

l'ECG dans les canalopathies de l'enfant à l'adulte



P Maury, Toulouse, France
2019

Maladies « électriques » responsables de MS sur cœur sain

**Long QT
(1957)**

**Brugada Syndrome
(1992)**

Short-coupled TdP
(1994)

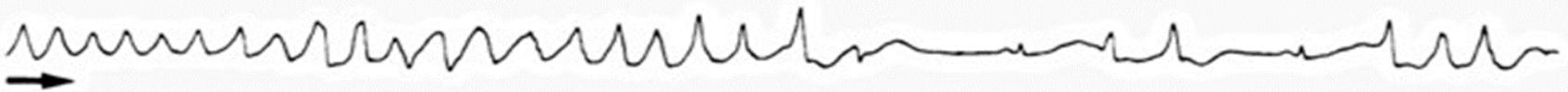
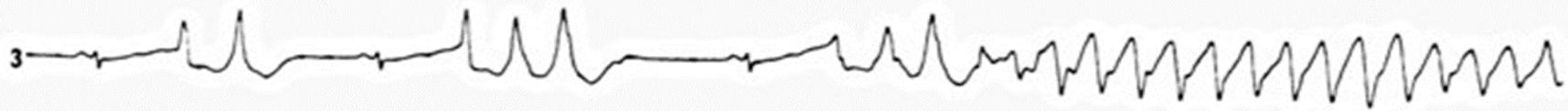
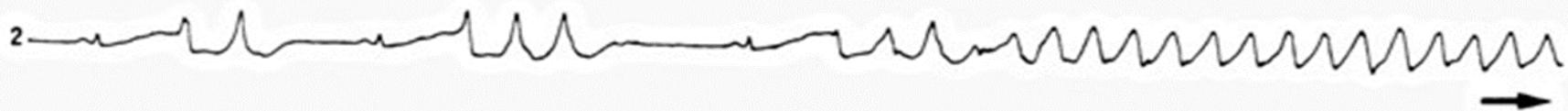
CPVT (1995)

Short QT (2000)

**Early
repolarization
(2008)**

Idiopathic VF
(1929)

éviter ca ...



Symptômes avant MS

LQT	70-90%
CPVT	50 %
Brugada	30 %
Repo précoce	40 %
QT court	65 %



Nécessité diagnostic avant événement fatal en cas de symptômes +++

Les occasions du diagnostic (avant la mort subite) signes d'appel +++

Syncope

Crise convulsive

Palpitations

Fièvre

Douleur thoracique

Surdit   (bilat  rale compl  te neuro-sensorielle)

Malformations visage, doigts

Paralysies hypokali  miques

ECG syst  matique: sport, grossesse, m  dications

MS familiale inexpiqu  e sujets jeunes

Les symptômes évocateurs (avant la mort subite)

Syncope d'effort

Noyade inexpiquée

Crise convulsive effort ou stress (contrariété)

Syncope ou convulsions après bruit

Syncope en phase fébrile

Convulsions nocturnes, cris ou respiration agonique, perte urines

Douleur thoracique inexpiquée

Les symptômes évocateurs (avant la mort subite)

- | | |
|---|------------------------------------|
| Syncope d'effort | LQT 1 et 2, CPVT |
| Noyade inexplicable | LQT1, CPVT |
| Crise convulsive effort ou stress (contrariété) | CPVT, LQT2 |
| Syncope ou convulsions après bruit | LQT2 |
| Syncope en phase fébrile | Brugada, LQT3 |
| Convulsions nocturnes, cris ou respiration agonique, perte urines | Brugada, repo précoce, LQT3 |
| Douleur thoracique inexplicable | Brugada |

Les anomalies ECG à repérer

Morphologie de la repolarisation

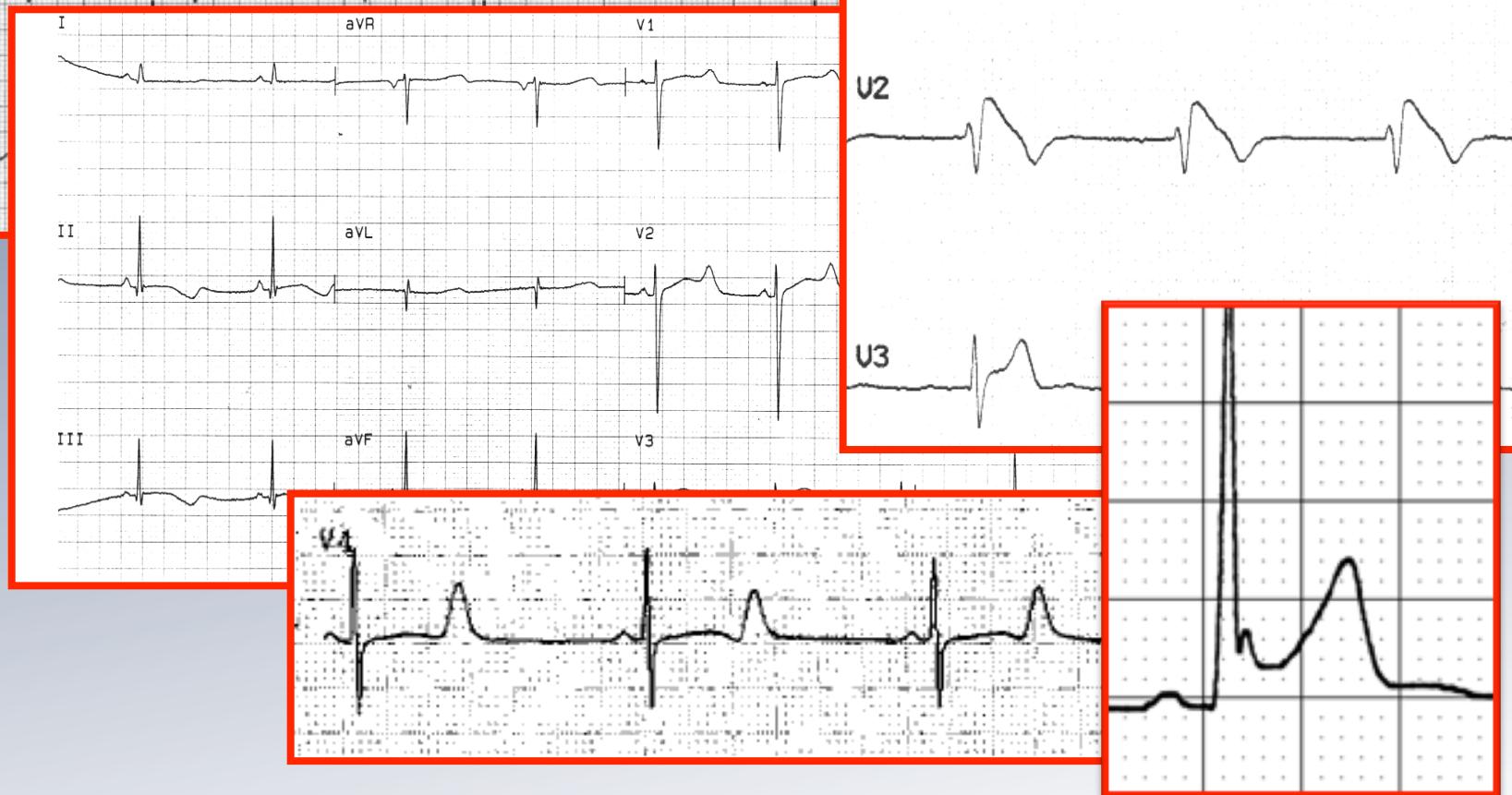
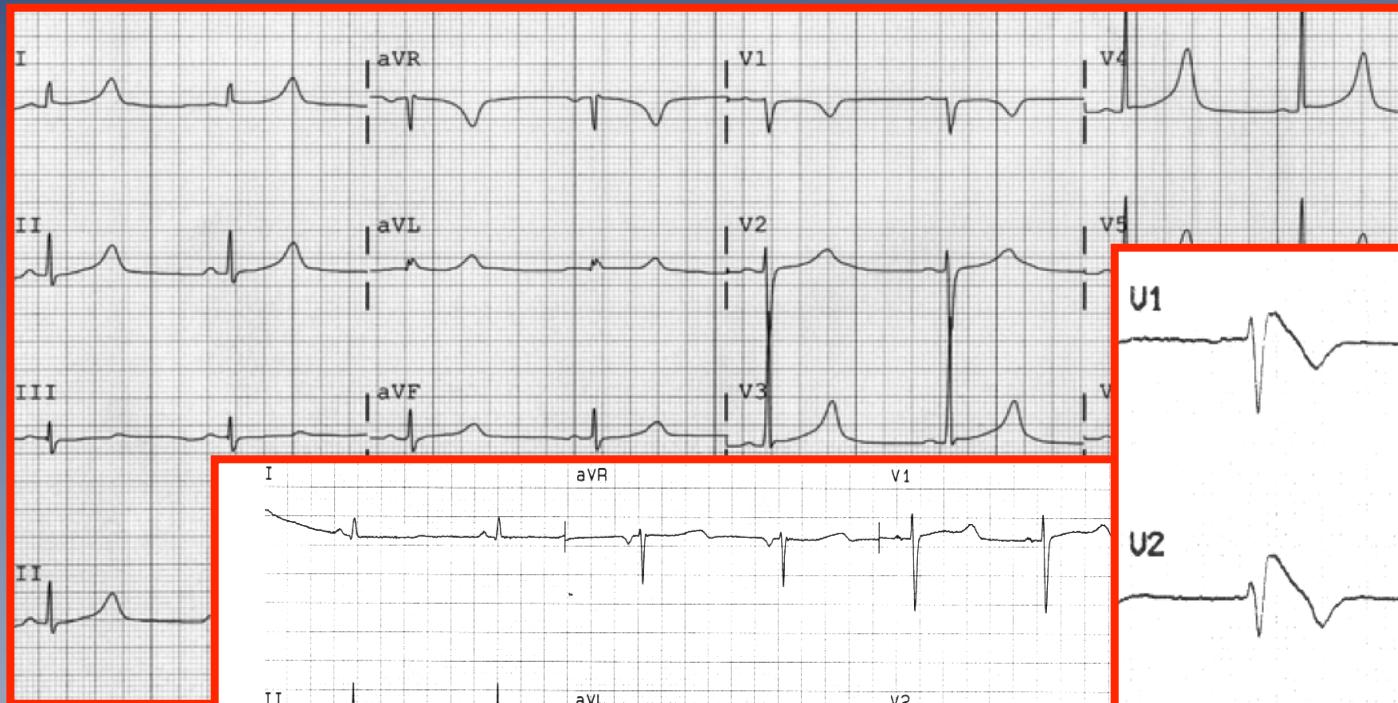
Troubles de conduction

Bradycardie sinusale

Extra systoles

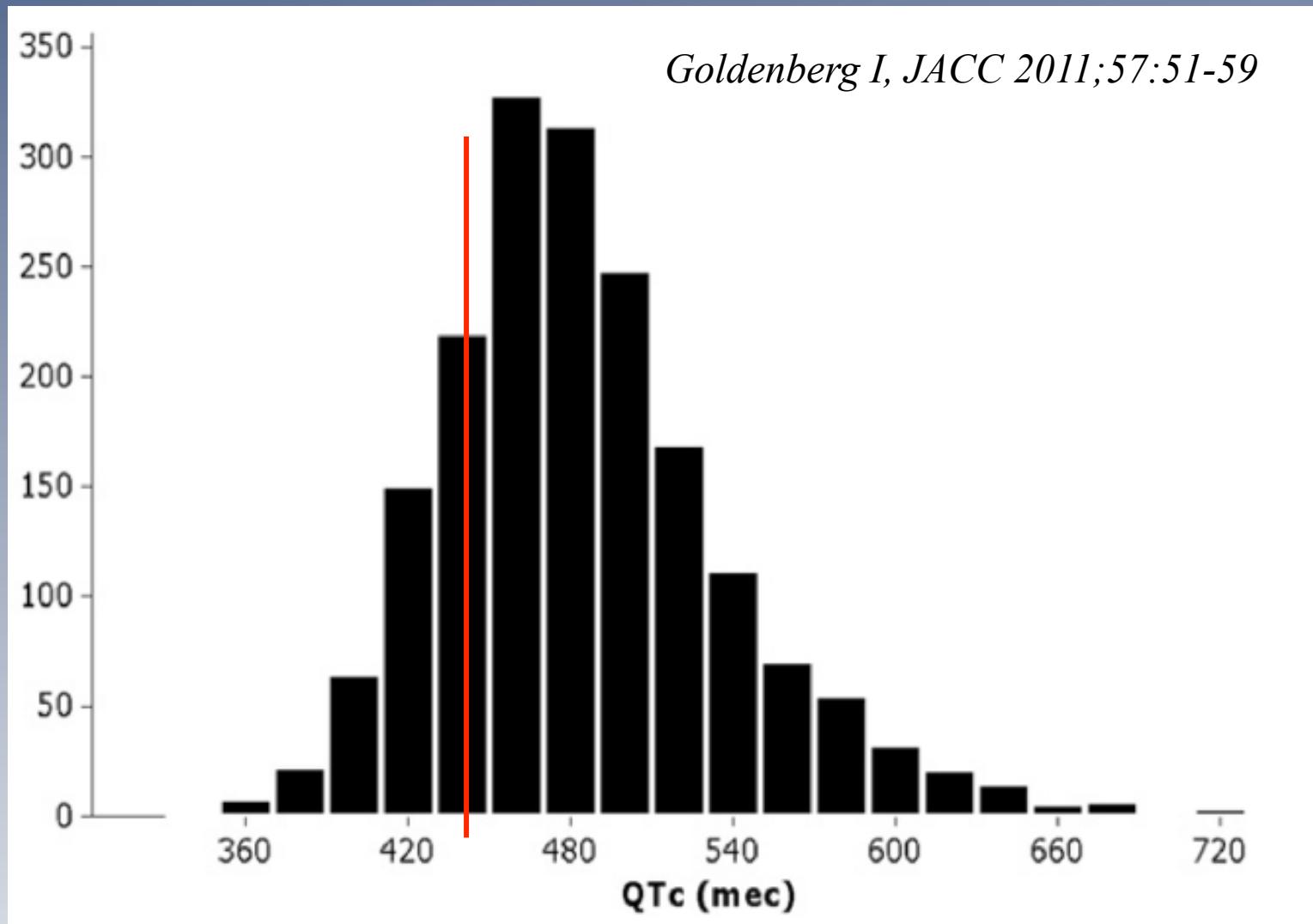
FA

Anomalie repolarisation sous drogues



QT Long

definition ?



