPVT.2

(**Sy2011; Sumitomo 2007**). Flecainide will probably play an important role in the treatment of CPVT patients. Yet, as previously commented, some issues are still unresolved, such as flecainide's efficacy in preventing arrhythmic events long term, its efficacy in genotype-negative CPVT patients, and whether flecainide could serve as first-line therapy (combined with β-blockers or even as monotherapy). Currently, a randomized clinical trial comparing flecainide on top of β-blocker vs. β-blocker monotherapy is ongoing to test the effect of flecainide prospectively (**http://clinicaltrials.gov: NCT01117454**).

Additional pharmacologic treatments

Additional pharmacologic treatment has been proposed for CPVT, but in the past failures with sodium channel blockers (**Leenhardt 1995; Sumitomo 2003**) and amiodarone (**Leenhardt 1995**) have been reported. Other authors have reported partial effectiveness with verapamil (**Sumitomo 2003; Swan 2005**). However, these reports remain anecdotal and have not been independently confirmed. Furthermore, the effect of chronic treatment with high doses of β-blockers and calcium antagonists on cardiac contractility in children is not known. At present, calcium antagonists cannot be considered an alternative for persons unresponsive to ICDs.

JTV519 (also known as K201) is an experimental drug that stabilizes the ryanodine receptor and has proven to be effective in vitro in counteracting the RyR2 channel instability caused by some CPVT-causing variants (**Lehnart 2004**). However, experimental data obtained in a CPVT mouse model do not support a significant antiarrhythmic effect with this drug (**Liu 2006**).

Genetic therapy

Adeno-Associated Viral vector serotype 9 (AAV9) viral gene transfer of wild type *CASQ2* has been shown to be effective in completely abolishing CPVT arrhythmias up to one year after infection in a recessive CPVT mouse model. Since this vector is already available for human use, gene therapy of recessive CPVT may become available in the future (**Denegri 2012; Liu 2013**). Lodola et al (**Lodola 2016**) investigated the efficacy of the virally mediated gene therapy in cardiomyocytes (CMs) differentiated from induced pluripotent stem cells (iPSCs) obtained from a patient carrying the homozygous CASQ2-G112+5X mutation. To this end, the authors infected cells with an AAV9 encoding the human CASQ2 gene (AAV9-hCASQ2). Administration of the human WT CASQ2 gene was capable and sufficient to restore the physiological expression of calsequestrin-2 protein and to rescue functional defects of the patient-specific iPSC-derived CMs. Indeed, after viral gene transfer, they observed a remarkable decrease in the percentage of DADs developed by the diseased CMs upon adrenergic (**Lodola 2016**).

Left cardiac sympathetic denervation (LCSD) may be considered in those with a diagnosis of CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or several appropriate ICD shocks while on β-blocking agents and in those who are intolerant of or with contraindication to β-blocker therapy (**Priori 2013a, Priori 2013b**). Recurrences of cardiac events have been also reported in those with LCSD. Therefore, pharmacologic therapy should be always optimized prior to considering LCSD. Hence, more data on the long-term efficacy of LCSD are required to determine its exact place in the therapeutic strategy in CPVT patients, including if the procedure's initial beneficial effects persist long term, and thus whether LCSD should be combined with drug therapy and/or ICD implantation.

In the first publication on its efficacy in CPVT, the excellent follow-up results in three young CPVT patients in whom VT could not be controlled by β-blocker therapy were reported, including 2 patients with a very long follow-up (**Wilde 2008**). This was followed by one case report (**Scott 2008**) and two case series (**Atallah 2008; Collura 2009**), all using video-assisted thoracoscopic LSCD. Atallah et al (**Atallah 2008**) described the results of LCSD in 4 CPVT patients who received recurrent ICD discharges for VT (n ¼ 3) or rapidly conducted supraventricular tachycardia (n ¼ 1) despite optimal drug therapy. One patient experienced one arrhythmic storm with recurrent ICD discharges in the first 8 h after the procedure, and remained event-free for the next 2 years. In the other three patients, there were no VTs up to 2 months post-procedure. Collura et al.(**Collura 2006**) published the results of LCSD in 2 severely symptomatic CPVT patients. One patient experienced recurrent post-operative VTs leading to an extended hospital stay, but thereafter no other arrhythmic events occurred during 15 months of follow-up. One case report suggested that the maximum benefit from LCSD may be several months instead of directly after the procedure (**Gopinathannair 2010**), whereas another case showed that bilateral cardiac sympathetic denervation may (also) be effective (**Scott 2008**). Pharmacologic sympathectomy using a high thoracic epidural catheter may be considered before performing LCSD to get information on its potential effectiveness (**Chen 2010**). In the 14 CPVT patients treated with LCSD that were collected by Odero et al (**Odero 2010**), the result was favorable in 93%. Long-term follow-up has only been available in one more patient, who had a significant decrease in ICD discharges during a 10-year follow-up (**Makanjee 2009**).

Left Cardiac Simpathetic Denervation(LCSD)/video-assisted thoracoscopic LSCD complications. These are rare (**Odero 2010**).

