

**somewhat
different**

CHANNELOPATHIES :
an increased risk for sudden cardiac death.
How could we deal with such applicants to life insurance

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INTRODUCTION

Thanks to the invasive electrophysiology and the progress of imaging techniques as well as the development of invasive cardiology for the diagnosis and treatment of cardiac disease, our knowledge about organic heart disease dramatically improved during the past 30 years.

Meantime, the molecular approach and the advent of genetic testing provide us a better approach in the pathophysiology of heart disease making the difference between the phenotype induced cardiac disease and our genetic individual pre-setting to develop some disease.

Once upon a time... we tended to consider that everything in medicine was more or less « organic » when we know today that some apparently unexpected events may be related to our genetic heritage.

Even though in terms of medical underwriting for the insurance industry, we're generally not allowed to rely on genetic data, the progress of science helps us to a better understanding and risk stratification of such disease.

UNEXPECTED SUDDEN DEATH ...

- ✓ Unexpected sudden death...
- ✓ Aborted cardiac arrest (ACA)...
- ✓ Life threatening arrhythmia with no underlying heart disease...
- ✓ Sudden death in young people...
- ✓ Family history of sudden death...

... all these deaths related to the sudden occurrence of a ventricular fibrillation recently merged into the global concept of CHANNELOPATHIES that are related to an intracardiac ionic channel dysfunction based upon a better knowledge of the cellular electrophysiology as well as its relationship with a gene mutation.

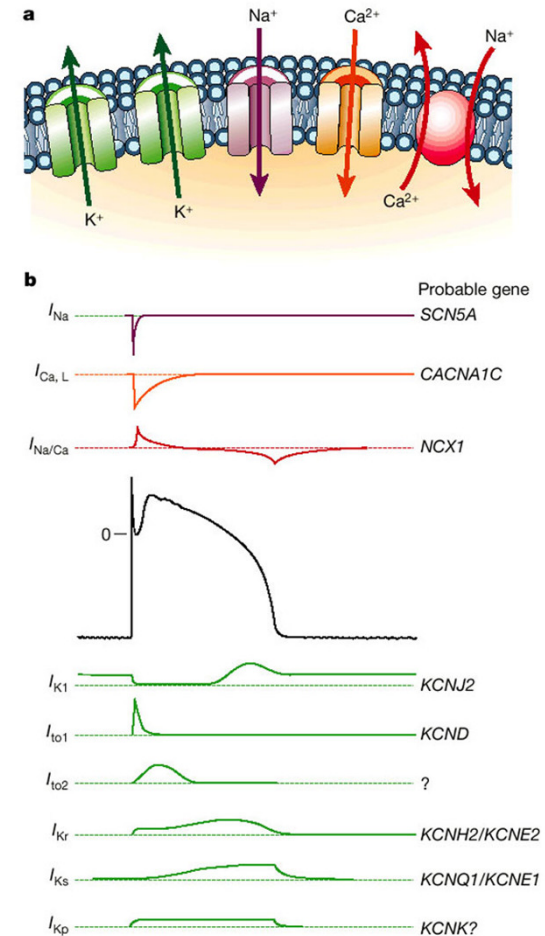
CHANNELOPATHIES

Channelopathies are disorders caused by mutations in genes encoding proteins that form or act with the specialised channels that conduct ions through the myocyte membrane. These mutations lead to disrupted flow of sodium (Na^+), Potassium (K^+) and Calcium (Ca^{++}) ions, in and out the cardiac cell.

Such mutations result in modifications of the ventricular repolarization and an increased risk of ventricular tachyarrhythmias such as :

- ✓Torsades de pointes,
- ✓Polymorphic ventricular tachycardia.
- ✓Ventricular Fibrillation

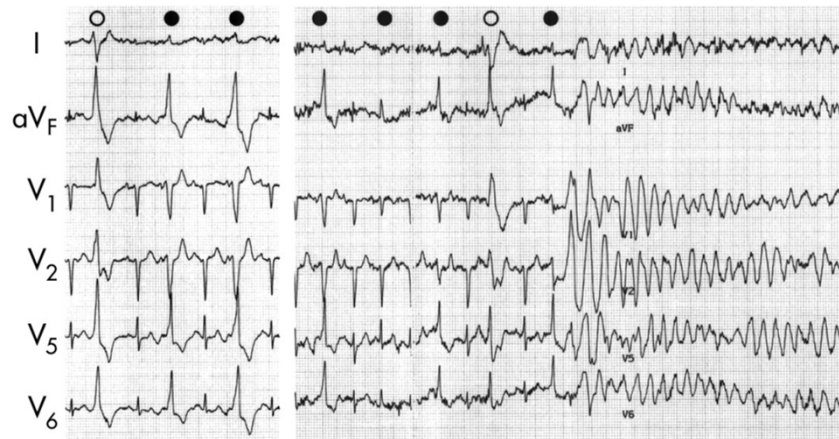
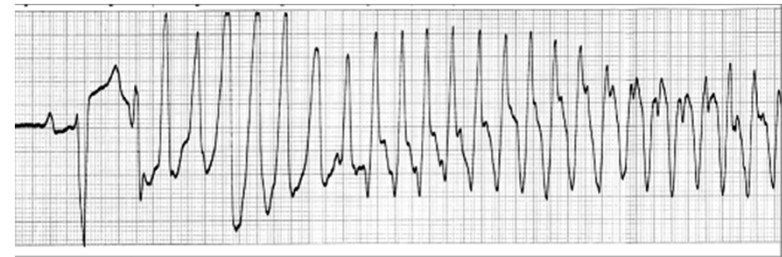
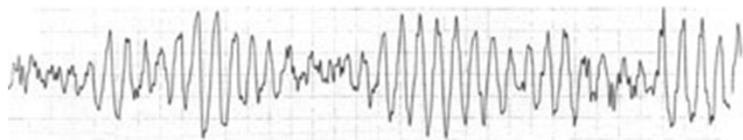
That can lead to syncope, aborted cardiac arrest and sudden cardiac death in patients without an underlying structural heart disease



CHANNELOPATHIES

Channelopathies result in an increased risk of life threatening ventricular arrhythmia such as :

- ✓Torsades de pointes,
- ✓Polymorphic ventricular tachycardia.
- ✓Ventricular Fibrillation



SO ... WHAT IS A « CHANNELOPATHY » ?

A CHANNELOPATHY IS :

- ✓ A dysfunction of an ionic intra cardiac channel (Na⁺, K⁺ or Ca⁺⁺).
- ✓ That may result in a life-threatening arrhythmia with no underlying structural heart disease.
- ✓ ⇒ **Increased risk of Sudden Death.**
- ✓ The mechanism of which is **genetically determined** (family history).

Most of the sudden cardiac death in childhood or young people without any associated known disease may be related to a Channelopathy.

Then comes a question : « how valuable could be a family genotyping » in order to try to prevent sudden death with specific therapy such as an AICD ?...

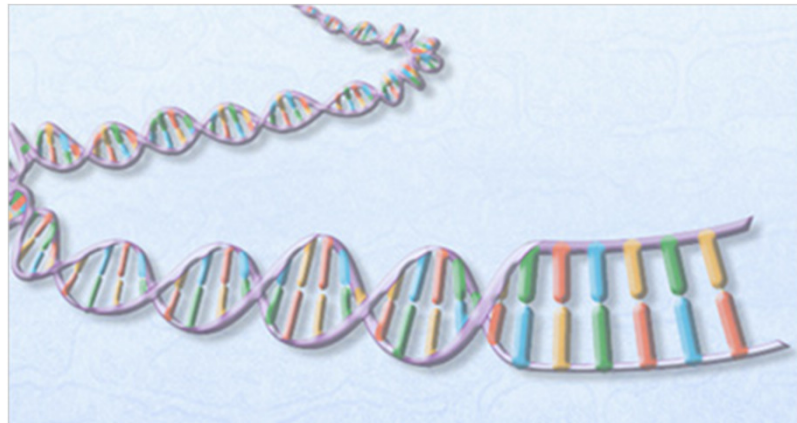
WHEN SHOULD WE THINK « CHANNELOPATHY » ?...

- SUDDEN DEATH with NEGATIVE AUTOPSY.
 - SYNCOPE – DROWNING.
 - NEUROLOGIC UNEXPLAINED SYMPTOMS (Epilepsy / Seizure).
 - SYMPTOMS OCCURRING DURING EFFORT / STRESS OR FEVER.
 - FAMILY HISTORY OF SYNCOPE OR SUDDEN DEATH.
 - + NO PERSONAL HISTORY OF A CARDIAC DISEASE.
-
- AND IN THE FIELD OF **LIFE INSURANCE MEDICINE**, THERE IS A NEW TYPE OF APPLICANTS, WHO MAY HAVE A FAMILY HISTORY OF S.C.D. and SOMETIMES HAVE BEEN IMPLANTED *PROPHYLACTICALLY* WITH AN AICD THOUGH THEY PERSONNALLY NEVER EXPERIENCED ANY MAJOR SYMPTOM...
 - Then comes again the question : « how valuable could be a family genotyping » in order to try to prevent sudden death with specific therapy or an AICD ?...