25% des QT longs génotypés... ont un QTc normal ! (LQT1, 2 ou 3)

definition ?

actuellement

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

1. LQTS is diagnosed:
 - a. In the presence of an LQTS risk score ≥ 3.5 in the absence of a secondary cause for QT prolongation *and/or*
 - b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes *or*
 - c. In the presence of a QT interval corrected for heart rate using Bazett's formula ($QTc \geq 500$ ms) in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.
2. LQTS can be diagnosed in the presence of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

definition ?

actuellement

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

1. LQTS is diagnosed:
 - a. In the presence of an LQT1 mutation and/or absence of a secondary cause
 - b. In the presence of an LQT2 mutation in one of the LQT genes
 - c. In the presence of a QT interval prolongation using Bazett's formula ($QTc = \sqrt{RR} \times 0.035 + 0.12$) on a 12-lead electrocardiogram (ECG) in the absence of a secondary cause for QT prolongation.

TABLE 2. 1993 LQTS Diagnostic Criteria

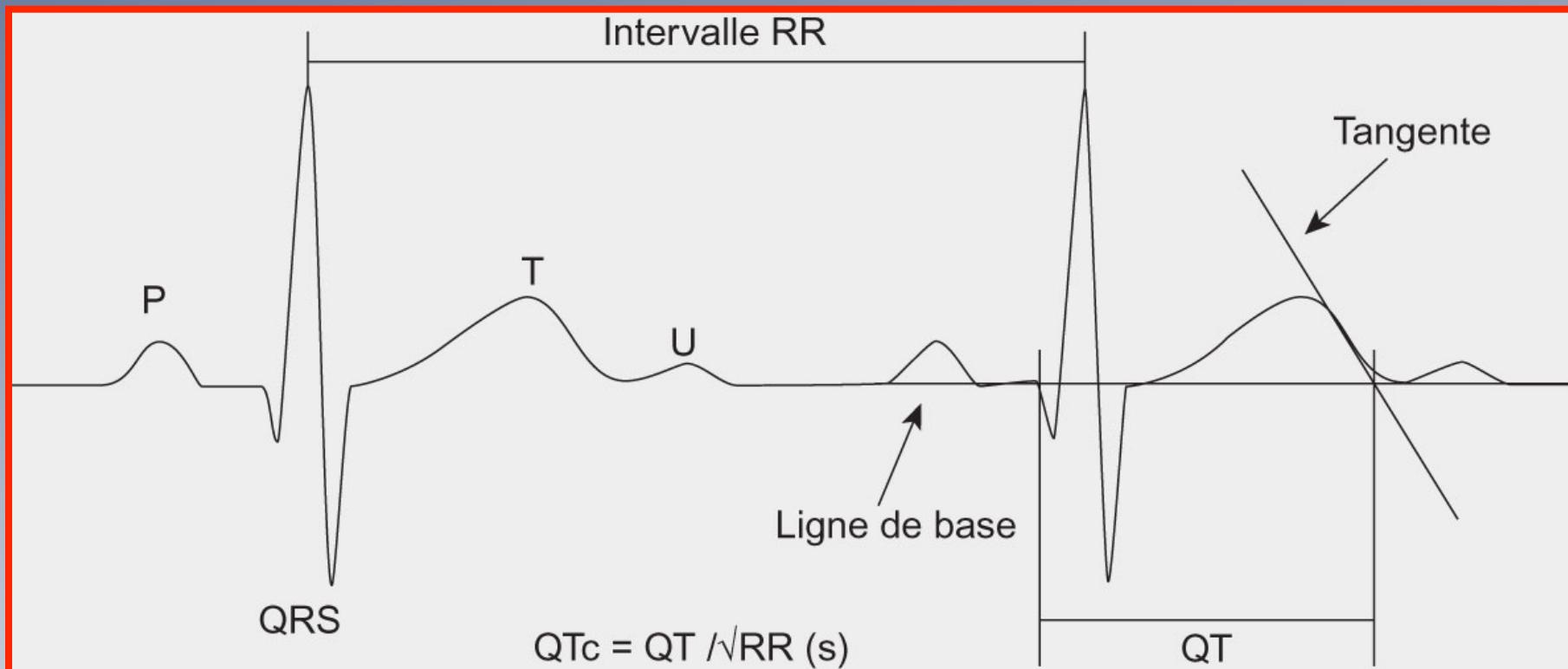
	Points
ECG findings*	
A. QTc† ≥480 msec ^{1/2}	3
460-470 msec ^{1/2}	2
450 msec ^{1/2} (in males)	1
B. Torsade de pointes‡	2
C. T-Wave alternans	1
D. Notched T wave in three leads	1
E. Low heart rate for age§	0.5
Clinical history	
A. Syncope‡ With stress	2
Without stress	1
B. Congenital deafness	0.5
Family history	
A. Family members with definite LQTS#	1
B. Unexplained sudden cardiac death below age 30 among immediate family members	0.5

Comment mesurer le QT ?

1. Mesure

II, V2 ou V5-V6 (ou le plus long) 50 mm/sec

Rythme sinusal stable 50 - 80 bpm (sinon moyenné 3-5 QRS)



2. Correction

Formule Bazett

$$QTc = QT (\text{ms}) / \sqrt{RR} (\text{sec})$$

Le QT long n'est pas un diagnostic aisé !

Sur 902 médecins interrogés ...

	LQTS	LQTS	Control	Control
Correct results (%)	QT	QTc	QT	QTc
Arrhythmia specialists	73%	73%	91%	72%
Cardiologists	75%	53%	67%	48%
Non-cardiologists	68%	32%	61%	31%

diagnostic correct de QT long vrais

> 80 % électrophysiologistes

< 50 % cardiologues

< 40 % non cardiologues

Diagnostic correct de tout QT (normal ou long)

62 % électrophysiologistes

< 25 % cardiologues and non cardiologues

Some help ?

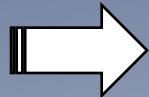
Ep effort

4 min récup: QTc > 445 ms

Swan H, JACC 1999

Sy RW, Circulation 2011

Horner RM, Heart Rhythm 2011



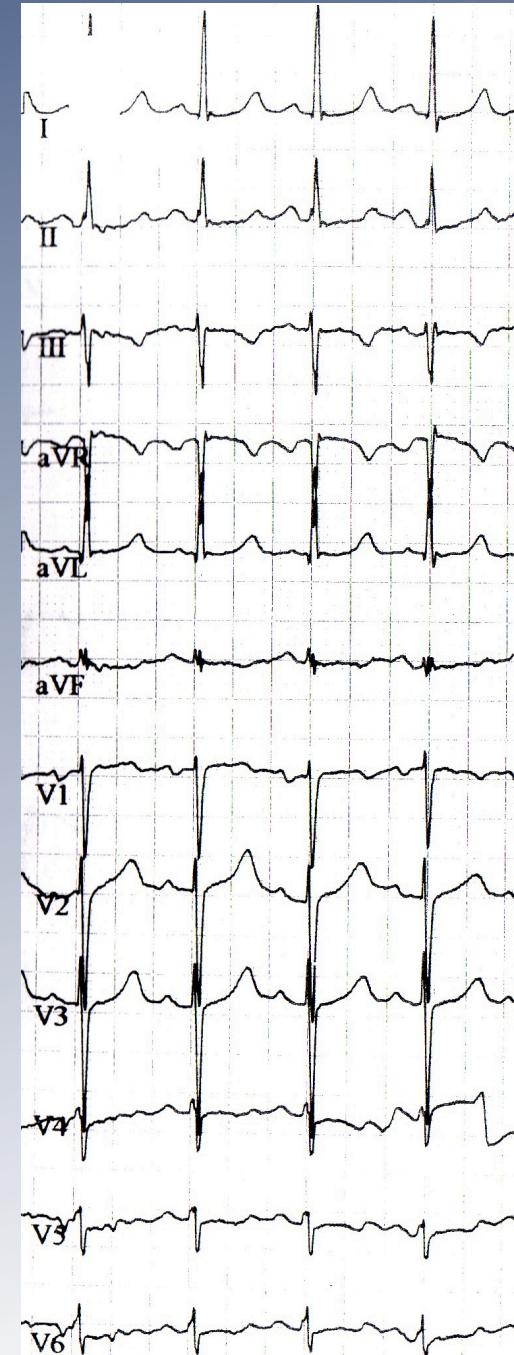
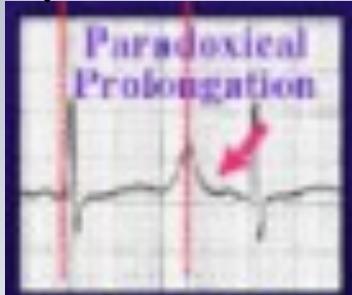
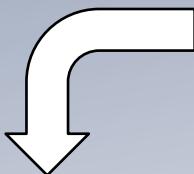
Standing ECG, stress mental

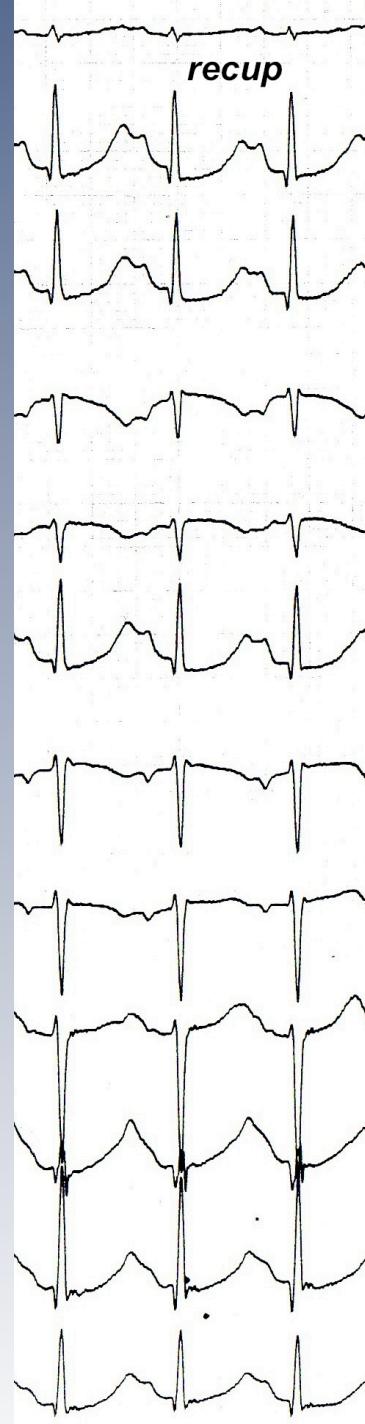
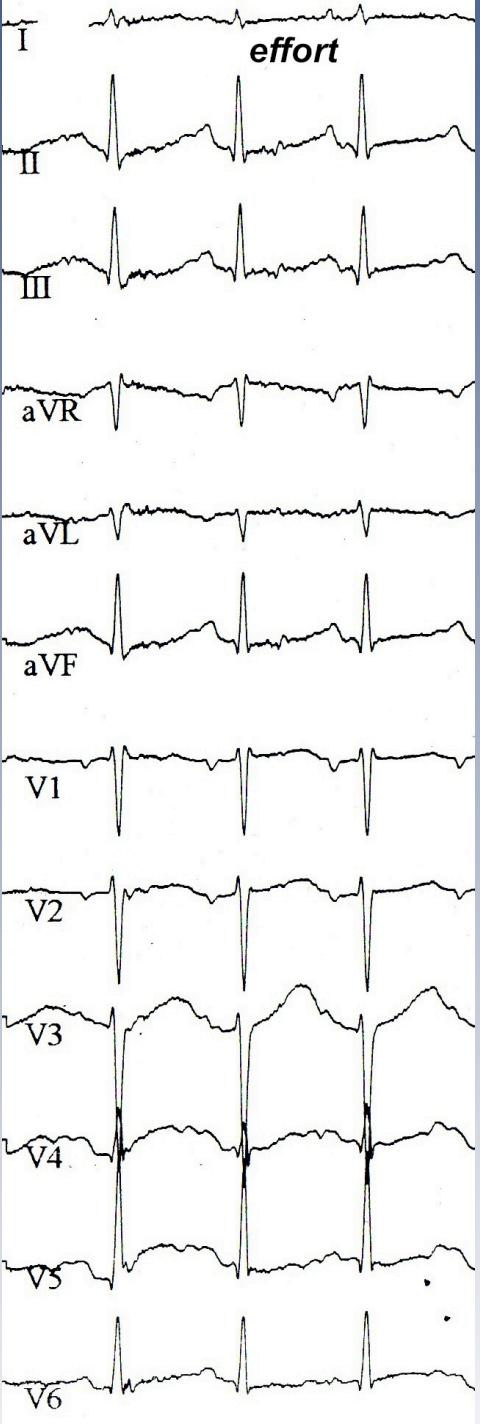
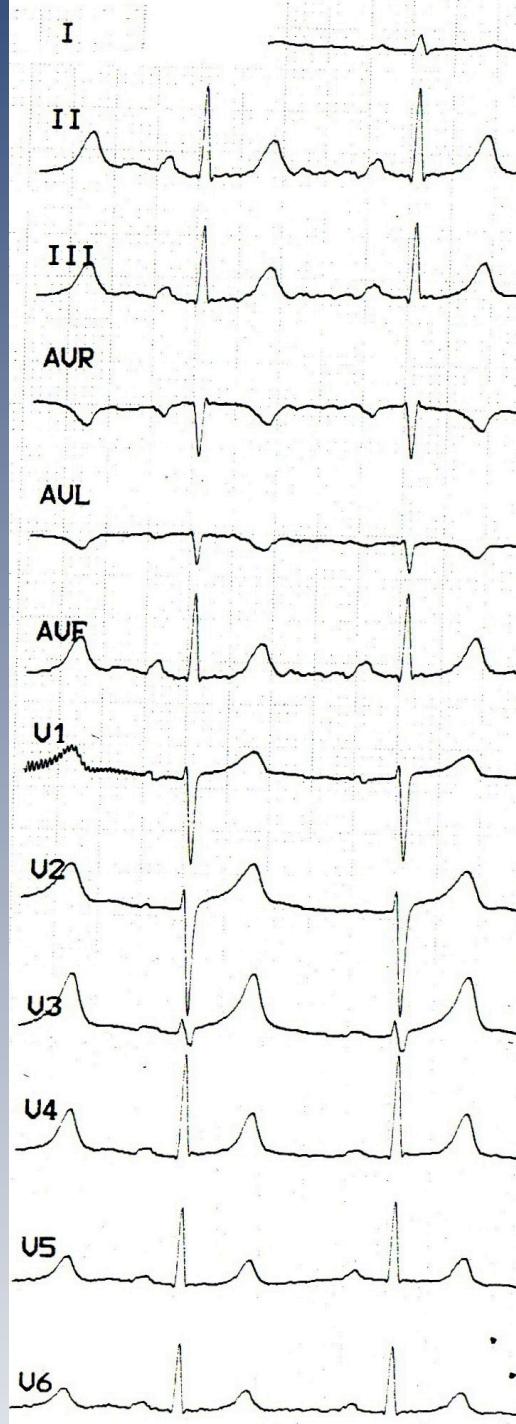
Viskin S, et al. 2010