I. Palpebral ptosis permanent or transient; II. Elevation of the left hemidiaphragm; III. Lack of sweating from the left arm and face: unilateral hand dryness, color or temperature variance between sides of the face) (**Antiel 2016**); IV. Horner syndrome (transient or persistent); V. Pneumothorax; VI. Harlequin-type (unilateral) facial flush (**Waddell-Smith 2015**); VII. contralateral hyperhidrosis.

Despite the anticipated side effects associated with LCSD, patients are satisfied with their surgery and indicate that they would recommend the surgery to another patient.

Implantable cardioverter defibrillator (ICD). Although β-blockers have been reported to be highly effective (**Postma 2005**), an ICD may become necessary for secondary prevention of recurrent cardiac arrest. Furthermore, in those individuals in whom the highest tolerated dose of β-blockers fails to adequately control arrhythmias (**Priori 2002, Sumitomo 2003**), an ICD can be considered for primary prevention of cardiac arrest/SCD (**Zipes 2006**). ACC/AHA/ESC Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention for SCD(2006), a Class I recommendation was given for implantation of an ICD in addition to β-blocker therapy for CPVT patients who are survivors of cardiac arrest (**Zipes 2006**). A Class IIa recommendation was given for ICD implantation in CPVT patients with syncope and/or documented Sustained VT despite β-blockers (**Zipes 2006**). The Heart Rhythm UK Statement on Clinical Indications for ICDs in Adult Patients with Familial SCD Syndromes concurred with these recommendations, while adding LCSD as a therapeutic consideration before ICD implantation (**Garratt 2010**).

ICDs have been implanted much more liberal by the cardiological community. This was most probably caused by the high mortality rates in untreated CPVT patients and in CPVT patients with β-blocker therapy reported in the first case series (**Leenhardt 1995; Priori 2002; Sumitomo 2003**), which gave CPVT a highly malignant reputation. Potentially this is a worrisome development, because ICDs may have harmful effect in CPVT patients. A least 5 cases have been described showing that both appropriate and inappropriate ICD shocks can trigger catecholamine release, resulting in multiple shocks, electrical storm, and death (**Sy 20011; Mohamed 2006; Palanca 2006**) and as such ICD therapy does have a proarrhythmic potential.

In a case report LCSD was performed simultaneously with ICD implantation to reduce the risk of fatal event (**Moray 2011**).

ICD implantation can lead to significant complications (**Sherrid 2008**), and because of the increased prevalence of supraventricular arrhythmias, CPVT patients with an ICD are at increased risk of receiving inappropriate ICD shocks. In Celiker manuscript (**Celiker 2009**) the number of patients with appropriate ICD shocks was equal to the number of patients with ICD shocks because of sensing errors, lead fracture, sensing errors, and lead migration. All 4 patients who received an ICD required psychological support because of signs of depression and anxiety.

Inappropriate shocks can partly be prevented by careful ICD programming, e.g. with one VF zone with a detection interval of 240 b.p.m. and (exceptionally) long detection intervals. Given these serious drawbacks and the discovery of promising treatment alternatives on top of β-blocker therapy associated with flecainide, was propose http://europace.oxfordjournals.org/content/europace/14/2/175.full.pdf (**van der Werf 2014**) a more conservative approach for ICD implantation, probably even with regard to those who were diagnosed with CPVT after experiencing acute cardiac arrest.

Prevention of Primary Manifestations β-blockers are indicated for primary prevention in all clinically affected individuals. Although no quantitative data on actual risk for cardiac arrest as the first manifestation of the disease are available, this treatment is probably also indicated for individuals with an *RYR2* pathogenic variant and no history of cardiac events (syncope) or no ventricular arrhythmias on exercise stress testing. Recommended drugs are nadolol (1-2.5 mg/kg/day) or propranolol (2-4 mg/kg/day).In Brazil we have not nadolol. For symptomatic individuals with CPVT, the maximum tolerated dosage should be maintained. Nebivolol, like carvedilol, possesses a RyR2-targeted action that suppresses store-overload induced Ca^{2+} release (SOICR) and SOICR-evoked VTs. Thus, nebivolol represents a promising agent for Ca^{2+}-triggered arrhythmias (**Tan 2016**). Flecainide can be added for primary prevention of a cardiac arrest when β-blockers alone cannot control the onset of arrhythmias during exercise stress test.

Prevention of Secondary Complications

Secondary complications are mainly related to therapy. β-blockers could worsen allergic asthma. Therefore, the cardiac-specific β-blocker, metoprolol, could be indicated in some individuals with CPVT who have a history of asthma. The dose of metoprolol is based on the need of the affected individual (≤3 mg/kg). It is important to keep in mind that metoprolol and newer β-blockers (e.g., bisorpolol) may not have the same efficacy as nadolol and/or propranolol; the reasons for this are under investigation.

For persons with an ICD, anticoagulation to prevent formation of thrombi may be necessary (particularly in children who require looping of the RV catheter).