CHANNELOPATHIES : WHO ARE YOU ??? (today... as in 2013)

1. **THE LONG QT SYNDROME (LQTS)** : at least 12 different genetic patterns from LQTS1 to LQTS12, 90% of them being concentrated among the first three types.
2. **THE BRUGADA'S SYNDROME** (SCN5A mutation).
3. **CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA** (CPVT).
4. **The SHORT QT SYNDROME.**
5. **The « EARLY REPOLARIZATION SYNDROME ».**

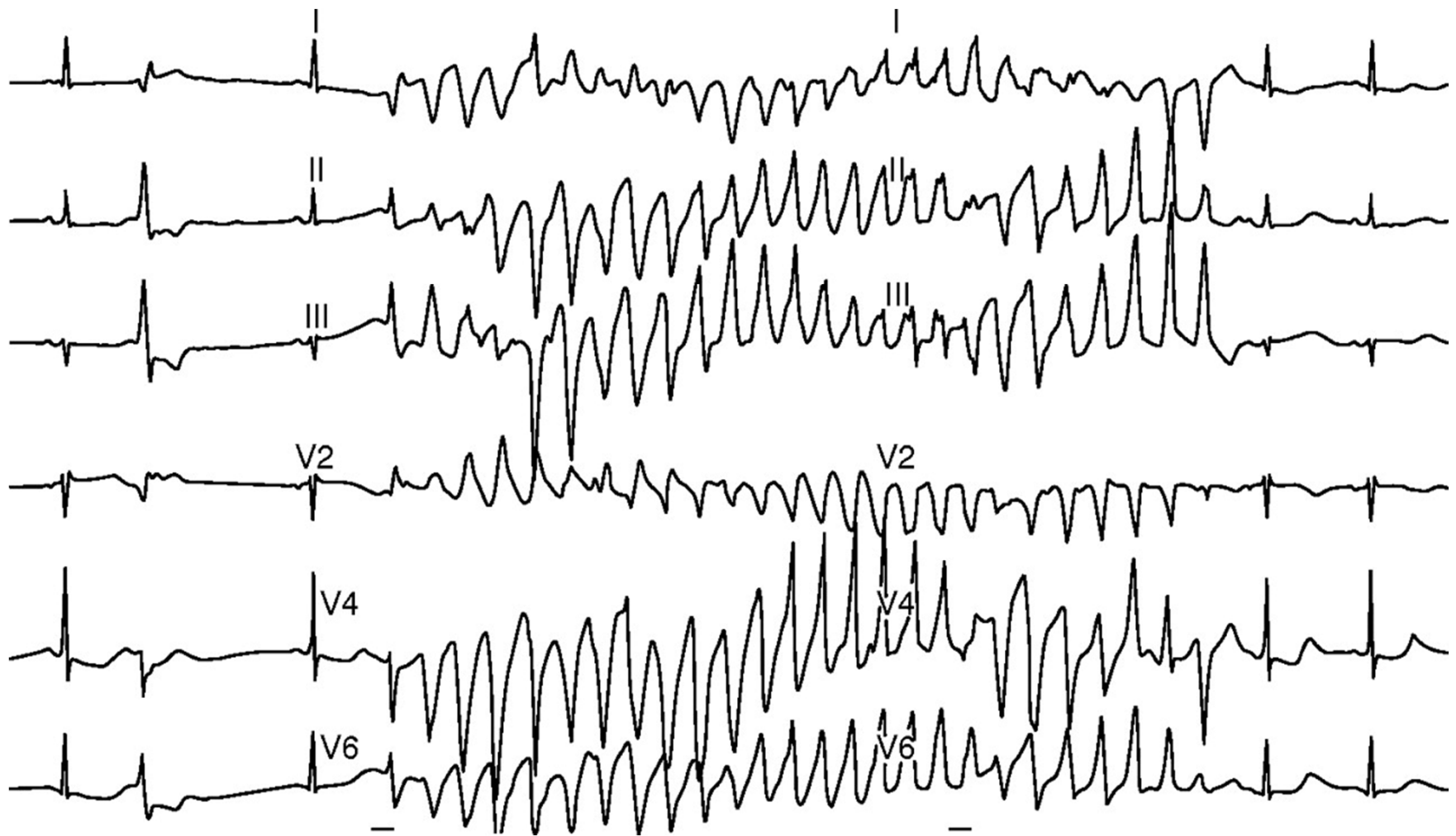
THE LONG QT SYNDROME



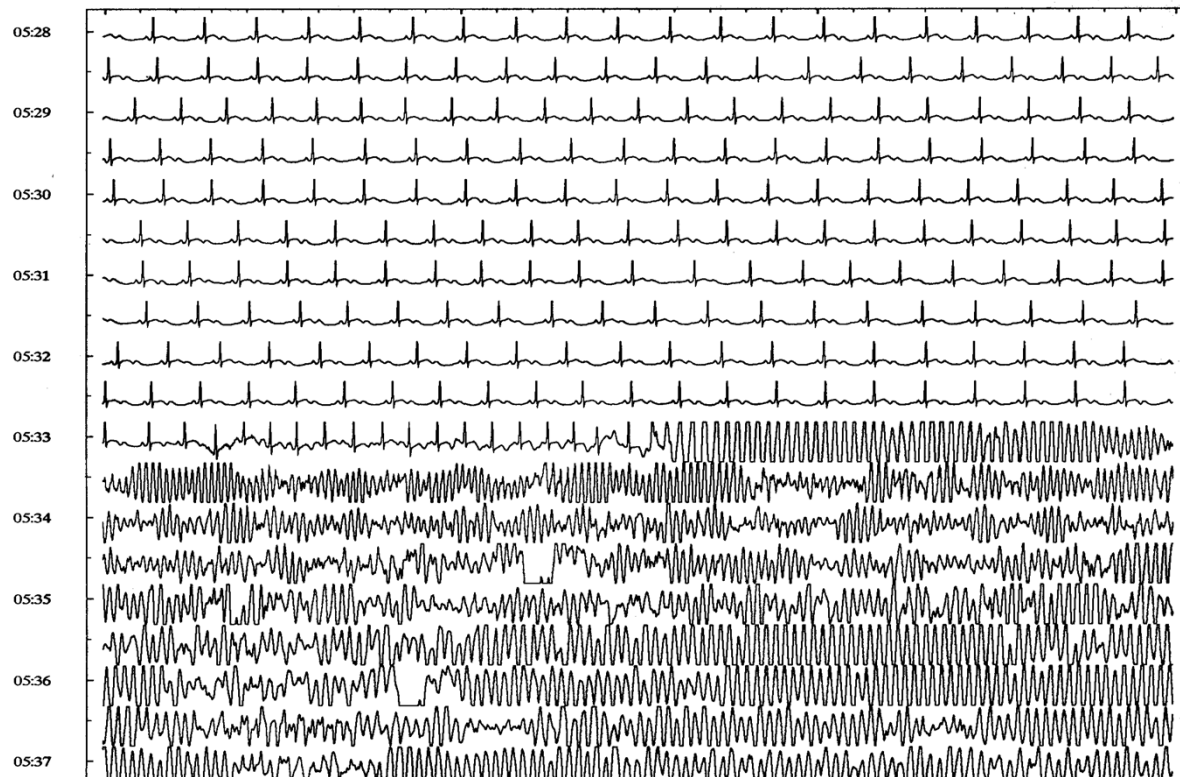
THE « CONGENITAL LONG QT SYNDROME » (LQTS)

- A GENETIC DISEASE (1/5000).
- AUTOSOMAL AND DOMINANT TRANSMISSION (95%).
- DIAGNOSIS : ON THE SURFACE ECG : QT_c PROLONGATION.
- CAUSED BY MUTATIONS IN ION CHANNEL ENCODING GENES
- ARRHYTHMIAS RELATED TO THE LQTS :
 - Torsades de Pointes.
 - Ventricular Tachycardia or Fibrillation.
- SYMPTOMS : SYNCOPE / S.D. in childhood and young adults.
- CONTRIBUTING FACTORS TO ARRHYTHMIA :
 - Adrenergic stimulation (effort, stress...).
 - Drugs increasing the QT interval (Quinidine, and class Ia and class II anti-arrhythmic drugs; neuroleptics, tricyclic anti-depressant drugs, some antibiotics).
- ARCHETYPE OF INHERITED ARRHYTHMIAS (CHANNELOPATHIES)

THE LONG QT SYNDROME (LQTS) → TORSADE DE POINTES

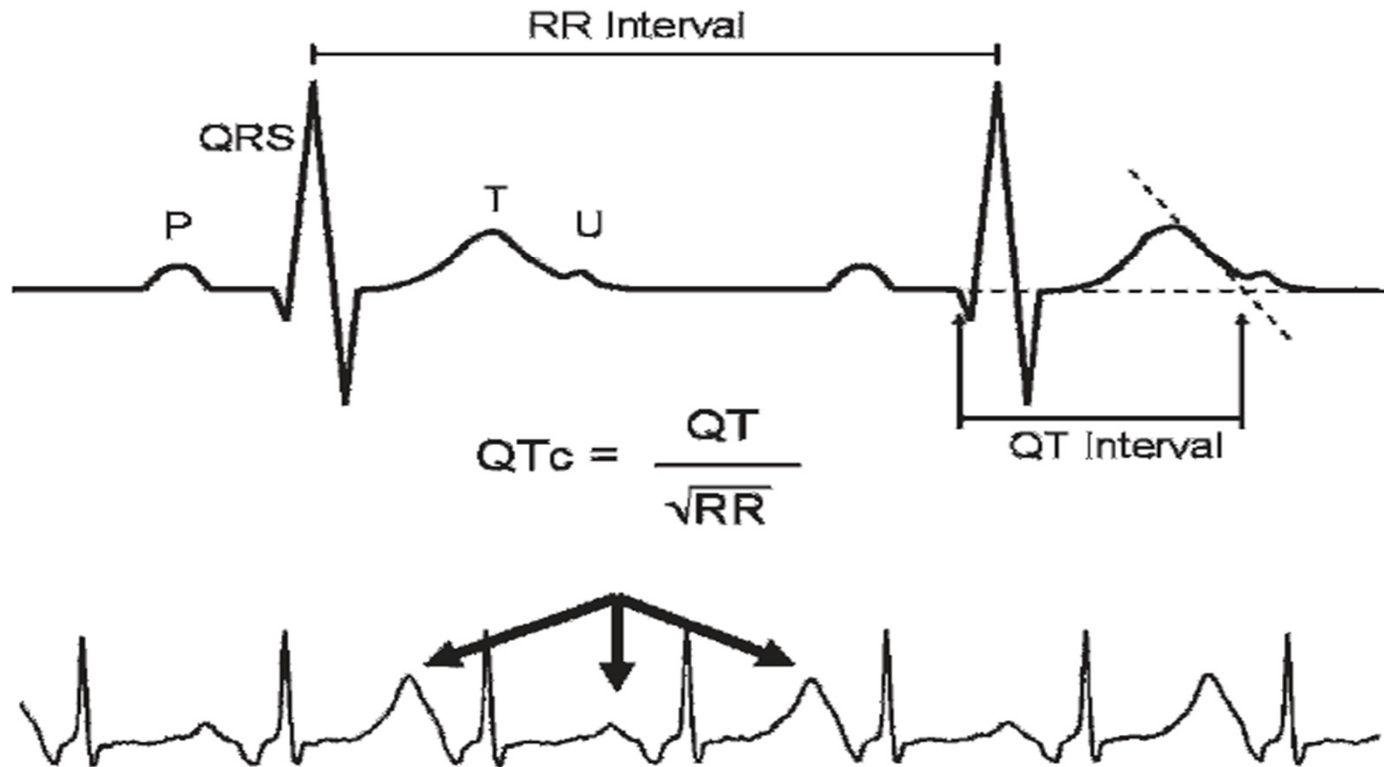


THE LONG QT SYNDROME (LQTS) → SUDDEN DEATH



Sinus Tachycardia
(telephone call ⇒ sudden
wake up at night) ⇒ TDP
⇒ Ventricular Fibrillation

THE LONG QT SYNDROME (LQTS)



JN Johnson & MJ Ackerman Br J Sports Med 2009;43:657–62.