adrénaline

Ackerman, Mayo Clin Proc 2002

Shimizu, Heart Rhythm 2004





Genetical heterogeneity

GENE	LOCUS	PROTEIN
Long QT Syndrome		
<i>Major LQTS Genes</i>		
KCNQ1 (<i>LQT1</i>)	11p15.5	I_{Ks} potassium channel α subunit (KvLQT1, Kv7.1)
KCNH2 (<i>LQT2</i>)	> 90% 7q35-36	I_{Kr} potassium channel α subunit (HERG, Kv11.1)
SCN5A (<i>LQT3</i>)	3p21-p24	I_{Na} sodium channel α subunit (NaV1.5)
<i>Minor LQTS Genes</i> (listed alphabetically)		
AKAP9	7q21-q22	Aktao
CACNA1C	12p13.3	Voltage gated L-type calcium channel (CaV1.2)
CALM1	14q32.1	Calmodulin
CALM2	2p21	Calmodulin
CAV3	3p21.3	Caveolin-3
KCNE1	12q22.1	Kv7.1 potassium channel beta subunit (MinK)
KCNE2	12q22.1	Kv11.1 potassium channel beta subunit (MiRP1)
KCNJ5	10q24.3	Potassium inwardly-rectifying channel (Kir3.4)
SCN4B	11q23.3	Sodium channel beta 4 subunit
SNTA1	20q11.2	Syntrophin-alpha 1
20% without (known) mutation		
Ankyrin-B Syndrome		
ANK2	4q25-q27	Ankyrin B
Andersen-Tawil Syndrome		
KCNJ2 (<i>ATS1</i>)	17q23	I_{K1} potassium channel (Kir2.1)
Timothy Syndrome		
CACNA1C	12p13.3	Voltage gated L-type calcium channel (CaV1.2)

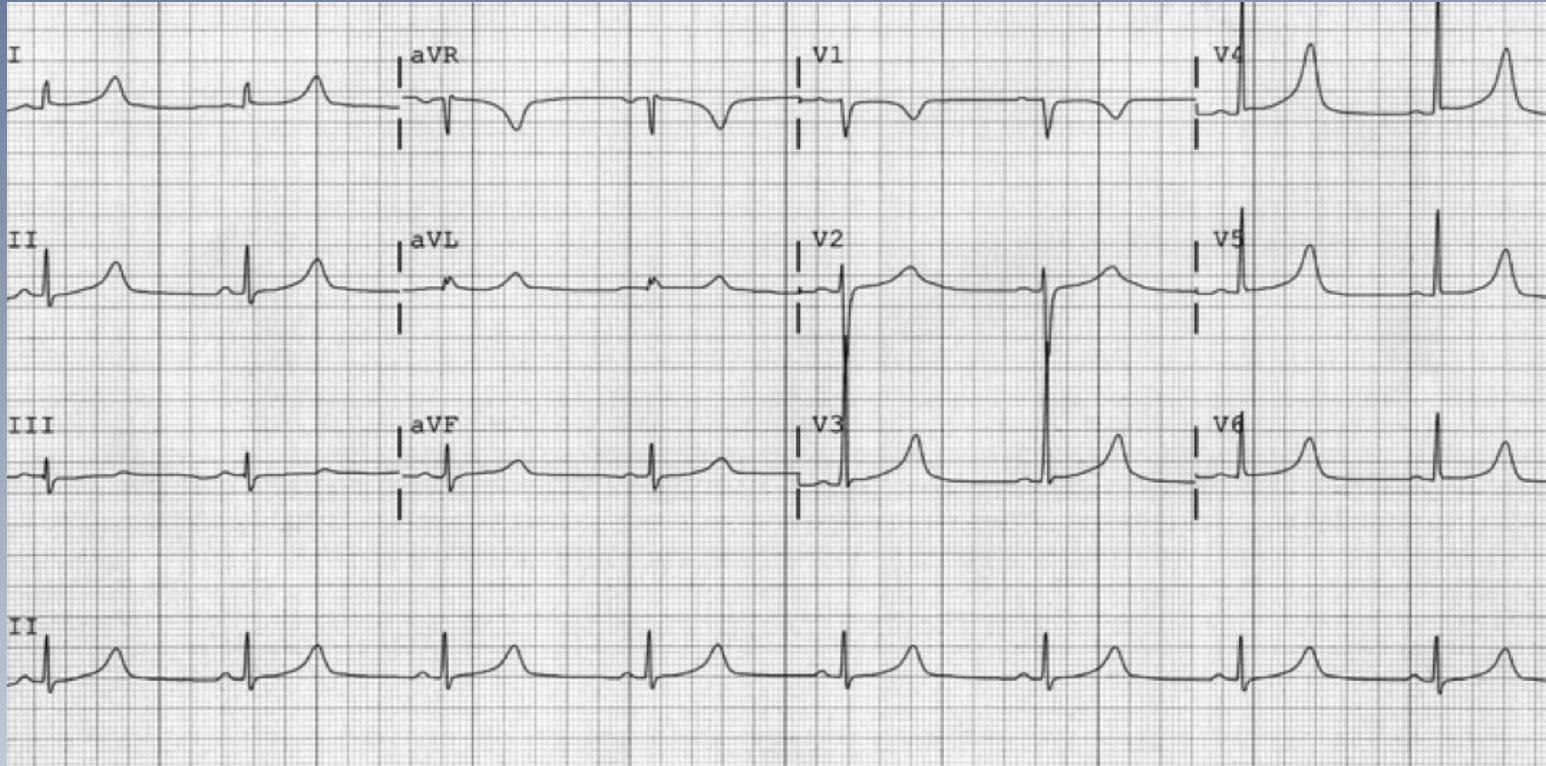
From Tester DJ, Ackerman MJ. Methodist Debakey Cardiovasc J. 2014

LQT 1

(Keating et al., Science 1991)

Mutation KCNQ1 (11p15.5)

α subunit IK_s



50 % cas (Khan et al., Am Heart J 2002, Splawsky, Priori)

Onde T ample et assymétrique (large base)

Arythmies: exercice (nage) ou emotion/stress > 95 %

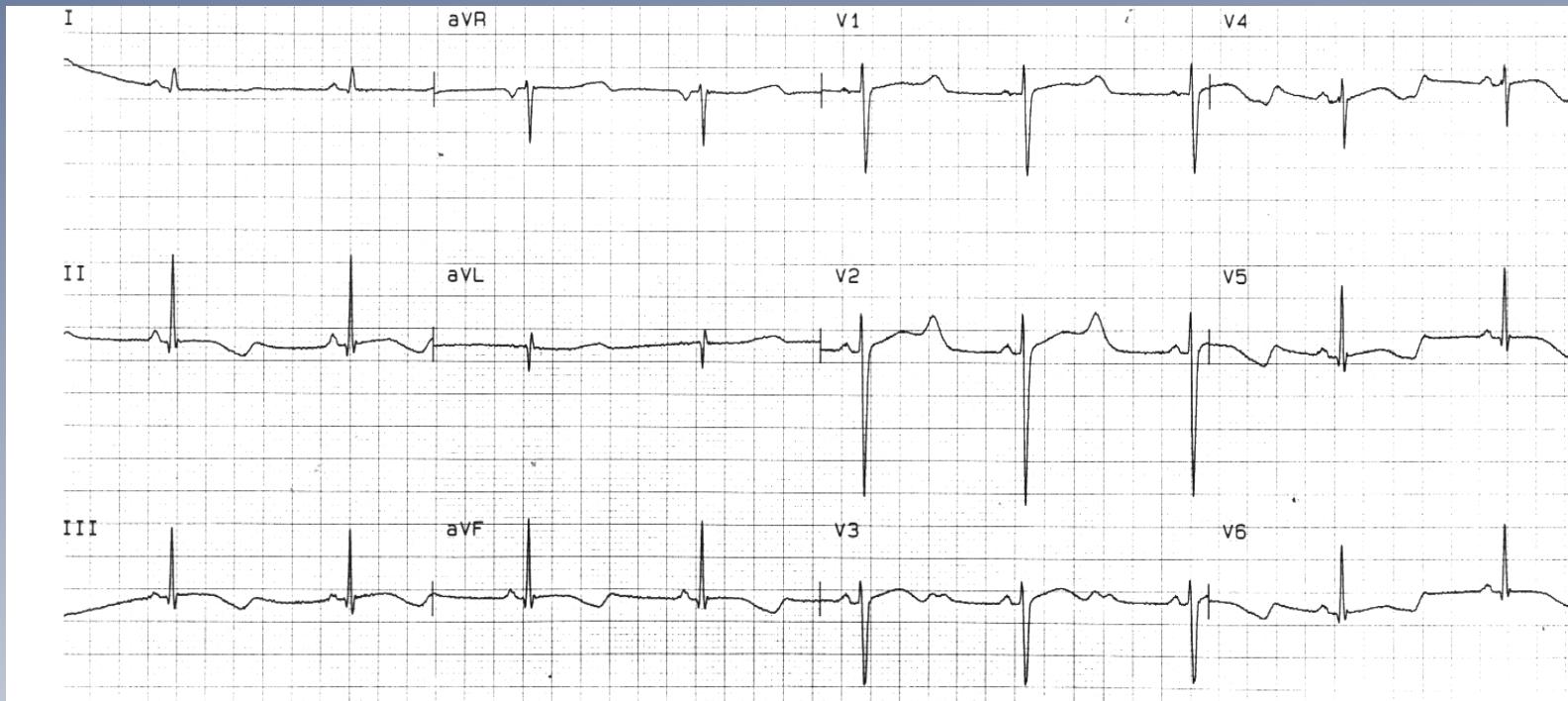
LQT 2

(Curran ME et al., Cell 1995)

Mutation KCNQ2 (HeRG)

(7q35-36)

α subunit IK_R



30/45 % cas (Khan et al., Am Heart J 2002, Splawsky, Priori)

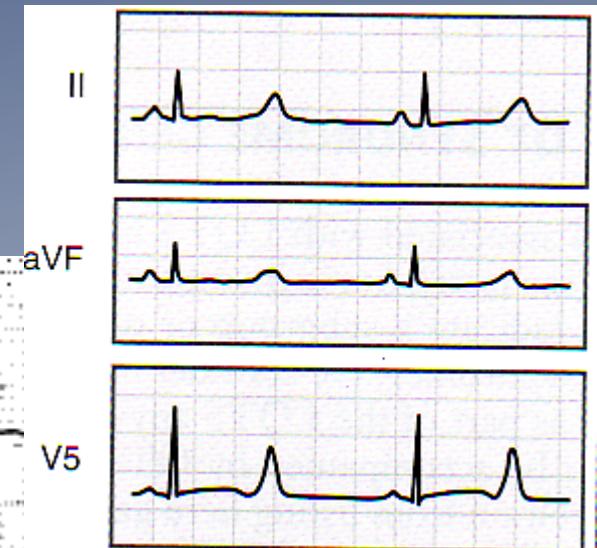
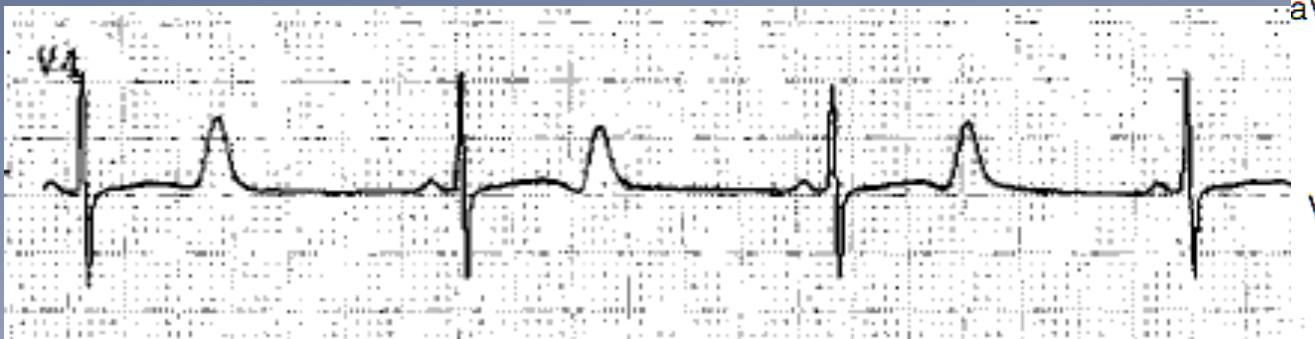
Onde T crochetée ou plate