Surveillance

I. Regular follow-up visits every six to 12 months (depending on the severity of clinical manifestations) are required in order to monitor therapy efficacy. These visits should include the following:
II. Resting ECG;
III. Exercise stress test; performed at the maximal age-predicted heart rate; For individuals on β-blocker therapy (in whom maximal heart rate cannot be reached), the test should be performed at least at the highest tolerated workload.
IV. Holter monitoring

The limit for any allowed physical activity can be defined on the basis of exercise stress test done in the hospital setting; the use of commercially available heart rate monitoring devices for sports participation can be helpful in keeping the heart rate in a safe range during physical activity but should not be considered as an alternative to medical follow-up visits.

Agents/Circumstances to Avoid

Competitive sports and other strenuous exercise are always contraindicated. All individuals showing exercise-induced arrhythmias should avoid physical activity, with the exception of light training for those individuals showing good suppression of arrhythmias on exercise stress testing while on therapy. It is important to note that efficacy needs to be periodically retested (**Heidbuchel 2006 a;b**).

A single case report highlighted the possible proarrhythmic effect of an insulin tolerance test (ITT), driven by severe hypokalemia and adrenergic activation secondary to the metabolic imbalance induced by the test . The author recommend ECG monitoring during ITT to enhance the detection of cardiac arrhythmias. In addition, in the case of a comatose child during ITT the determination of the glucose and potassium level as well as adequate treatment are necessary (**Binder 2004**).

Digitalis favors the onset of cardiac arrhythmias due to DAD and triggered activity; therefore digitalis should be avoided in all individuals with CPVT.

Evaluation of Relatives at Risk

Because treatment and surveillance are available to reduce morbidity and mortality, first-degree relatives should be offered clinical work up and molecular genetic testing if the family-specific pathogenic allelic variant(s) are known. Indeed the availability of effective preventive therapies can reduce the number of fatal arrhythmic events if individuals with pathogenic variants are diagnosed early.

If the family-specific pathogenic variant(s) are not known, all first-degree relatives of an affected individual should be evaluated with resting ECG, Holter monitoring, and – most importantly – exercise stress testing.

Pregnancy Management

β-blockers (preferentially nadolol or propranolol) should be administered throughout pregnancy in affected women. Unfortunately, we do not have nadolol in the market. Case reports only. Critical to continue β-blockade throughout (no reported events while compliant with β-blocker); exercise restriction; titrate β-blocker each trimester to Holter monitor and treadmill stress test response; optimal management of labor and delivery unclear, but safe caesarian section and vaginal delivery have been reported (aim is to reduce circulating catecholamines) (**Chan 2002; Friday 2015; Wilders 2012**).

Stress Hormone Levels and Mode of Delivery

Lower level of maternal circulating catecholamines (epinephrine, norepinephrine, cortisol) with caesarian section compared to vaginal delivery with or without epidural anesthesia (**Vogl 2006**).

Risk to Family Members — AD — CPVT

Parents of a proband ≈ 50% of individuals with AD CPVT have an affected parent. A proband with autosomal dominant CPVT may have the disorder as the result of *de novo* mutation. Accurate data on the prevalence of *de novo RYR2* pathogenic variants are not available but they are estimated at approximately 40%. This finding suggests that some probands with *RYR2*-related CPVT do not reach reproductive age. Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include a maximal exercise stress test and molecular genetic testing if the variant has been identified in the proband. Although ≈ 50% of individuals diagnosed with AD PVT have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance.

Sibs of a proband The risk to the sibs of a proband depends on the genetic status of the proband's parents. If a parent of the proband is affected, the risk to the sibs is 50%. If a pathogenic variant cannot be detected in the DNA extracted from the leukocytes of either parent, two possible explanations are germline mosaicism in a parent or *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with autosomal dominant CPVT has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent is affected, his or her family members are at risk.

Risk to Family Members — AR CPVT Parents of a proband The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele. Heterozygotes (carriers) are asymptomatic. Rare and benign arrhythmias have been reported. It is possible (rare) that one or both parents of a proband is actually themselves affected. Therefore, a maximal exercise stress test and molecular genetic testing can be considered for the parents of a proband **Sibs of a proband** At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygotes (carriers) are usually asymptomatic. Minor abnormalities (rare and benign arrhythmias) have been reported in anecdotal cases. **Offspring of a proband.** The offspring of an individual with AR CPVT are obligate heterozygotes (carriers) for a pathogenic variant in *CASQ2* or *TRDN*. **Other family members of a proband.** Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection Carrier testing for at-risk family members is possible if the pathogenic variants in the family are known. **Related Genetic Counseling Issues** Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with anautosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant or less likely that a parent has germline mosaicism. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Testing of asymptomatic at-risk family members. Testing of asymptomatic at-risk family members for CPVT is possible using the techniques described in Molecular Genetic Testing. Although this testing is not useful in predicting age of onset, severity, or specific symptoms that may occur in asymptomatic individuals, it does allow for initiation of treatment and surveillance. When testing at-risk individuals for CPVT, an affected family member should be tested first to identify the specific pathogenic variant(s).

Family planning

The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the pathogenic variant(s) have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing.

Requests for prenatal testing for conditions such as CPVT are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for families in which the pathogenic variant(s) have been identified.

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