THE LONG QT SYNDROME (LQTS)

How to measure the QT interval :

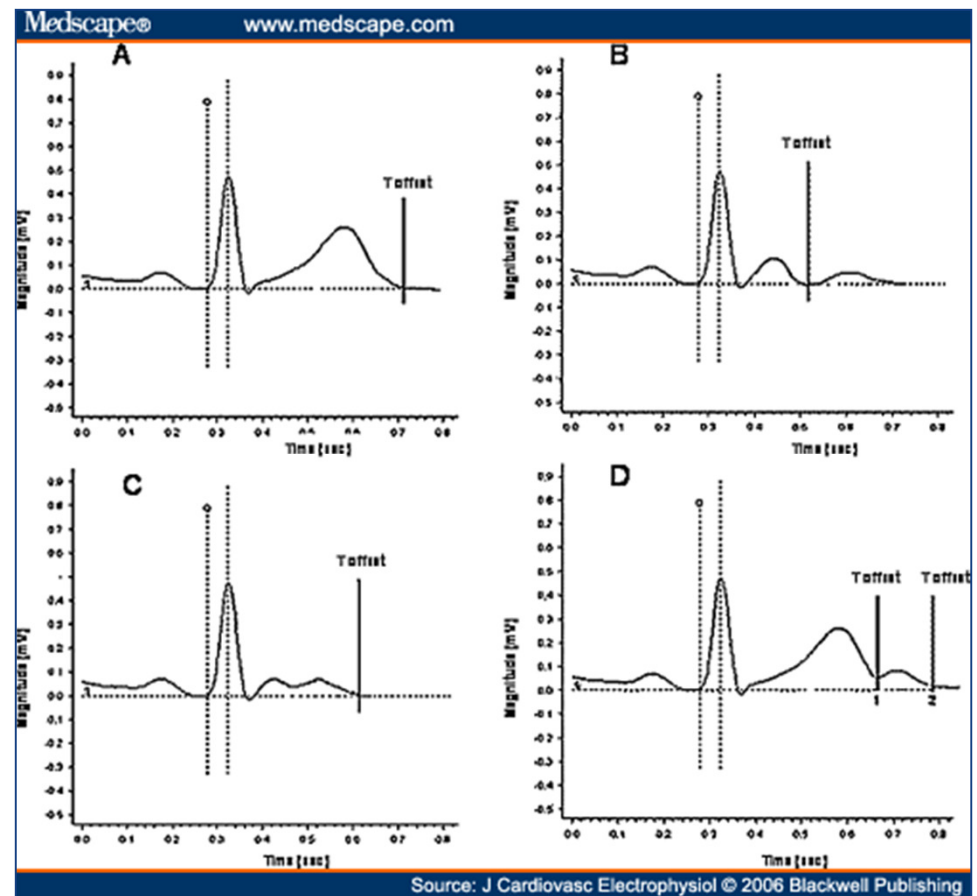
The Long QT syndrome is defined as a prolongation of the QTc interval longer than 440 msec (« borderline LQTS ») and over 470msec (LQTS).

- QTc may (also) be prolonged by (« acquired LQTS ») :
 - Sex ratio (women > men) and age.
 - Ionic balance (Hypokaliemia, hypoMg⁺⁺).
 - Bradycardia, ischaemia, heart failure
 - Drugs :
 - ✓ Neuroleptics
 - ✓ some antibiotics (quinolones, macrolides)
 - ✓ Class Ia AAA (Quinidine)
 - ✓ Anti-histaminic drugs...

QT MEASUREMENT

QT MEASUREMENT :

- The accuracy of the automatic measurements of the corrected QT (QTc) interval is questionable in many cases and should be supplemented by **manual reading**.
- A standard **12-lead ECG tracing at 25 mm/s** paper speed at 10 mm/mV amplitude is generally adequate for accurate measurement of QT-interval duration.
- QT interval should be determined as a mean value derived from at least 3–5 cardiac cycles, and is measured **from the beginning of the earliest onset of the QRS complex to the end of the T wave**.
- QT measurement should be made **in leads II and V5 or V6, with the longest value being used**.



THE CONGENITAL « LONG QT SYNDROME » (LQTS)

- Some clinical features that have been historically described :
 - **The Jervell (Lange Nielsen) syndrome** (first described - published in 1957) :
 - Autosomal
 - Recessive
 - Very rare (#1% of the LQTS)
 - Associating the cardio-vascular risk to a sensorineuroal deafness.
 - Genetically : LQTS type 5
 - **The Romano Ward syndrome** (described and published in 1963):
 - Autosomal
 - Dominant
- Some other (rare) clinical / ECG associations :
 - The LQTS 7 associated with the Andersen Tawil syndrome
 - The LQTS 8 associated with the Timothy syndrome.

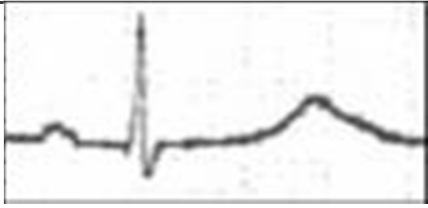
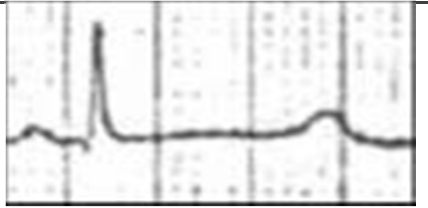
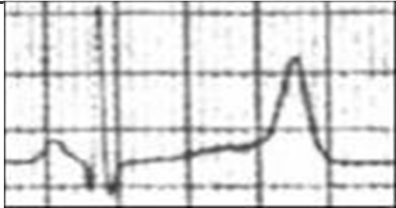
THE GENETIC PATTERNS OF THE LONG QT SYNDROME (LQTS)

Long QT Syndrome (LQTS)* including Sudden Infant Death Syndrome

	Gene	Locus	Syndrome	Protein & subunit	Function & abnormality	Occurs In [¶]
1	KCNQ1	11p15.5	LQTS1, SIDS [£]	K _v 7.1 α	I _{Ks} ↓ KvLQT1	30-35%
2	KCNH2	7q35	LQTS2, SIDS [£]	K _v 11.1 α	I _{Kr} ↓ HERG	25-30%
3	SCN5A	3p21	LQTS3, SIDS [£]	Na _v 1.5 α	I _{Na} ↑	5-10%
4	ANK2	4q25	LQTS4, ABS [§]	Ankyrin-B	I _{Na,K} ↓ I _{NCX} ↓	1-2%
5	KCNE1	21q22.1	LQTS5	minK β	I _{Ks} ↓	1%
6	KCNE2	21q22.1	LQTS6, SIDS [£]	MiRP1 β	I _{Kr} ↓	rare
7	KCNJ2	17q23	LQTS7, <u>S Andersen</u>	Kir2.1 α	I _{K1} ↓	rare
8	CACNA1C	12p13.3	LQTS8, <u>S Timothy</u>	Ca _v 1.2 α _{1c}	I _{Ca,L} ↑	rare
9	CAV3	3p25	LQTS9, SIDS [£]	Caveolin-3	I _{Na} ↑	rare
10	SCN4B	11q23	LQTS10	Na _v 1.5 β4	I _{Na} ↑	rare
	KCNQ1	11p15.5	JLNS1 ⁺	K _v 7.1 α	I _{Ks} ↓ KvLQT1	rare
	KCNE1	21q22.1	JLNS2 ⁺⁺	minK β	I _{Ks} ↓	rare

THE LONG QT SYNDROME (LQTS)

Definition / QTc > 440 ms.

	LQT1	LQT2	LQT3
GENES	KCNQ1	KCNH2	SCN5A
PROPORTION	50%	46%	4%
T Wave			
TRIGGER	Sports, Drugs QT ↑	Stress, Drugs QT ↑	Rest, Drugs QT ↑

Genetic testing and long QT syndrome

Class I (is recommended)

- ▶ Comprehensive or **LQT1-3** (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of **the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.**
- ▶ Comprehensive or **LQT1-3** (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any **asymptomatic patient with QT prolongation** in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined **as QTc >480 ms (prepuberty) or >500 ms (adults).**

MJ Ackerman et al. Heart Rhythm 2011; 8: 1308-39.

Genetic testing and long QT syndrome

Class I (recommended)

- ▶ Mutation-specific genetic testing is recommended for **family members and other appropriate relatives** subsequently following the identification of the LQTS-causative mutation in the index case

Class IIb (may be considered)

- ▶ Comprehensive or **LQT1-3** (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing may be considered for any **asymptomatic patient with otherwise idiopathic QTc values 460 ms (prepuberty) or 480 ms (adults)** on serial 12-lead ECGs.