Arythmies: exercice 15 %, stress (bruits) 35 % repos 50 %

LQT 3

(Wang Q et al., Cell 1995)

Mutation SCN5A (3p21-24) α subunit IN_A

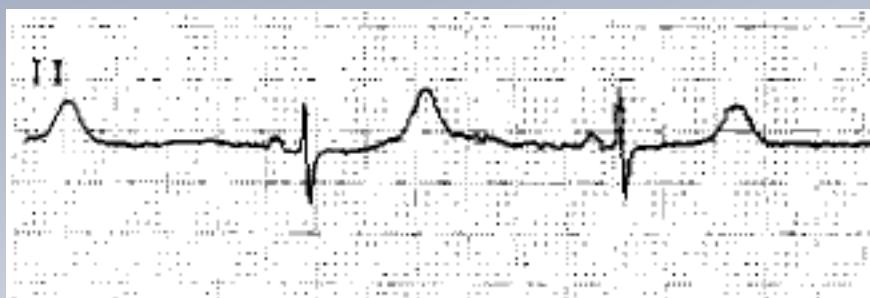


Moss AJ et al., Circulation 1995

Onde T ample et
ST segment long

5/15 % cas (Khan et al., Am Heart J 2002,
Splawsky, Priori)

Arythmies: ¾ repos (pause dependant)



Andersen-Tawill syndrome (LQT 7)

(Plaster NM et al., Cell 2001)

paralysie périodique hypoK Malformations

Arythmies:

ESV, TV bidirectionnelles

Torsades de pointes

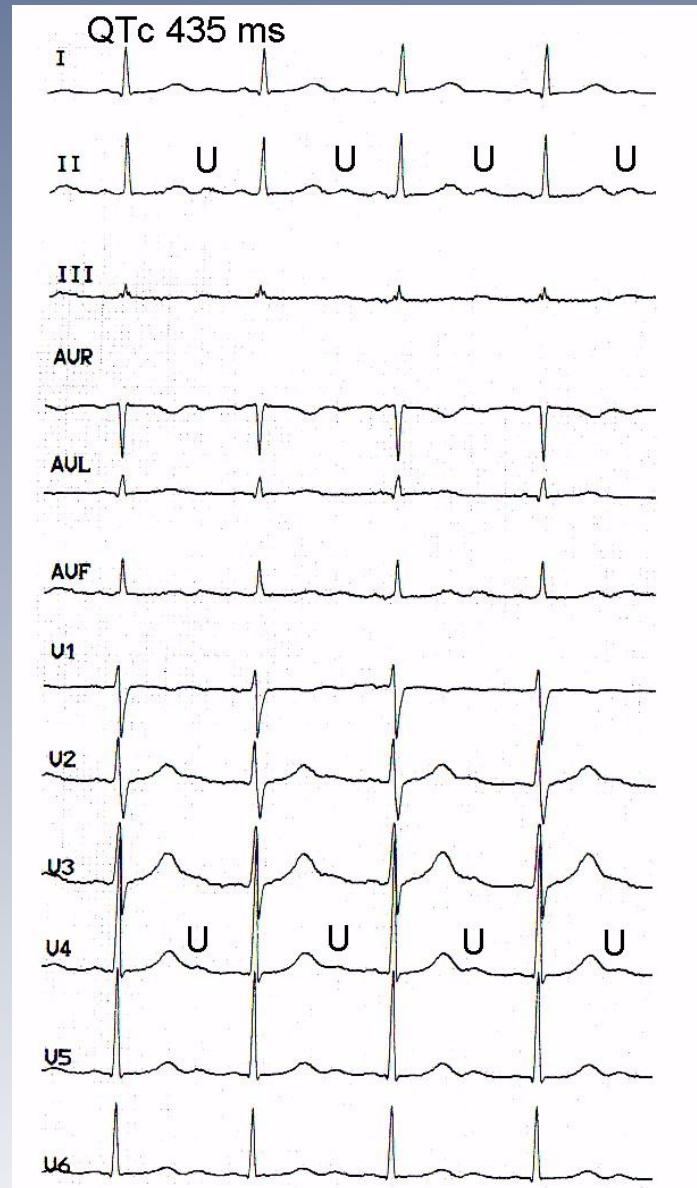
MS plus rare

Surtout si hypoK

Mutation KCNJ2 (17q23) (IK1)

« normal » QT et ondes U +++

Arythmies: adrénergique



LQT 4

(Schott JJ et al., Am J Human Genet 1995)

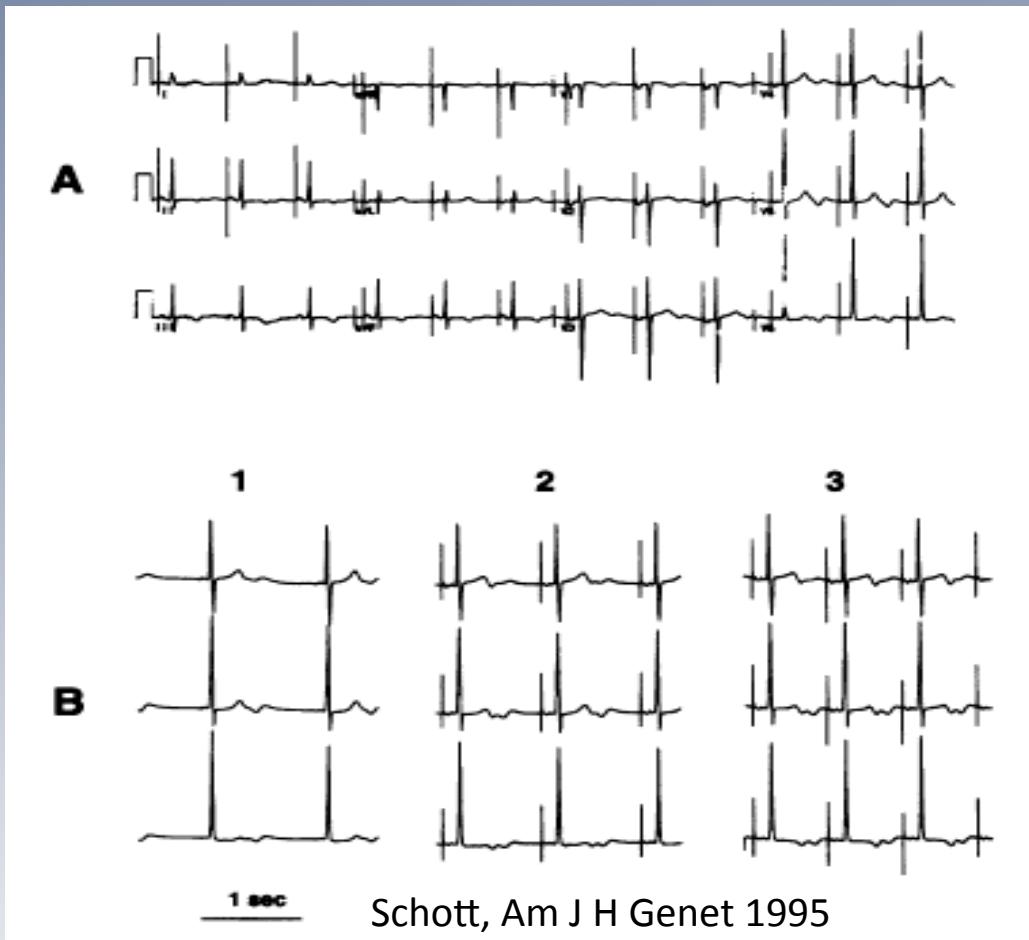
(2009 : 21 mutations sur Ank2)

Mutations sur l'ankyrine B (protéine d'ancre des canaux à la mb)

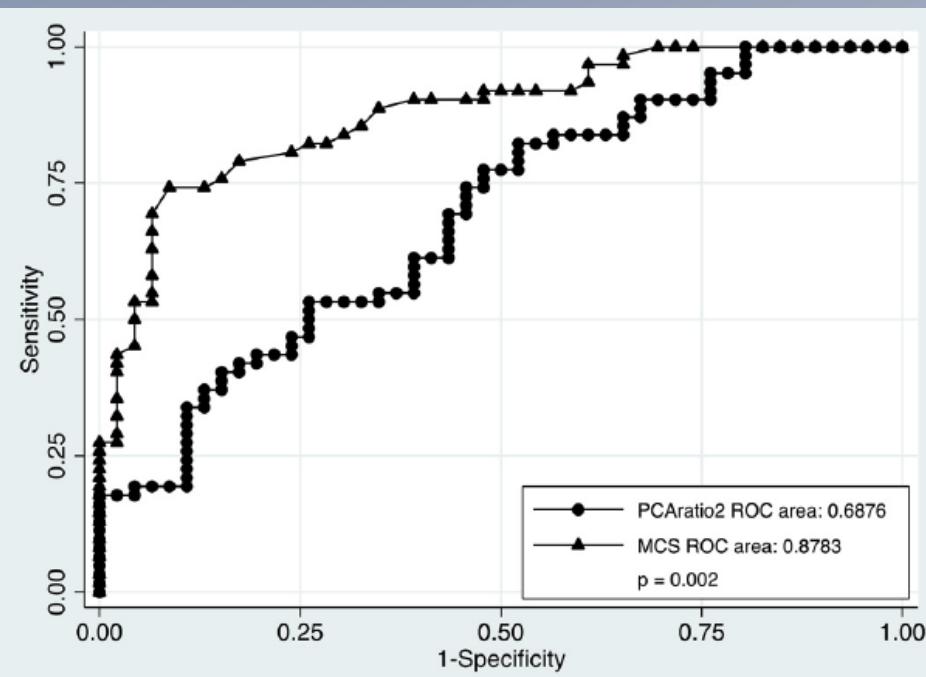
perte d'expression
et défaut de localisation de

- échangeur Na-Ca
- pompe Na-K
- récepteur InsP3

**Dysfonction sinusale
et arythmies atriales**



T wave morphology



assymétrie
amplitude (« flatness »)
notching
diff entre 1 et 2eme composants

T-Wave Morphology Analysis in Congenital Long QT Syndrome Discriminates Patients From Healthy Individuals

Andreu Porta-Sánchez, MD,^a David R. Spillane, MSc, MDCM(c),^b Louise Harris, MD,^a Joel Xue, PhD,^c Pat Dorsey, BS,^c Melanie Care, MSc,^c Vijay Chauhan, MD,^a Michael H. Gollob, MD,^a Danna A. Spears, MD^a

(J Am Coll Cardiol EP 2017;3:374-81)

Diff significatives entre témoin et LQT avec QT c normaux

Syndrome de Romano - Ward

**Immense majorité des cas
pas de surdité
transmission dominante**

hétérozygote KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2 etc

Syndrome de Jervell - Lange Nielsen

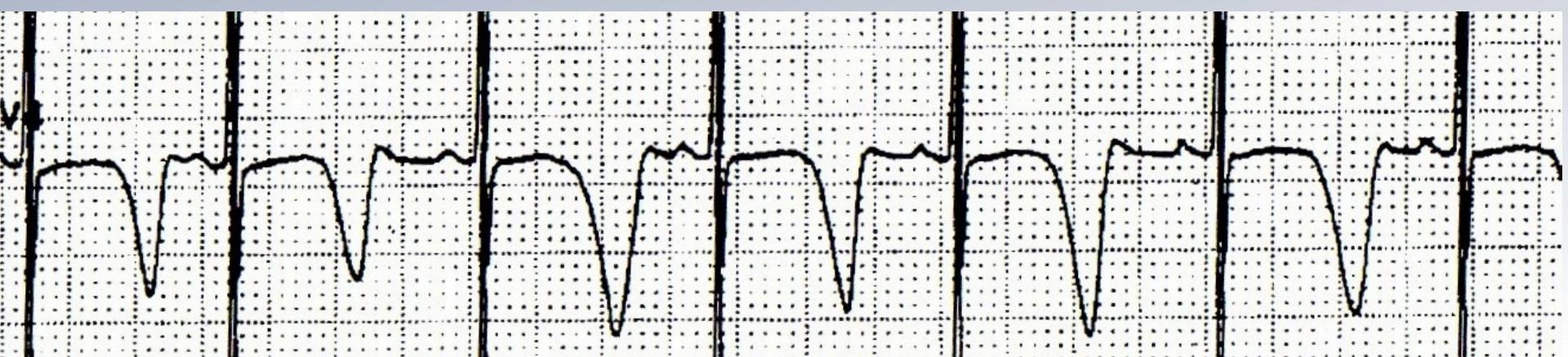
< 1% LQT 1/300.000 naissances, 0,3 % des sujets sourds

récessif

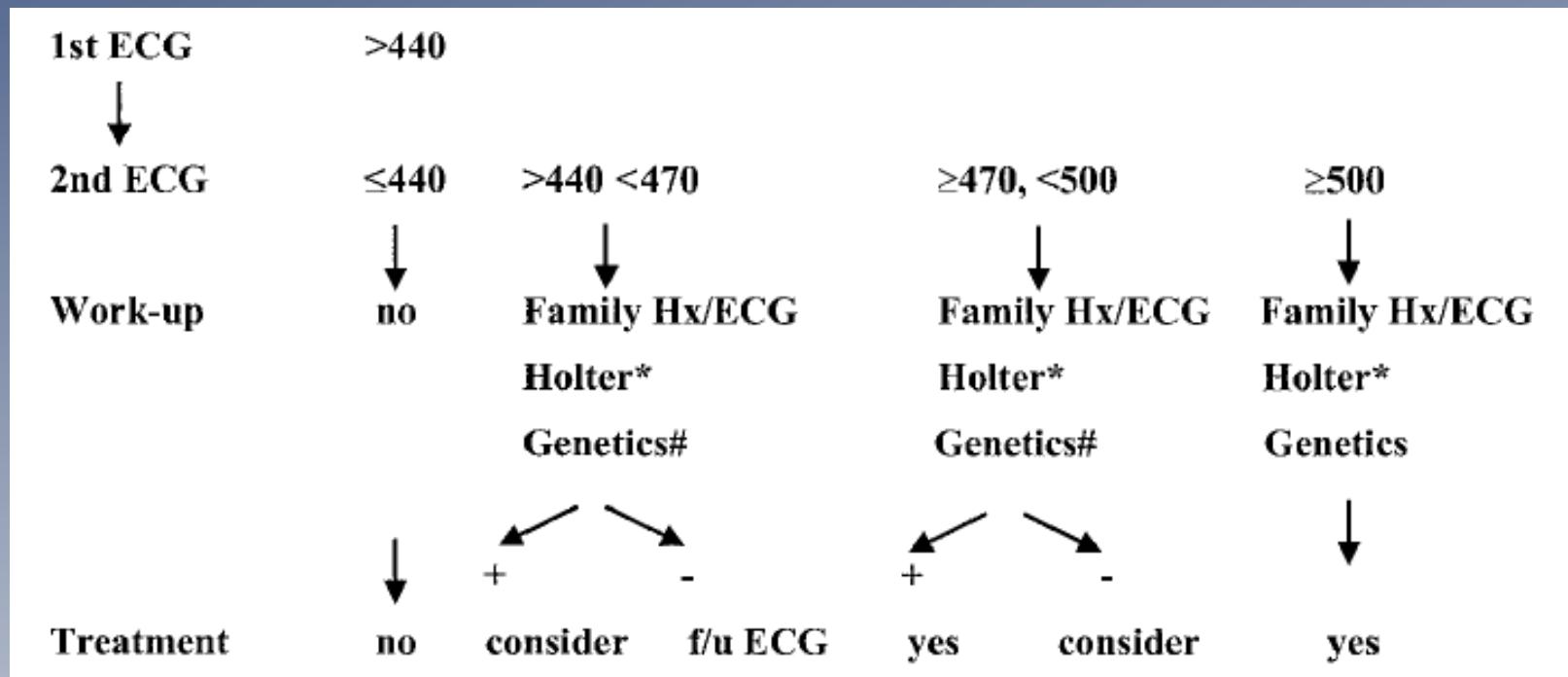
surdité: congénitale, bilatérale, de transmission, totale

perte de fonction IKs oreille interne (cellules marginales de la strie vasculaire,
rôle dans homéostasie K⁺ de l' endolymph)

homozygote (ou double heterozygote) mutations KCNQ1 ou KCNE1



Chez le n né ?

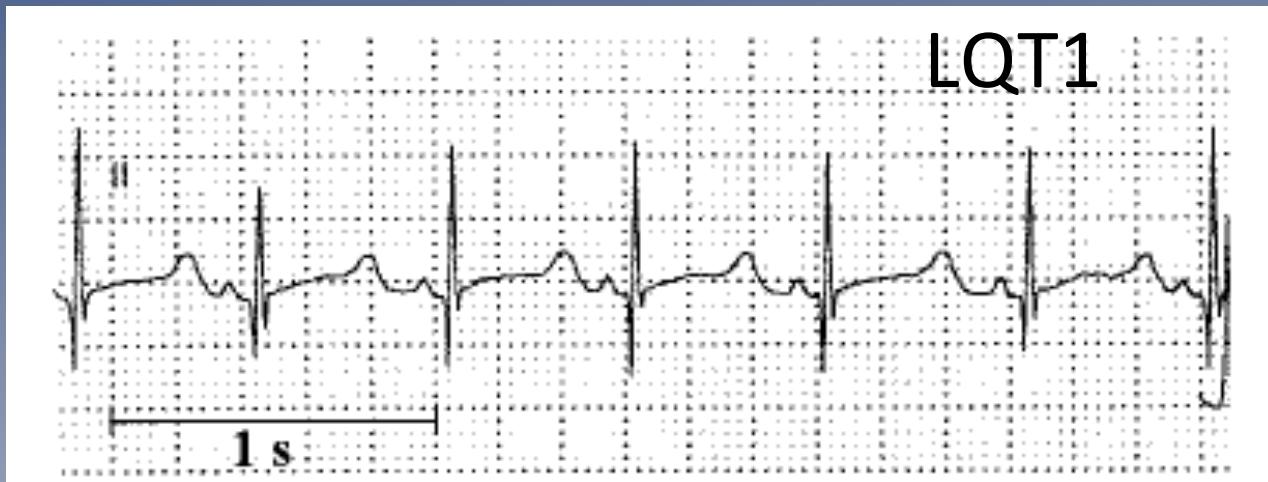


repeated ECG + bradycardia + family ECG/history + Holter + genetic

De novo mutation 30%

Guidelines for the interpretation of the neonatal electrocardiogram.
Eur Heart J. 2002 Sep;23(17):1329-44.

Chez le nouveau-né ?



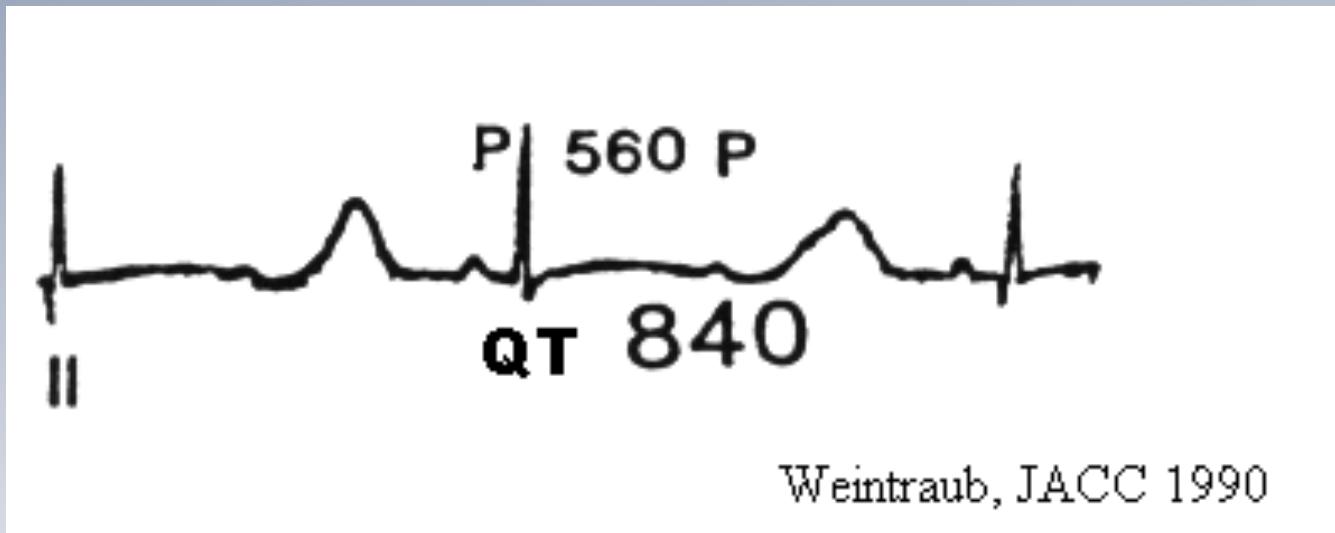
*Guidelines for the interpretation of the neonatal electrocardiogram.
Eur Heart J. 2002 Sep;23(17):1329-44.*

Other arrhythmias

Sinus node bradycardia / sick sinus syndrome (pauses)

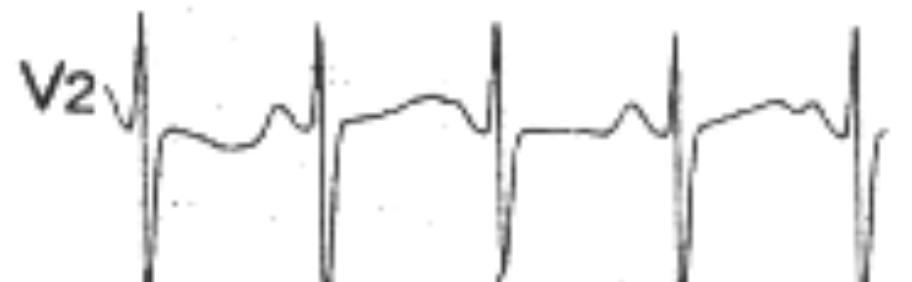
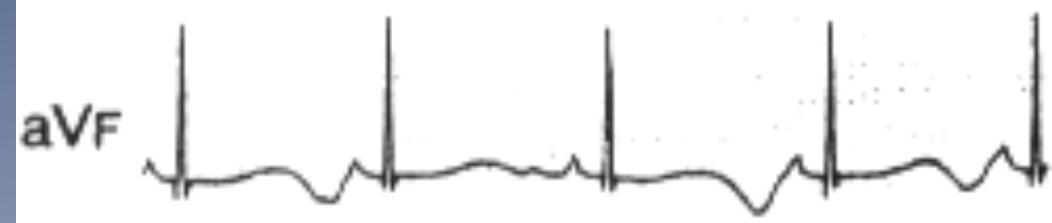
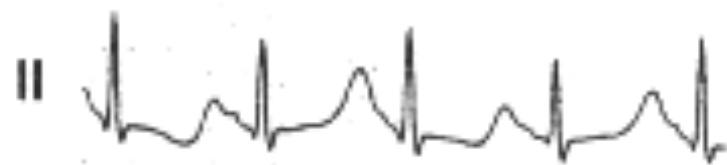
1/3 patients (LQT 3 and LQT 4)

Atrial arrhythmias (Afib, atrial salvos) (LQT 4)



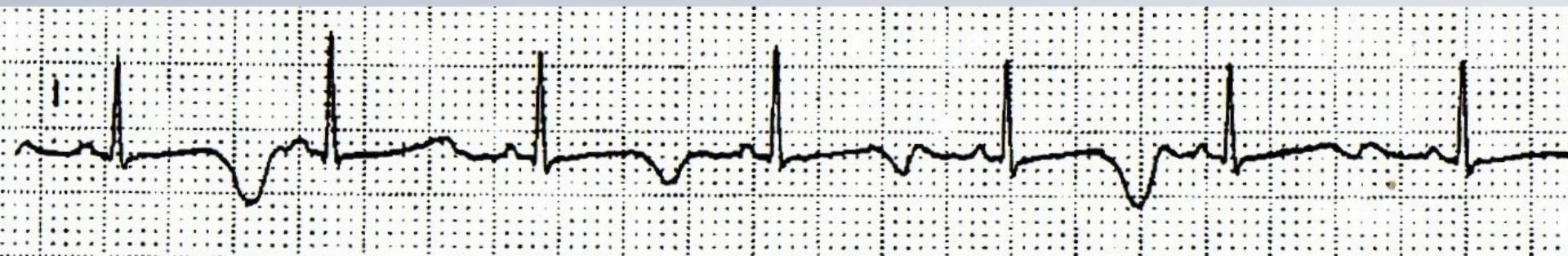
AV block and « pseudo » AV block (neonates) (LQT 2 and LQT 3)