MJ Ackerman et al. Heart Rhythm 2011; 8: 1308-39.

RISK ASSESSMENT /LQTS

- **CLINICAL PHENOTYPE REMAINS THE KEY OF THE RISK ASSESSMENT :**
 - Female adulthood
 - QTc \geq 500ms
 - Previous syncope or ACA or Torsade de Pointes

- **GENOTYPE- PHENOTYPE STUDIES:**
 - LQT1 : broad T waves and syncope during sports (swimming).
 - LQT2 : low amplitude or notched T waves and and syncope at audio stimuli (alarm)
 - LQT3 : Long flat ST segment, bradycardia and SCD at sleep.

- **ROLE OF GENOTYPE IN RISK PREDICTION:**
 - Mutation + and QTc < 440 ms : 4%
 - Mutation + and QTc \geq 440 ms : 15 %
 - Mutation – and QTc < 440 ms: 0,4 %

Risk factors in LQTS according to QTc , genotype, type of mutation, sex

	LQT1, M	LQT1, F	LQT2/3, M	LQT2/3, F
QTc > 500 ms	++	+++	+++	+++
QTc < 500 ms	+	++	++	++
QTc < 440 ms + mutation TM	++	++	++	++
QTc < 440 ms, no mutation TM	+	+	+	+

Goldengerg et al, JACC 2011: 57: 51- 9.
Napolitano et al, Circulation 2012; 125: 2027-34

LQTS – THERAPEUTIC ISSUES

- **β Blockers (nadolol) :**
 - Check the compliance : ECG, Holter, Stress test.
 - Sometimes difficult as primary prevention.
 - Because of the side effects in young people.
- **Contraindicated drugs (↗ QT):**
 - List of the contraindicated drugs.
 - Web Site : www.QTDrugs.org
- **Sports :**
 - ± No Sports (NO competition).
 - Try to find an alternative leisure occupation.

AICD implantation ?

- After discussion in all the cases.
- In patients with TDP, ACA, or syncope in spite of the medical therapy.
- LQT1 - LQR2 with QTc > 500ms.
- Sometimes **on prophylactic purpose, or « on request » of a patient or his family ...**

Appropriate shocks in Long QT syndrome

Age	36 +/- 19 years
N	55
Sex	31 % male
Follow -up	54 months
ICD 1 prevention	14/55 (25%)
ICD 2 prevention	41/55 (75%)
Appropriate shocks	1/14 for 1 prevention (72 years, angina) 15/41 for 2 prevention

Olde Nordkamp LRA et al, Circulation 2013

LONG QT SYNDROME – CONCLUSION AND SUMMARY

- 1.the LQTS diagnosis is done on a clinical and ECG basis.
- 2.The diagnosis of the disease may then be confirmed by molecular biology (e.g. Genotyping) after informed consent obtained from the patient.
- 3.A pre-symptomatic diagnosis may be sometimes recommended based upon a family history.
- 4.Most of these patients are effectively treated by β -blockers; lifestyle and behavioral changes (sports, leisure, drug therapy recommendations).
- 5.Some patients (or family members) might be implanted with an automatic defibrillator cardioverter the indication of which is sometimes more or less unclear mainly in case of so called « primary prevention » ...

From a « medical underwriting point of view »

- 1.As the ECG is a decisive factor for the diagnosis of LQTS, Medical Officers working in the field of life insurance should take great care when analyzing ECG tracings and measuring QTc interval on standard ECG in order not to miss a LQTS.
- 2.People that underwent a resuscitated sudden death and that have been implanted with an AICD and/or receive β -blockers are usually considered as non insurable whatever the expected guarantees.
- 3.Asymptomatic people that have been implanted upon the result of a genetic testing are usually considered as not eligible for life insurance policies even though the risk (at least for death) could be fairly acceptable in this population.

THE BRUGADA SYNDROME



THE BRUGADA SYNDROME

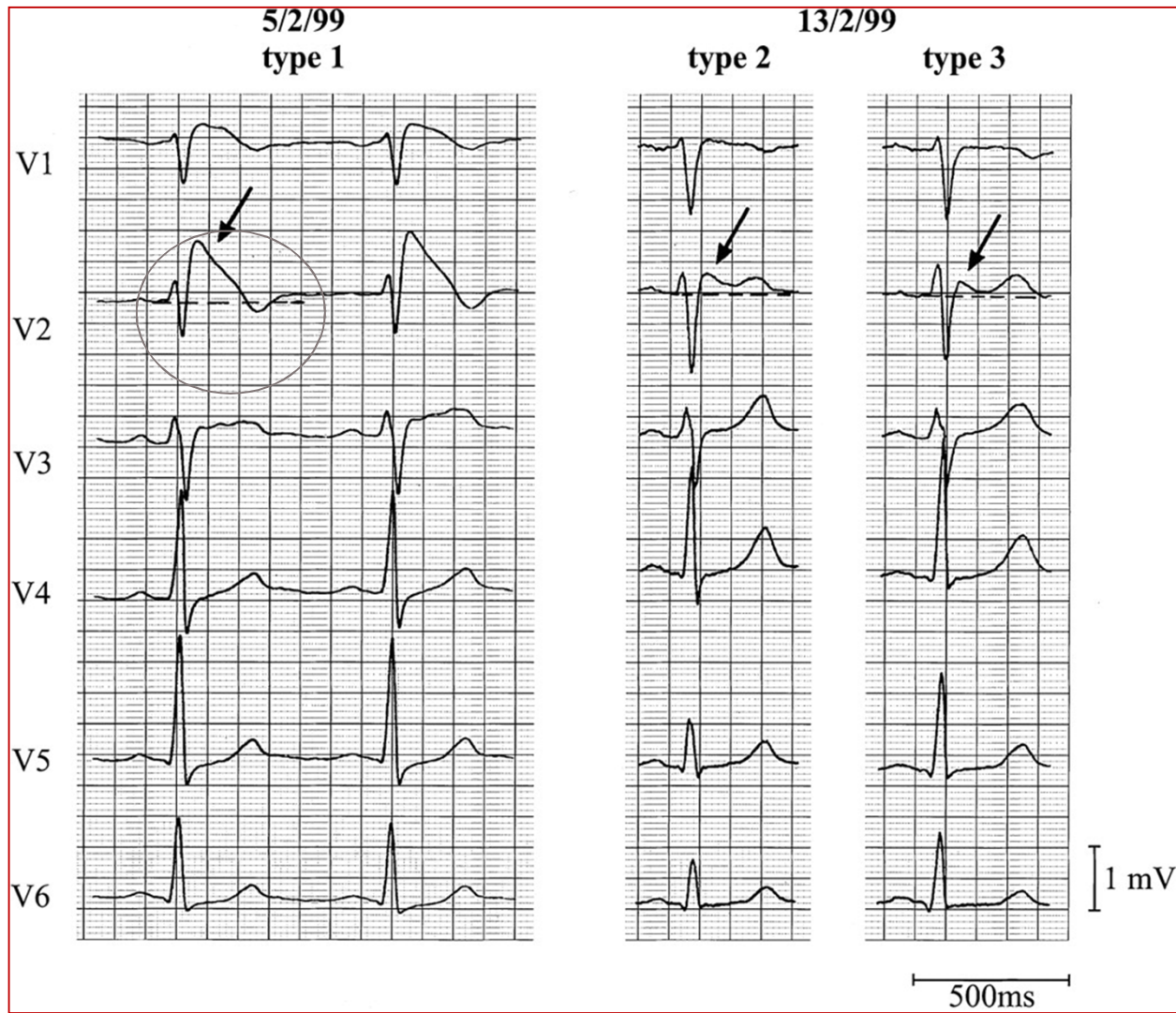
- Described in 1992 by the three BRUGADA Brothers (Pedro, Ramon and Giusep) in patients who underwent syncope and sudden death.
- Associated with a typical ECG pattern associating a right ventricular conduction delay with a ST segment elevation in leads V1 to V3 (sometimes transient).
- Prevalence : mainly men aged 30-50 yrs.
- With Family history of sudden death .
- Autosomal / Dominant transmission (though variable penetrance).
- Mutation on the gene *SCN5A* coding for $Na_v1.5$ channel in 20% of the cases.
- This mutation implies a loss of function of the $Na_v1.5$ channel.
- Many other complex mutations are known for the BrS (8 ?...)
- Some bridging the BrS with the « Short QT syndrome ».
- Estimated Prevalence : 1 : 5000-10 000

THE BRUGADA SYNDROME

EPIDEMIOLOGICAL DATA :