ECG

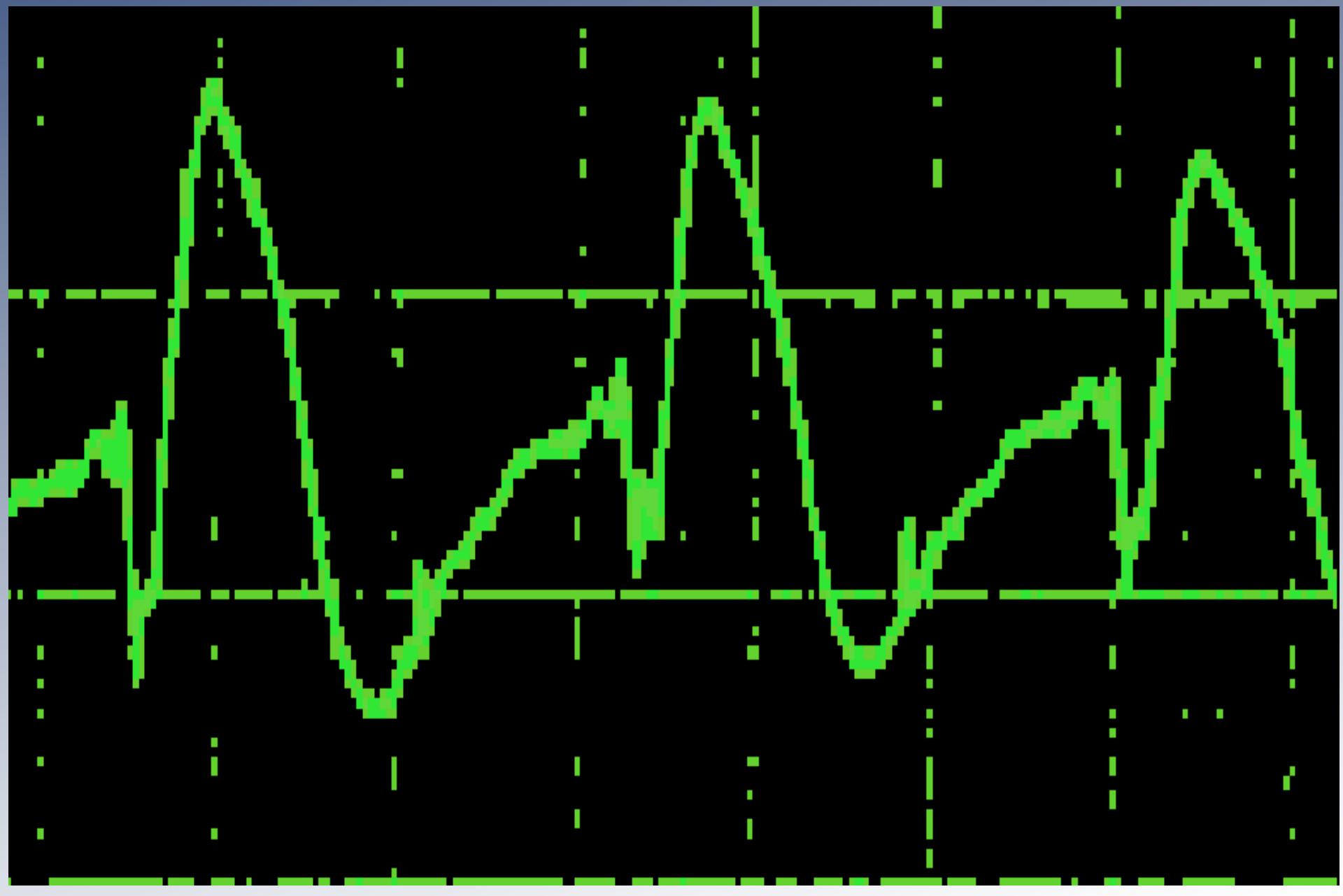


(Shimizu, PACE 1996)

T wave alternans highly predictive of torsades-de-pointes
(Zareba, JACC 1994)



Le syndrome de Brugada



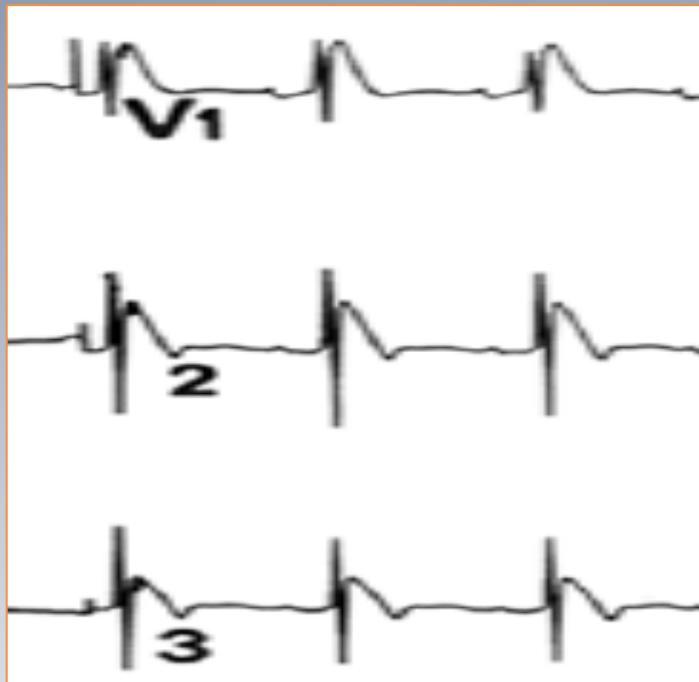
1992 ...

Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome

A Multicenter Report

JACC Vol. 20, No. 6
November 15, 1992:1391-6

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD*†

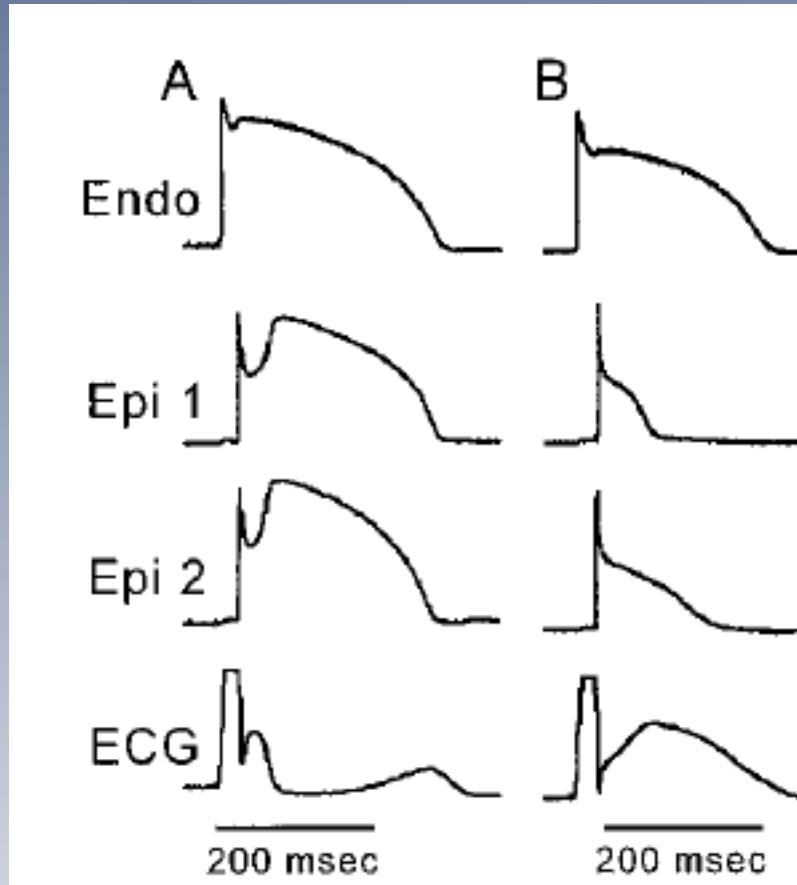


Définition
pas de cardiopathie structurelle

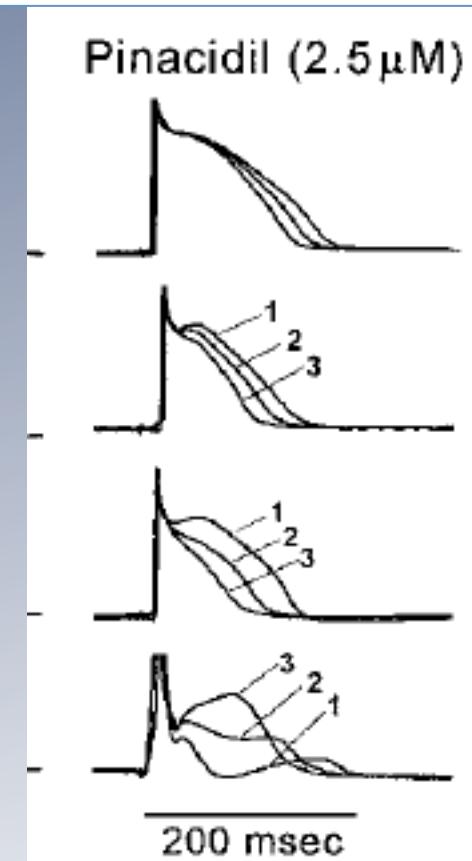
... repolarisation vs depolarisation ...

Cellular Basis for the Brugada Syndrome and Other Mechanisms of Arrhythmogenesis Associated With ST-Segment Elevation

Gan-Xin Yan, MD, PhD; Charles Antzelevitch, PhD



pinacidil (K channel opener)

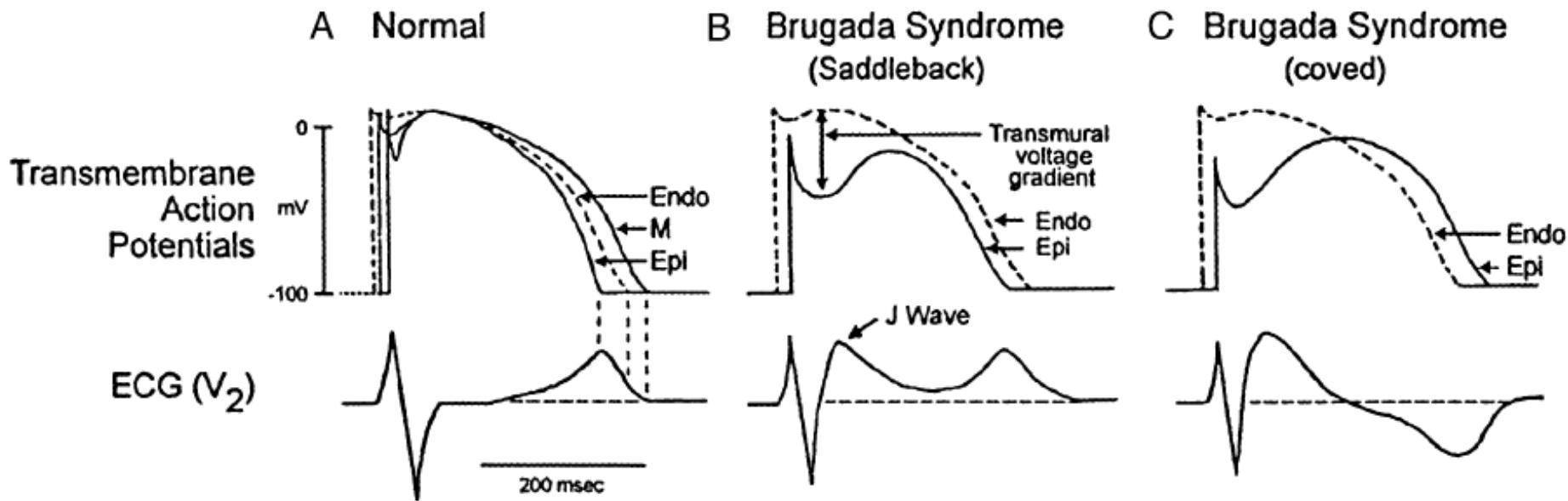


abnormal repolarization hypothesis (based on the canine wedge preparation)

... repolarisation vs depolarisation ...

Cellular Basis for the Brugada Syndrome and Other Mechanisms of Arrhythmogenesis Associated With ST-Segment Elevation

Gan-Xin Yan, MD, PhD; Charles Antzelevitch, PhD



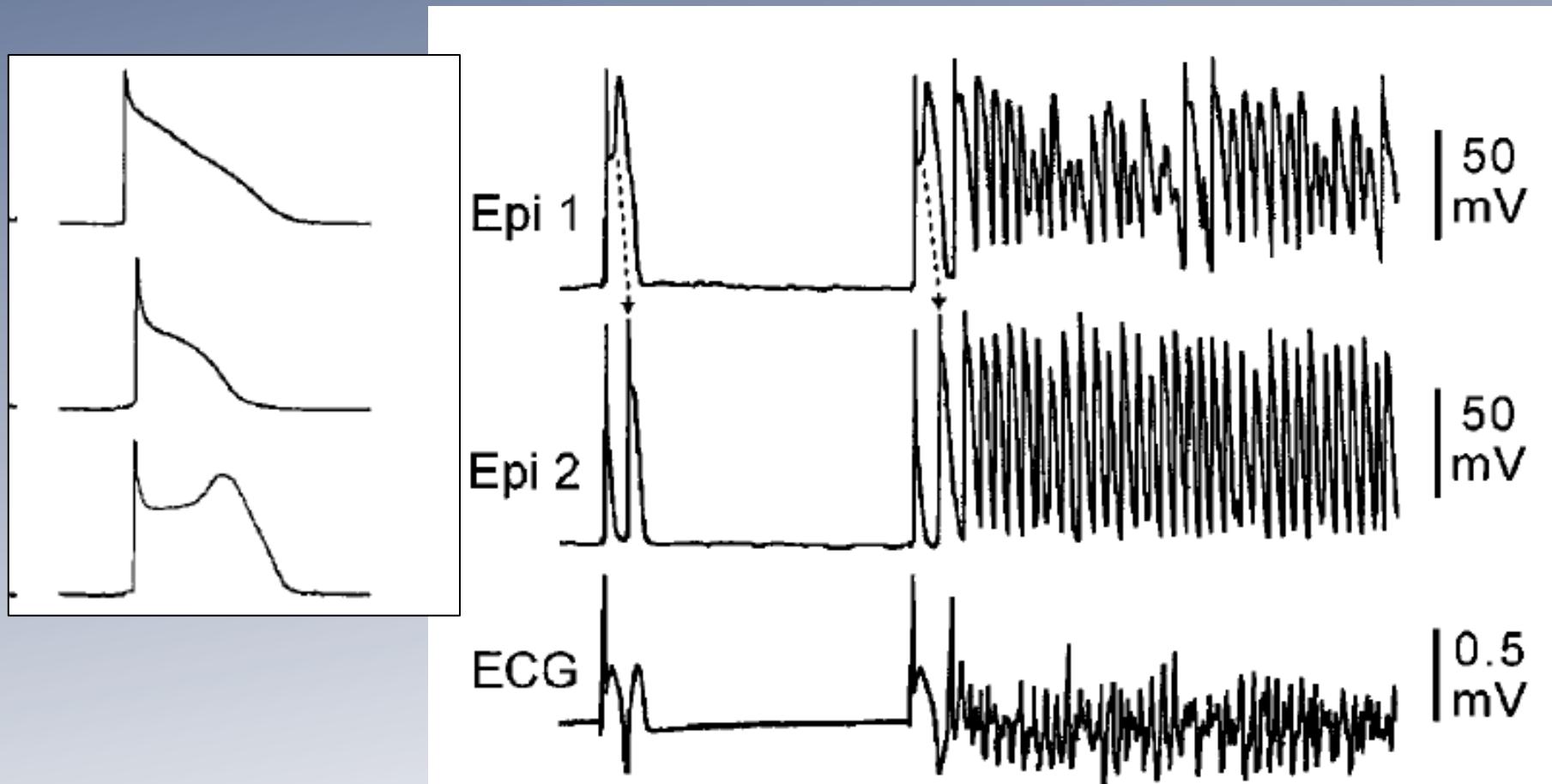
abnormal repolarization hypothesis (based on the canine wedge preparation)

... repolarisation vs depolarisation ...

« phase 2 » reentry

Cellular Basis for the Brugada Syndrome and Other Mechanisms of Arrhythmogenesis Associated With ST-Segment Elevation

Gan-Xin Yan, MD, PhD; Charles Antzelevitch, PhD



abnormal repolarization hypothesis (based on the canine wedge preparation)

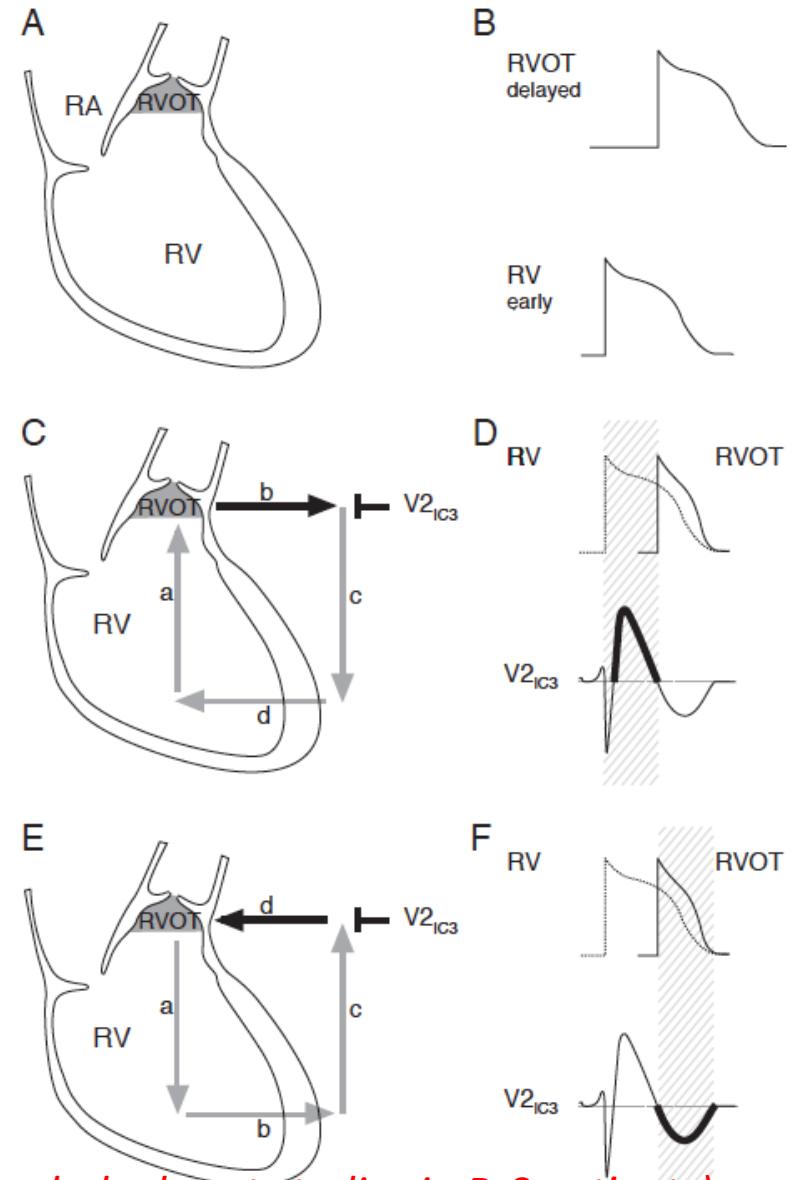
... repolarisation vs depolarisation ...

Pathophysiological mechanisms of Brugada syndrome:
Depolarization disorder, repolarization disorder, or more?

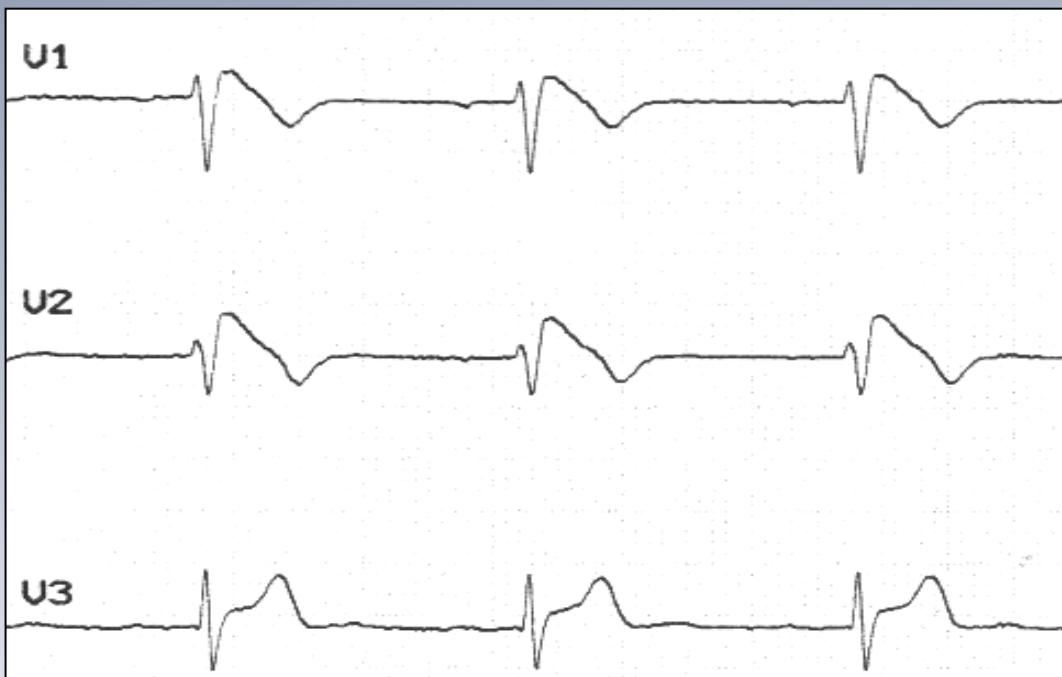
Paola G. Meregalli, Arthur A.M. Wilde, Hanno L. Tan*

pot tardifs
Troubles conductifs
délai RVOT
pot fractionnés
SCN5A
fibrose

structural heart disease ????

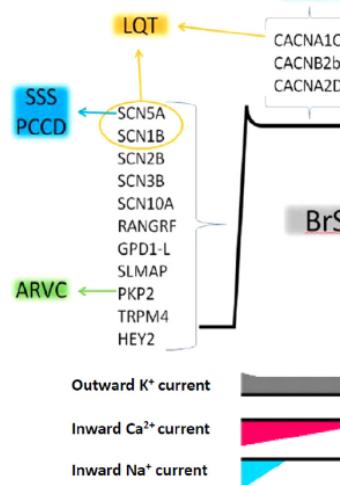


The abnormal conduction hypothesis (based on whole-heart studies in BrS patients)

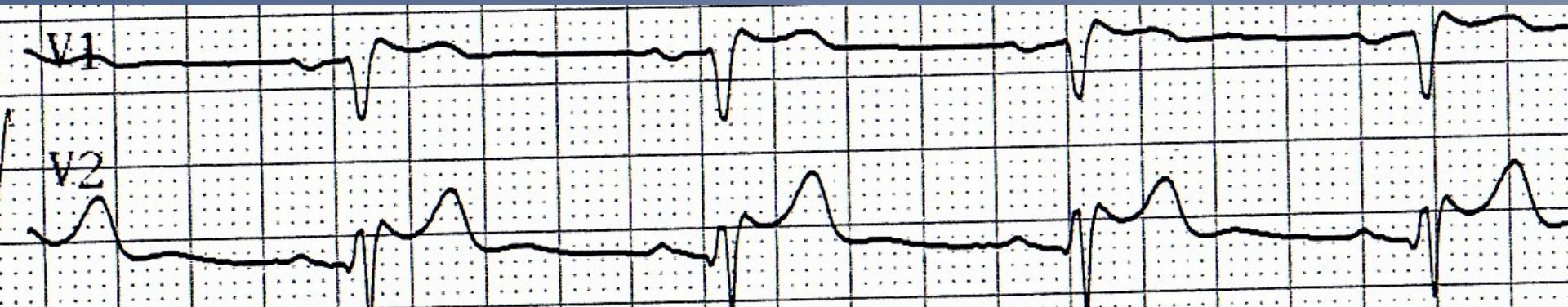


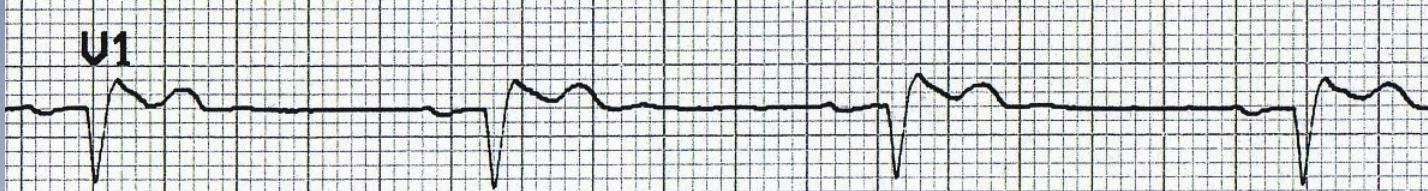
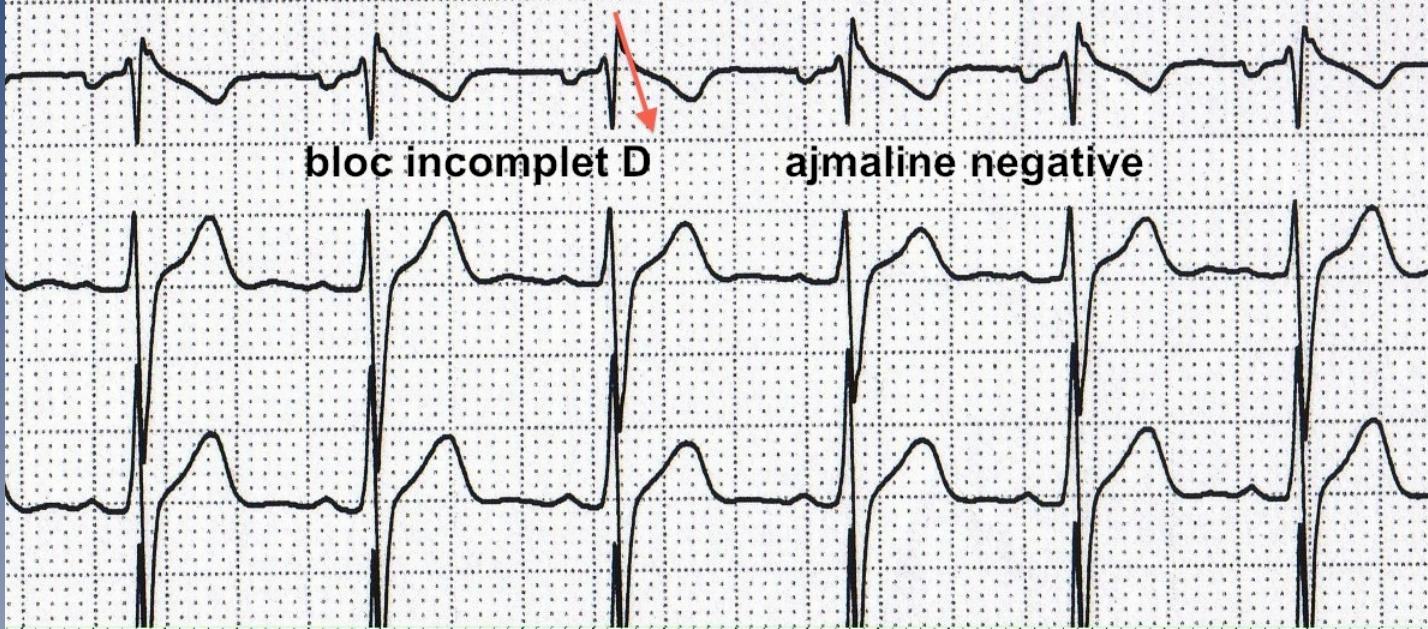
Brugada = Type 1 ST +

forme	gene	canal	chromosome	transmission
BrS 1	SCN5A	Na	3	dominant
BrS 2	GPD1-L	Na	3	dominant
BrS 3	CACNA1C	Ca	10	dominant
BrS 4	CACNB2b	Ca	12	dominant
BrS 5	SCN1B	Na	19	dominant
BrS 6	KCNE3	I_K_{ATP}	11	dominant
BrS 7	SCN3B	Na	11	dominant
BrS 8	KCNH2	I_K_R	7	dominant
BrS 9	KCNJ8	I_K_{ATP}	12	dominant
BrS 10	CACNA2D1	Ca	7	dominant
BrS 11	RANGRF	Na	17	dominant
BrS 12	KCNES	I_{to}	X	récessif X
BrS 13	KCND3	I_{to}	1	dominant
BrS 14	HCN4	If	15	dominant
BrS 15	SLMAP	Na	3	dominant
BrS 16	TRPM4	Ca	19	dominant
BrS 17	SCN2B	Na	11	dominant
BrS 18	SCN10A	Na	3	dominant
BrS 19	HEY2	Na	6	dominant
BrS 20	PKP2	Plakoglobin \rightarrow Na	20	dominant
BrS 21	ABCC9	I_K_{ATP}	12	dominant