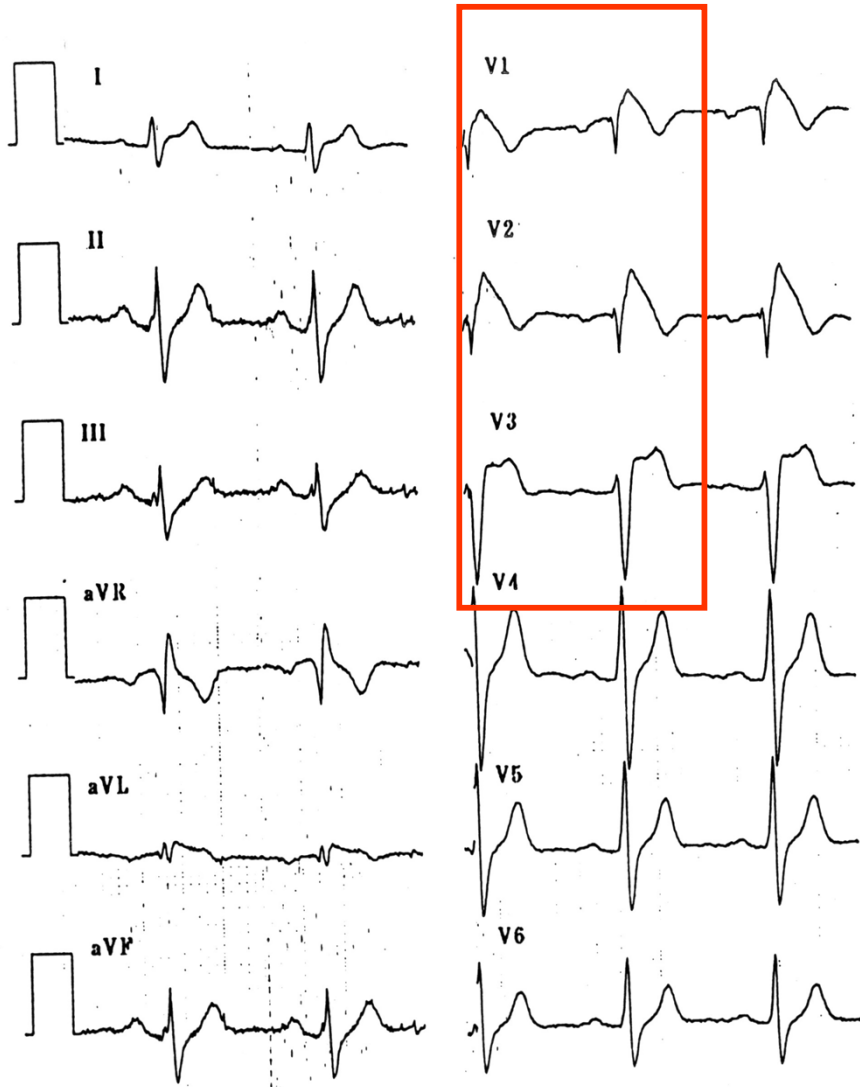
- Prevalence: 1 - 5 / 10 000 inhabitants
 - Mainly in Thailand, Philippines
[Bangungut – Pokkuri – Lai Tai] [SUNDS]
- 4 to 12 % of the « sudden deaths ».
- 20 % of the sudden deaths with no associated structural heart disease.
- Prevalence Male +++ (M/F=10/1)
- Mean age for diagnosis or S.D.: 40 ± 22 years.
- Increase in case of fever, or certain drugs (www.brugadadrugs.org)

THE BRUGADA SYNDROME - ECG PATTERN



Type 1 **only** is specific of the Brugada's syndrome

THE BRUGADA SYNDROME - ECG PATTERN



TYPICAL ECG PATTERN OF THE BRUGADA'S SYNDROME

1. PR \nearrow

2. Right BBB

3. ST V1-V3 \nearrow

SUSPECTED BrS : PHARMACOLOGIC TESTS :

- **Ajmaline:** 1 mg/kg/5 min i.v.
- **Flecainide:** 2 mg/kg/10 min i.v.
(400 mg, p.o.)
- **Procainamide:** 10 mg/kg/10 min i.v.
- **Pilsicainide:** 1 mg/kg/10 min i.v.

In ICU condition with a continuous ECG and a defibrillator available.

Stop test when : Type1 pattern unmasked, VPB's or QRS enlargement >130%

Basal

Ajmaline

V1



V1



V2



V2



20 mV



400 ms



V3



V3



THE BRUGADA'S SYNDROME

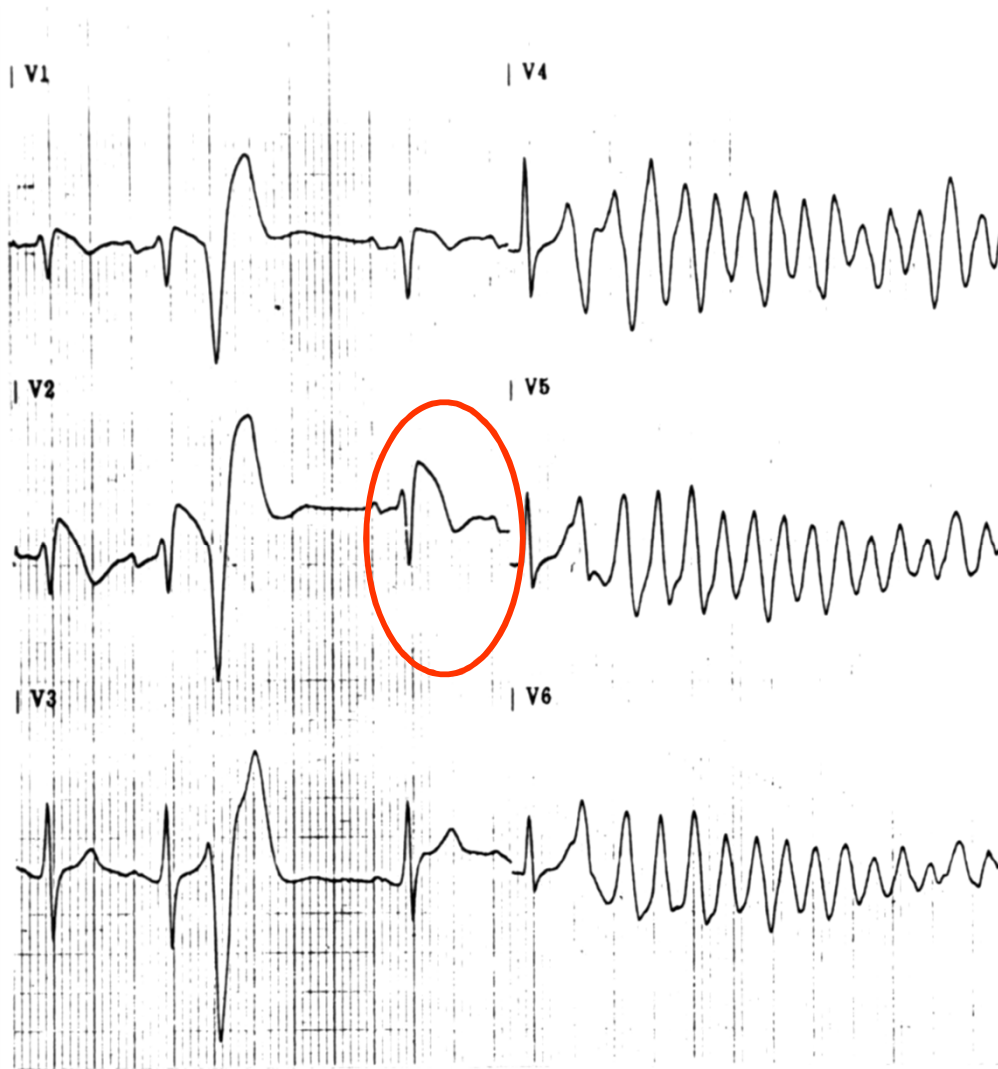
AJMALINE TEST : VALUE

- ▶ Sensitivity: 80%
- ▶ Specificity: 94%
- ▶ Positive PV: 93%
- ▶ Negative PV: 83 %

So the “penetrance” of the BrS switch from 33 to 79%

After Ajmaline test

THE BRUGADA'S SYNDROME → SUDDEN CARDIAC DEATH



Ventricular Fibrillation in a patient with the Brugada Syndrome

BRUGADA AND GENOTYPING

- GENETIC TEST POSITIVE TO SCN5A IN 20-25% (sodium channel).
- ECG to be performed in all the cases to the parents, brothers and sisters.
- Pharmacologic testing:
 - In case of type 2 or type 3 ECG pattern.
 - In case of sudden death in the family.
 - In case of normal baseline ECG.
- Electrophysiology (EPS) :
 - If the pharmacological testing is abnormal.
 - In case of symptoms.
 - Only for their negative predictive value.

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)

Class I (is recommended)

Mutation-specific genetic testing is **recommended** for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

Class IIa (can be useful)

Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

Class III (is not indicated/recommended)

Genetic testing is **not indicated** in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

KEYWORDS Genetics; Cardiomyopathies; Channelopathies (Heart Rhythm 2011; 8:1308–1339)

THE BRUGADA'S SYNDROME / TREATMENT

- THE **AUTOMATIC IMPLANTABLE CARDIOVERTER DEFIBRILLATOR** IS THE MAIN THERAPEUTIC OPTION RECOMMENDED FOR PREVENTING SUDDEN DEATH IN PATIENTS WITH THE BRUGADA'S SYNDROME.
- HOWEVER, ALTERNATIVE THERAPEUTIC ISSUES HAS BEEN DEVELOPPED DURING THE PAST 10 YEARS SUCH AS THE **CATHETER ABLATION** OVER THE ANTERIOR RIGHT VENTRICULAR OUTFLOW TRACT EPICARDIUM. (HAISSAGUERRE et al).
- BUT THERE IS A NUMBER OF PATIENTS THAT UNDERWENT **AICD** « **PREVENTIVE** » **IMPLANTATION** UPON A FAMILY HISTORY AND SOMETIMES SOME MINOR (OR ±ASPECIFIC) ECG PATTERNS SO ONCE AGAIN HERE, WHEN THEY ARE TOTALLY ASYMPTOMATIC THE QUESTION RISES UP TO KNOW WHAT COULD WE SUGGEST IN TERMS OF ASSURABILITY ?...

Appropriate shocks in Brugada syndrome

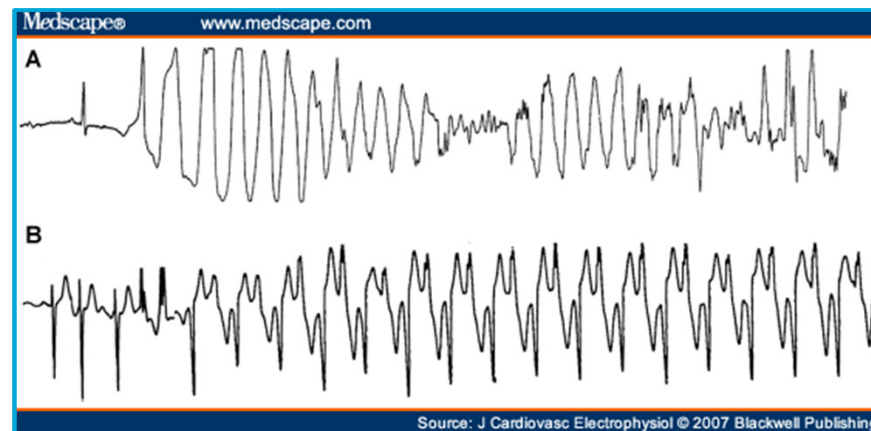
Age	46 +/- 12 years
N	75
Sex	88% male
Follow -up	62 months
ICD 1 prevention	29/75 (39%)
ICD 2 prevention	46/75 (61%)
Appropriate shocks	0/29pts for 1 prevention 7/46pts for 2 prevention

Predictor : history of VT/VF (univariate analysis)

Olde Nordkamp LRA et al, Circulation 2013

CATECHOLAMINE INDUCED POLYMORPHIC VENTRICULAR TACHYCARDIA

(CPVT)



CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)



- ✓ Baseline ECG is quite often NORMAL
- ✓ Children with a history of syncope or sudden death during an effort.
- ✓ Holter Monitoring : Polymorphic VPB's during effort, followed by a bigeminy or a bidirectional couplets, and then salvos of polymorphic ventricular extrasystoles.
- ✓ Diagnostic value of the treadmill test showing polymorphous V.Tach (at very fast and irregular ventricular rate).

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

- Syncope : related to mental stress, exercise or sports.
- Family History of sudden death or syncope (same trigger).
- CPVT inducible :
 - During stress or exercise (Holter/ Treadmill) : HR > 110 bpm
 - After catecholamine (Isopreterenol) infusion.
 - NOT inducible by E.P.S.
- ECG normal at rest.
- No associated organic heart disease.
- Genotyping : autosomal transmission of a mutation concerning :
 - Genes encoding cardiac Ryanodine type 2 receptors / RyR 2 (65%), - Dominant
 - Genes encoding cardiac Calsequetrin 2 / CASQ2 (10%) - recessive

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

- SYMPTOMS : EARLY IN LIFE (< 10 YRS).
- THE EARLIER THE SYMPTOMS, THE HIGHER THE MORTALITY RATIO.
- WITHOUT TREATMENT , THE **MORTALITY RATIO** IS 30-50% BETWEEN 20 AND 30 YRS OF AGE.
- HIGHLY MALIGNANT ARRHYTHMIA.
- β BLOCKERS NOT SUFFICIENT IN A NUMBER OF CASES.
- **TREATMENT :**
- β BLOCKERS (NADOLOL) +/- VERAPAMIL
- ASSOCIATED WITH AN **AICD** IN THE MOST SEVERE FORMS.

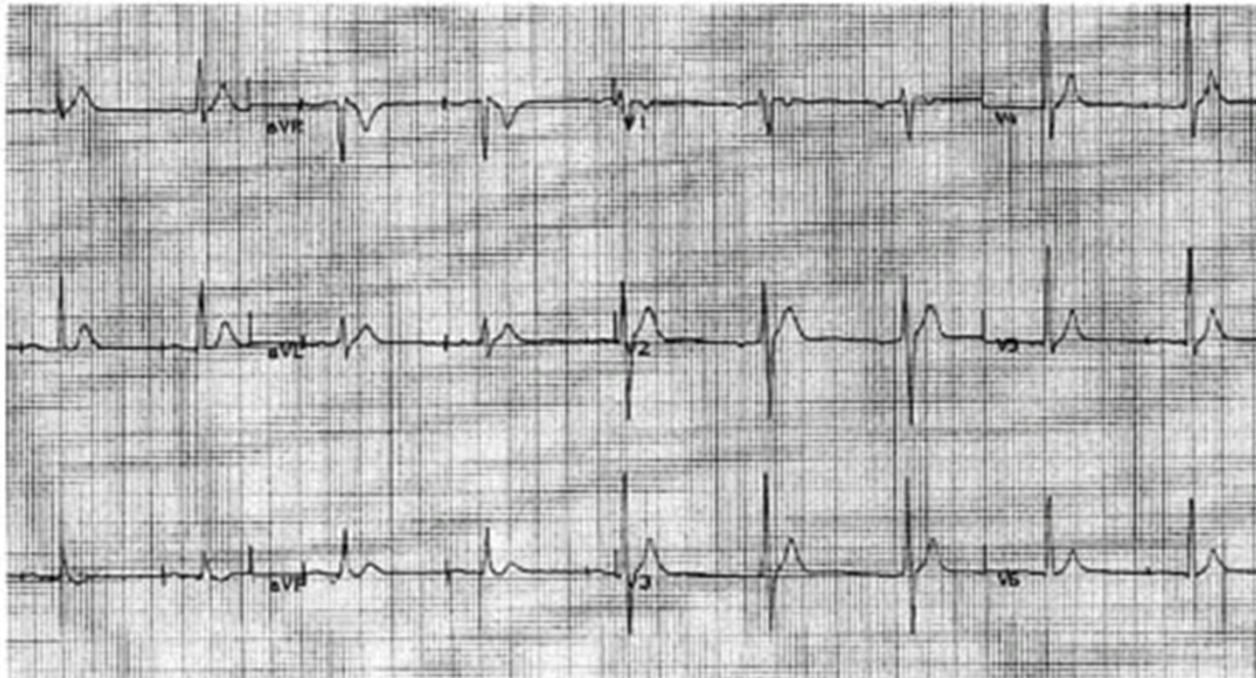
CPVT – RISK STRATIFICATION - THERAPEUTIC ISSUE

- Too few patients with CPVT have been reported to allow the definition of a risk stratification scheme.
- Beta blockers appear to be effective.
- Patients who have had an episode documented arrhythmic event are considered at higher immediate risk and usually implanted with an AICD associated with beta-blocker therapy.
- EP testing is not useful for management and risk stratification because CPVT patients are usually not inducible.

ACC/AHA/ESC 2006 Guidelines JACC 2006;48:e247–e346
ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy.
Circulation. 2008;117:e350-e408

SHORT QT SYNDROME and the EARLY REPOLARIZATION Sd

SHORT QT SYNDROME



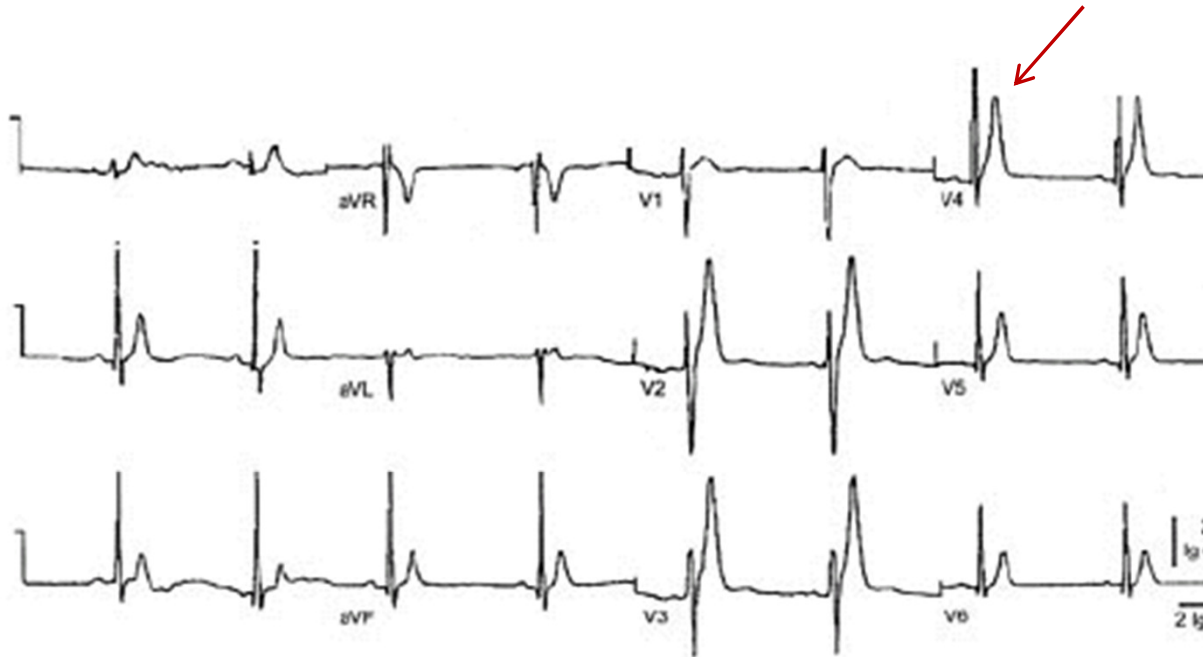
FAMILY 30-339, PATIENT I:2
QTc 288 msec

DEFINITION

QTc < 320 ms

Family History of S.D.
Palpitations, syncope
at rest or during efforts.
History of
ressuscitated sudden
death.

SHORT QT SYNDROME



Short QT on all leads

Paroxysmal A.F.

Inducible V.F.

GENES :

-HERG

-KCNQ1

-KCNJ2

-CACNA1C

-CACNB2

FAMILY 30-339: PATIENT II:2

QTc 293 msec

SHORT QT SYNDROME

First description of the Short QT Sd in 2000.

Family history with sudden deaths, syncope, palpitations.
Atrial Fibrillation.

Clinical and echocardiogram \Rightarrow No structural Heart disease.

Prevalence : remains unknown.
seems to be **very rare**.

« some » families.

No more than a few dozens.

Transmission : Autosomal / Dominant.

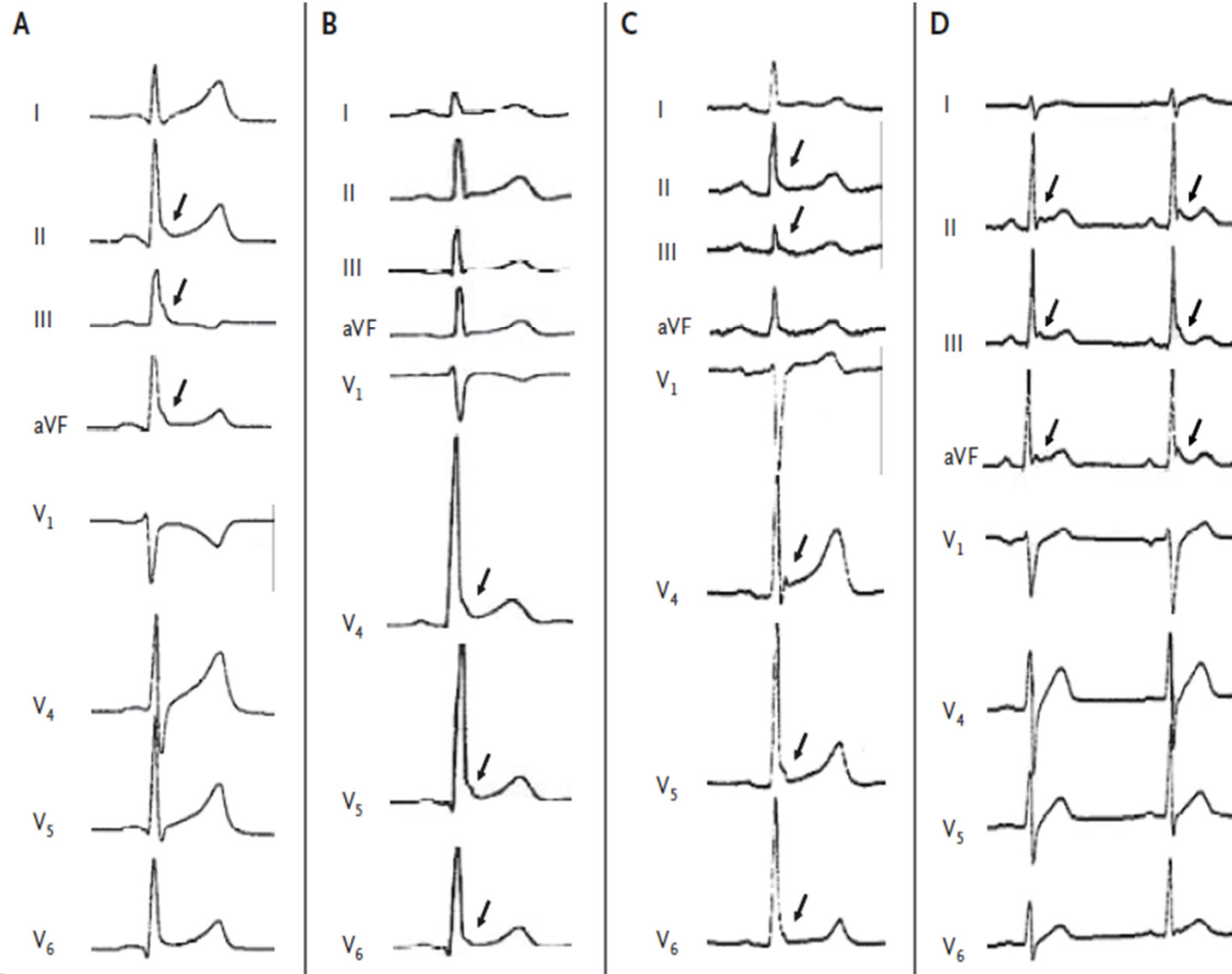
Treatment : AICD \pm Quinidine.

Insurability : **No** in our current knowledge.

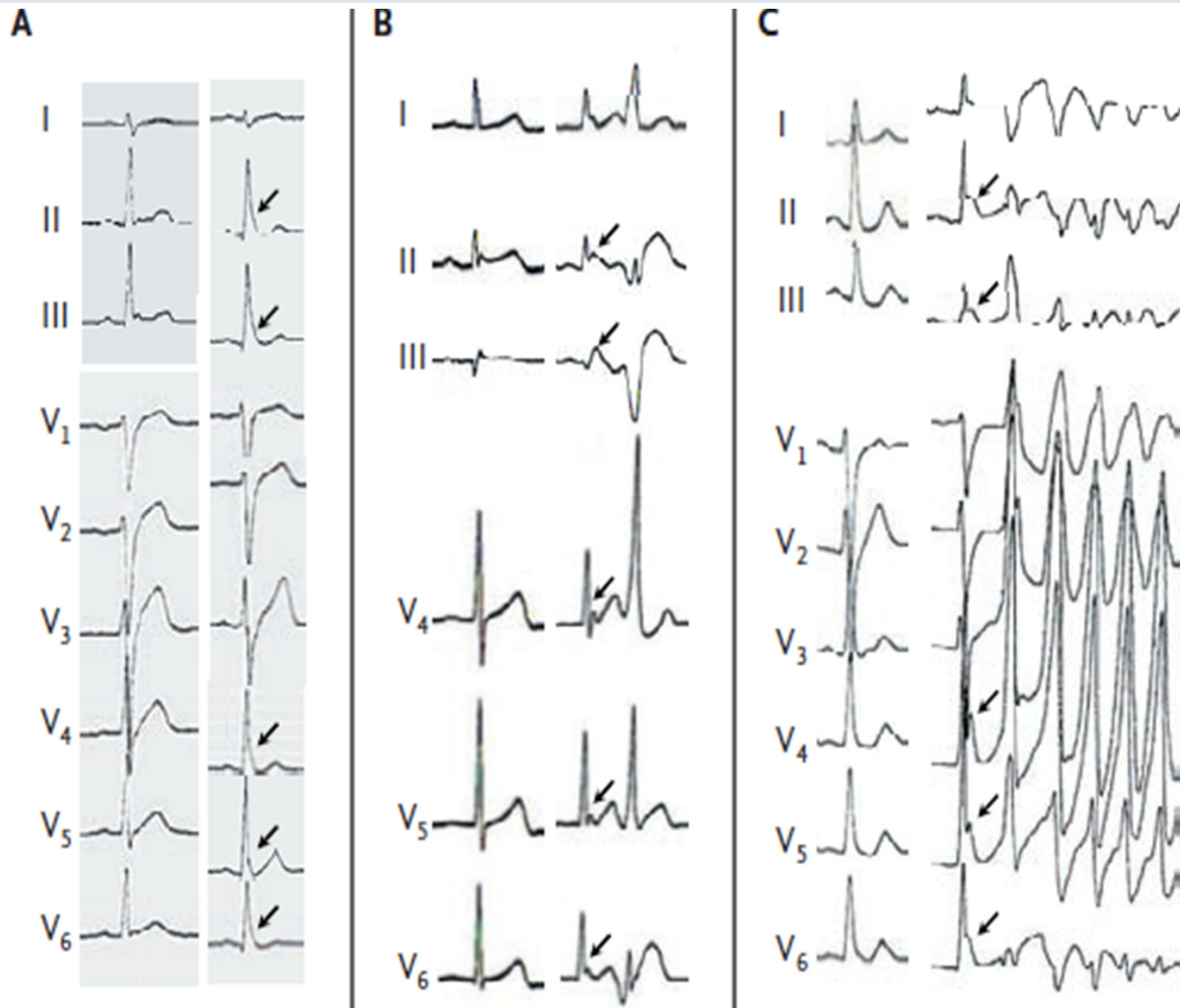
EARLY REPOLARIZATION SYNDROME

- Considered for a long time as a variant of « normal E.C.G. » (as there was no underlying heart disease).
- More recently : shown as linked with an increased risk for S.C.D.
- More particularly the Early Repolarisation in the inferolateral leads is associated with idiopathic VF.
- Several different mutations have been correlated to the ER.
- There are some similarities between ER and the BrS and some authors suggest that they could be both form part of the same spectrum of disease.
- Different mutation patterns have been found that sometimes recall the BrS...
- Diagnostic :
 - On the surface E.C.G.
 - Early repolarization potentials.
 - On leads V4V5V6 and DII, DIII, Vf
 - Male > Female (among those that have ventricular arrhythmias).

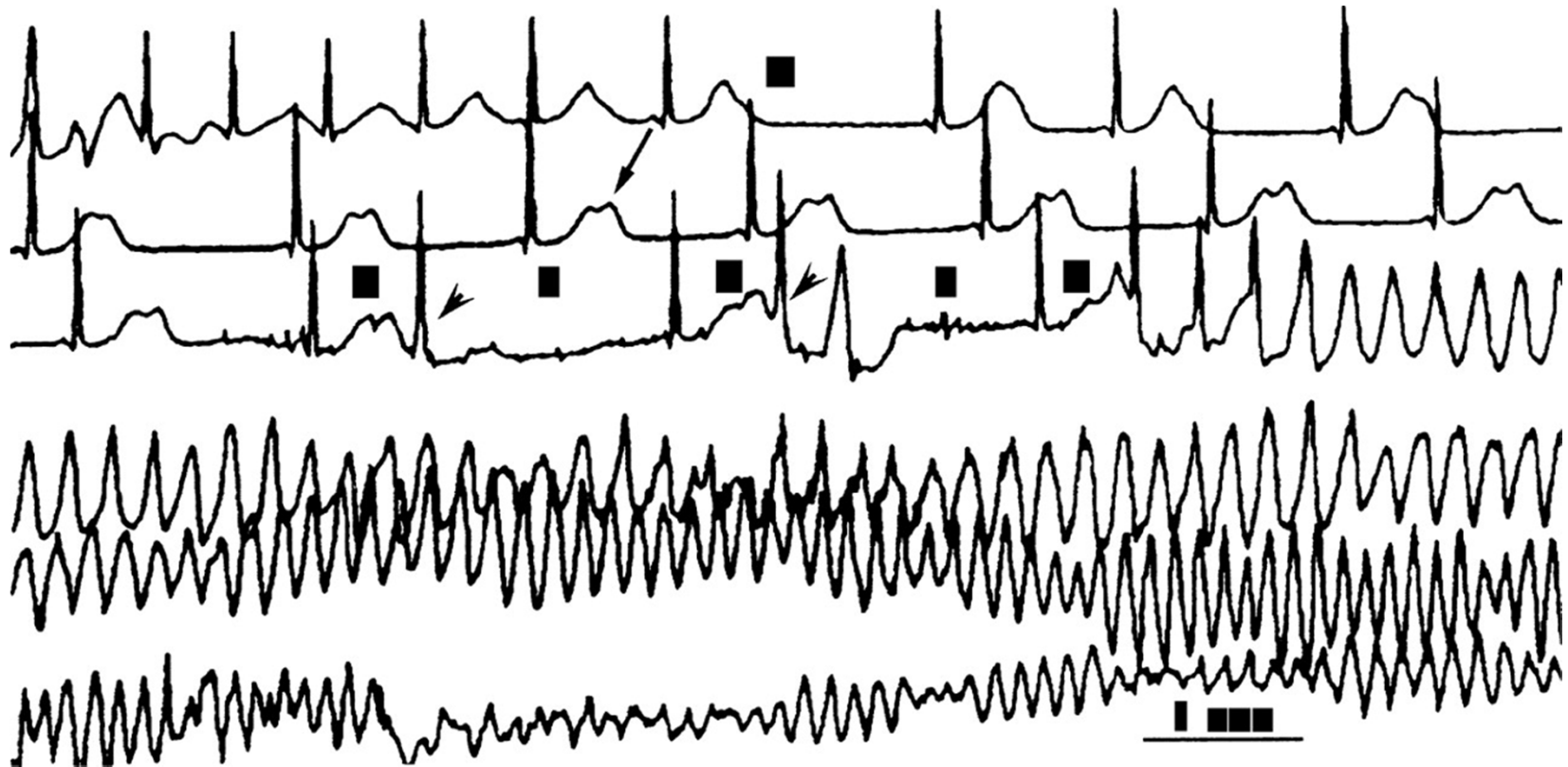
EARLY REPOLARIZATION SYNDROME



EARLY REPOLARIZATION SYNDROME



UNDEWRITING THE CHANNELOPATHIES



CHANNELOPATHIES AND LIFE INSURANCE BUSINESS

- Patients who experienced sudden death and have been successfully resuscitated are eligible to the implantation of an automatic implantable cardioverter defibrillator (AICD), possibly associated with a specific drug therapy (such as β -blockers) and lifestyle modifications.
- Among such patients with a history of sudden death, it has been statistically shown that the **implantation of an AICD improves the long term survivor's ratio**; and upon a clinical experience, sudden death in such patients is extremely rare after the implantation of a cardioverter-defibrillator.
- As these diseases are genetically transmitted and as far as there are often some family genetic testing after a channelopathy has been discovered, there are now more people who are asymptomatic, without any organic heart disease who are known as “carriers of a channelopathy”.
- Though such an attitude might be doubtful as this therapy is not harmless, some people today may be implanted with a cardioverter on a so called “prophylactic purpose”.

CHANNELOPATHIES AND LIFE INSURANCE BUSINESS

- Most of the patients who underwent a sudden death and have been resuscitated and implanted then with an AICD are considered as **uninsurable** even though we know that this therapy is now to be considered as safe and reliable. As a matter of fact, “Channelopathies” a pretty heterogeneous cohort and mutualized statistics on purpose of life and health insurance are currently impossible. Moreover, there are some complications like the rythmic storms that may happen in such patients , the prognostic of with is often severe.
- There’s a “**grey zone**” concerning those with few, atypical or no symptoms that might be treated by drug therapy (β -blockers) and lifestyle changes, and sometimes implanted by an AICD, considering their family history and/or the results of an electrophysiological study. Such people, without any organic heart disease, and sometimes without symptoms, but in whom an AICD has been “preventively implanted”, would have been considered as insurable at normal rate before the genotyping and the family inquiry was done. .. And They become “uninsurable” then, because of the therapeutic issue they have underwent, on a so called “prophylactic purpose” only.

CHANNELOPATHIES AND LIFE INSURANCE BUSINESS

- As a matter of fact, such patients (applicants) are rather rare today but, as far as we improve our knowledge about these Channelopathies, it is likely that their number will increase in the near future.
- The therapeutic issues seem to be more accurate and reliable and their impact on the death ratio should be taken into consideration in the near future.
- Should such patients or people with a preventive therapy remain uninsurable? Or should we think about some underwriting hypothesis for them, at least for the death coverage?



- ✓ Taking also in consideration the fact that the AICD itself may sometimes be responsible for pro-arrhythmic effects ...
- ✓ And / or electrical or mechanical dysfunction may cause severe side effects and even lead to death...

ADVERSE EFFECTS OF THE AICD

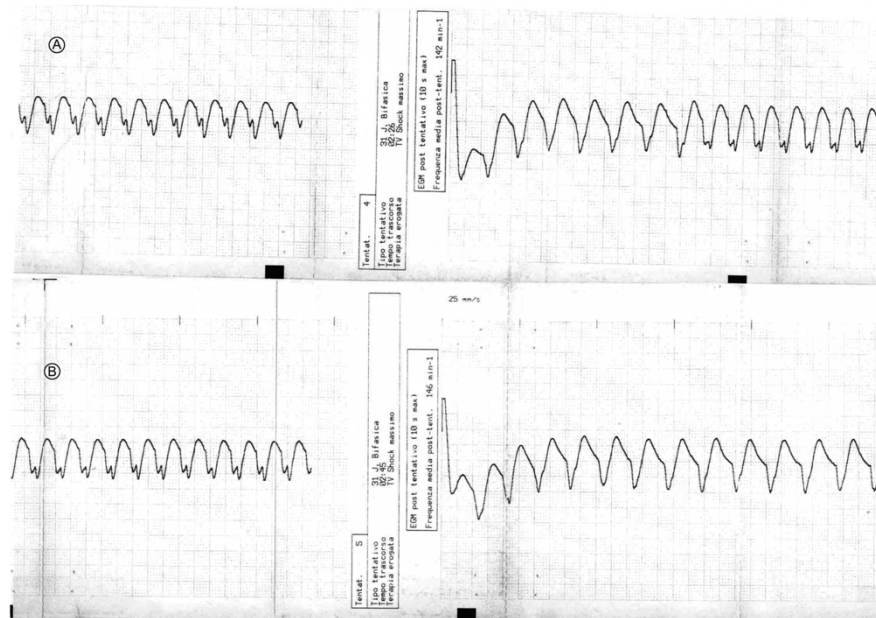
- THE AICD is probably the most important technological advance since Mirowski conceived the first implantable defibrillator cardioverter in the early 80ies.
- THE DEVICE ARE MORE EN MORE RELIABLE AND « INTELLIGENT » :
 - Making the diagnostic of a given arrhythmia.
 - Checking the best possible converting procedure (S1S2 - S1S2S3 - overdrive - Shock)
 - Able to pace in case of post-tachycardic pause.
 - Able to be equipped by a resynchronization process.
 - They also record any event and intervention of the AID /Holter function/
 - They are supposed to be setted on measure for any patient and its arrhythmia.
- BUT THERE ARE SOME ADVERSE EFFECTS THAT MAY OCCUR IN SUCH PATIENTS AND SOME AUTHORS, REGARDING THESE SIDE EFFECTS TALK ABOUT « REPROGRAMMING THE MODE OF DEATH »...

SIDE EFFECTS OF THE AICD

1. Infection - Bad tolerance of the device. Psychiatric incidence.
2. Compliance of the patient for the follow up and survey of the system that requires to be checked and replaced at the end of life of the batteries or in case of deterioration of the leads conduction capacities.
3. Misunderstanding from the AICD of the electrical signal => inappropriate pacing and/or inappropriate shocks that may lead to arrhythmias.
4. Technical problems related to the device (lead fractures, the case of Sprint Fidelis) => over detection of myopotentials that may lead to inappropriate shocks that can lead to a lethal arrhythmia.
5. Pacing hazards that may trigger an arrhythmia.
6. Proarrhythmia from local lead effects (mechanical stimulation).

THE ARRHYTHMIC STORMS.

- Arrhythmic Storm (AS) is defined as an occurrence of more than two episodes of malignant ventricular tachycardia over 24 hours.
- In patients with AICD, AS causes several shocks.
- Incidence of AS is almost 11% of ICD patients.
- mortality is # 25% (Krivan '99).
- pro arrhythmic effect of drugs, electrolytic disorders are the main causes of AS in the patients with channelopathies.



QUESTIONS IN TERMS OF CONCLUSION ...

- Could we consider that a patient with a long QT syndrome or a Brugada syndrome, an history of ACA who has been implanted by an AICD becomes an insurable after a certain time of follow up ?
- Should we consider that an applicant remaining asymptomatic, with a family history and/or a genotyping result that lead to the implantation of an AICD as being insurable ? at standard rate (*because he underwent some superlative therapy*) ?
- Any ECG of an applicant to Life Insurance policy should be carefully checked, QT interval being measured, the repolarization requires a close look to the shape of the ST-T as well as the possible existence of early depolarization...



QUESTIONS IN TERMS OF CONCLUSION ...

- Could we consider that a patient with a long QT syndrome or a Brugada syndrome, an history of ACA who has been implanted by an AICD becomes an insurable after a certain time of follow up ?
 - **Today the Brugada's syndrome, the long QT syndrome, remain generally uninsurable even though the risk of sudden death among those that have been implanted with an AID is quite low. The risk remains of an uncontrolled arrhythmia and the other channelopathies remain too rare and severe and severe to be insured.**
- Should we consider that an applicant remaining asymptomatic, with a family history and/or a genotyping result that lead to the implantation of an AICD as being insurable ? at standard rate (*because he underwent some superlative therapy*) ?
 - **We might be optimistic and assume that in the near future, the risk will be considered as insurable but probably with a substantial extra-mortality ratio as considering the risk related to the AID itself.**
- **Any ECG of an applicant to Life Insurance policy should be carefully checked, QT interval being measured, the repolarization requires a close look to the shape of the ST-T as well as the possible existence of early depolarization...**

Thank you for your attention!

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