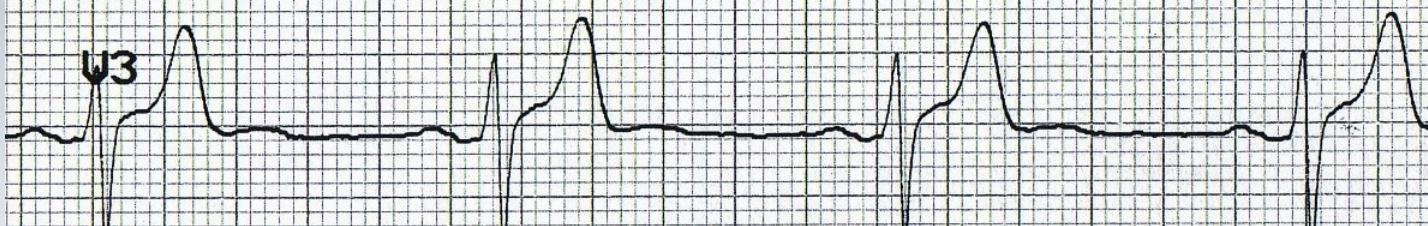
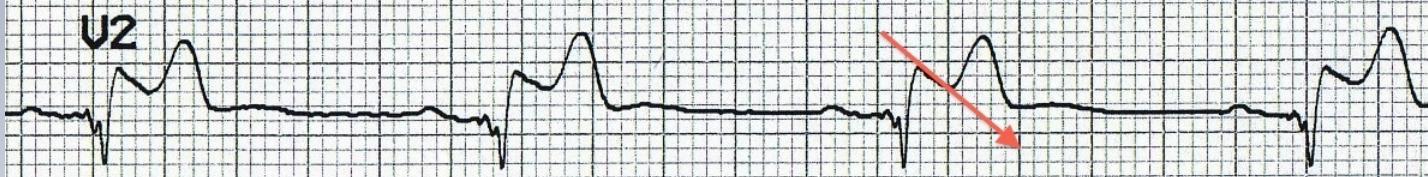


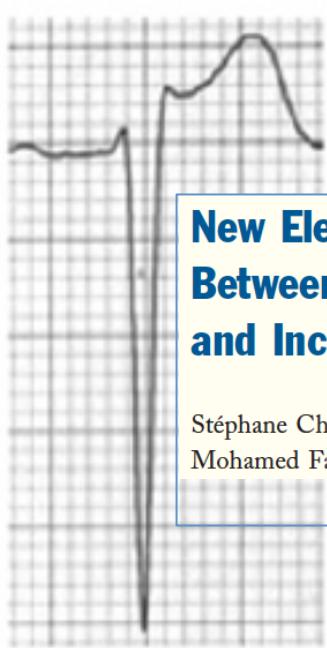
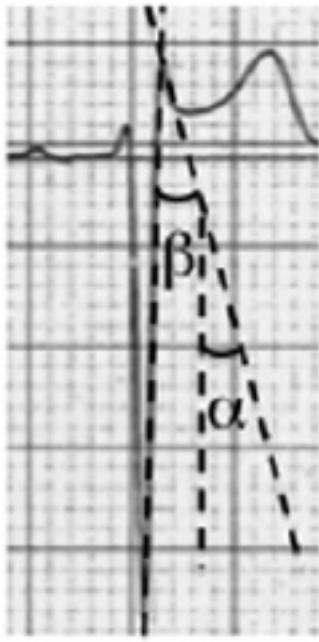
Types 2 et 3 ???





type 2 ... Brugada sous ajmaline

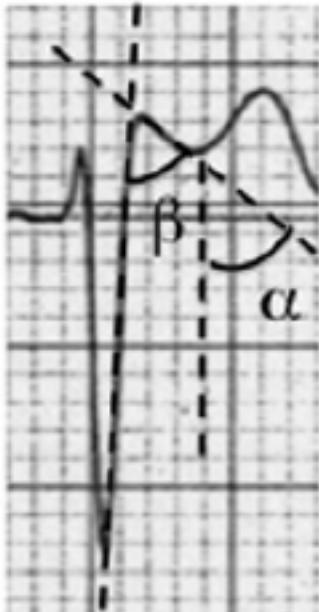




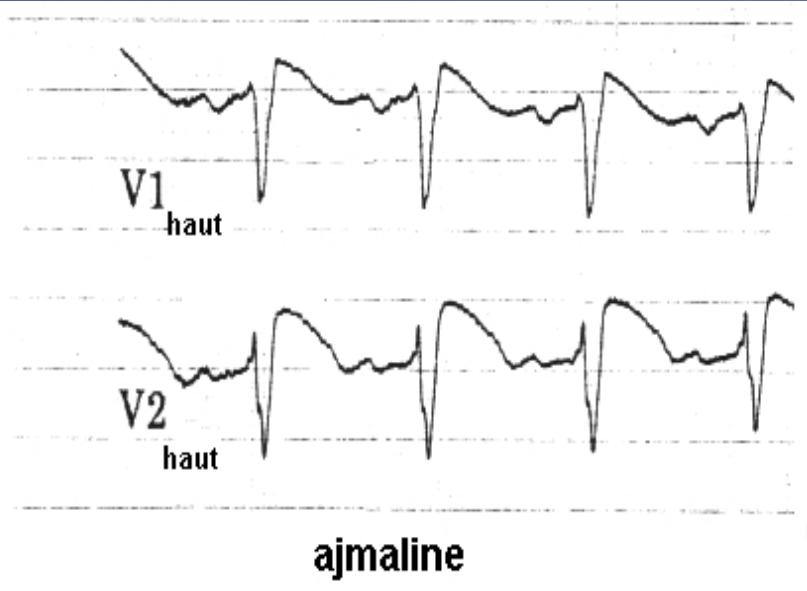
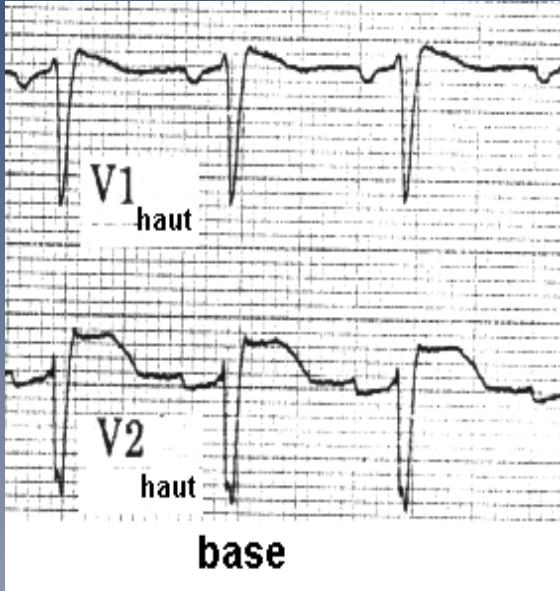
New Electrocardiographic Criteria for Discriminating Between Brugada Types 2 and 3 Patterns and Incomplete Right Bundle Branch Block

Stéphane Chevallier, MD,* Andrei Forclaz, MD,* Joanna Tenkorang, MD,* Yannis Ahmad Mohamed Faouzi, MD,† Denis Graf, MD,* Luerg Schlaepfer, MD,* Etienne Pruvot, MD*

(J Am Coll Cardiol 2011;58:2290-8)



Angle 60° meilleur discriminant



test medicamenteux ajmaline (flecainide)

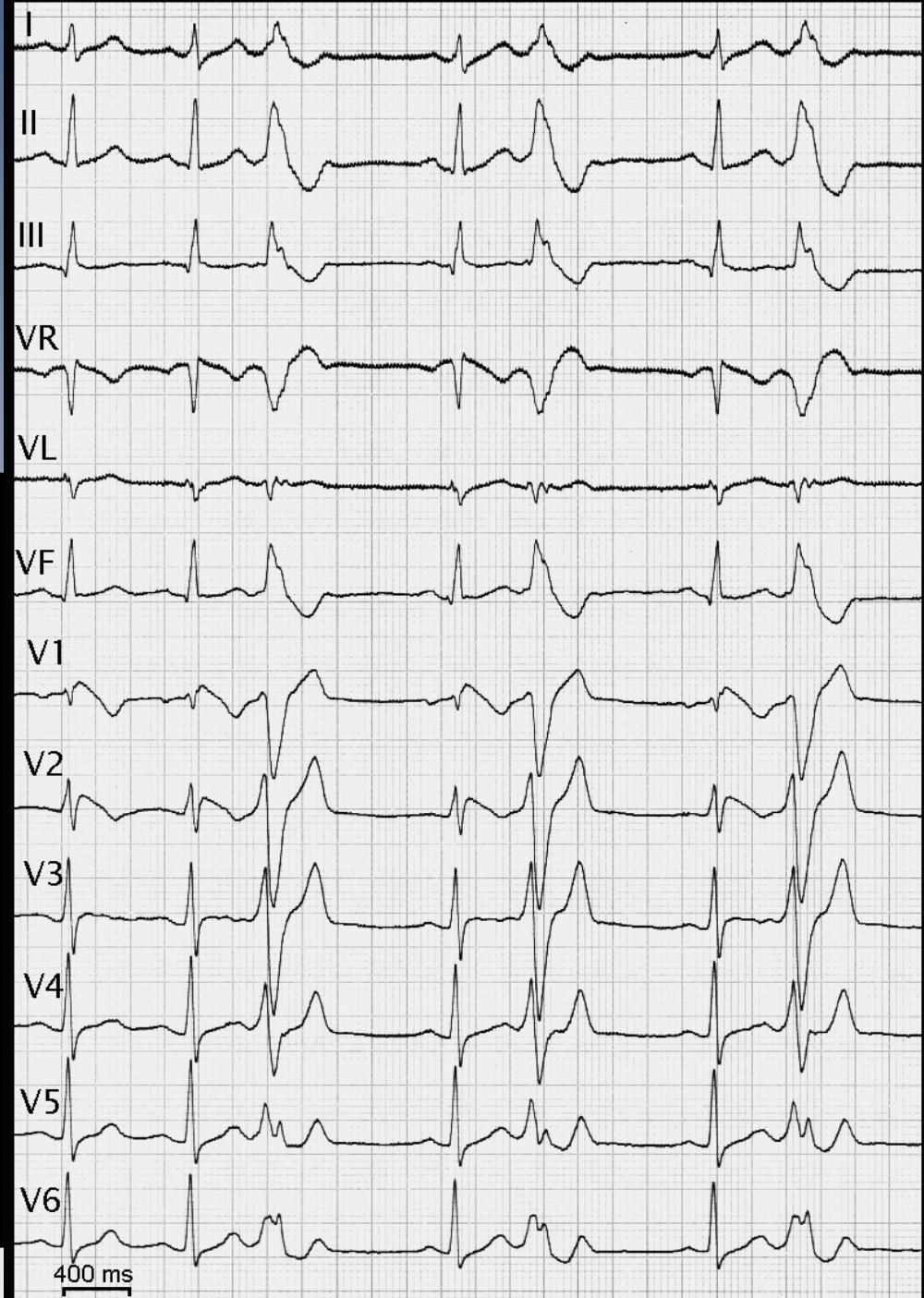
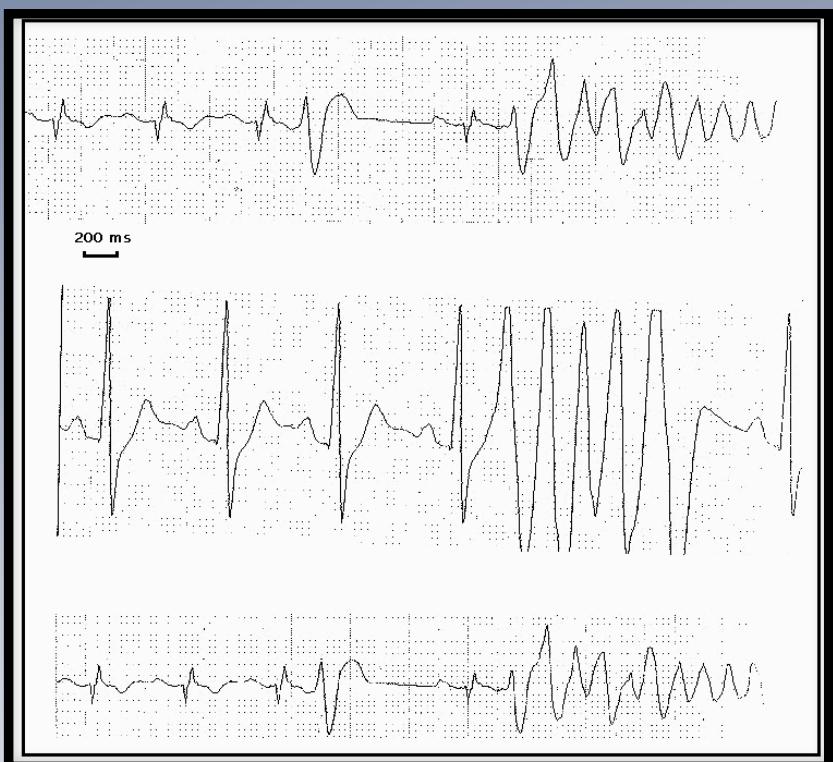


basal

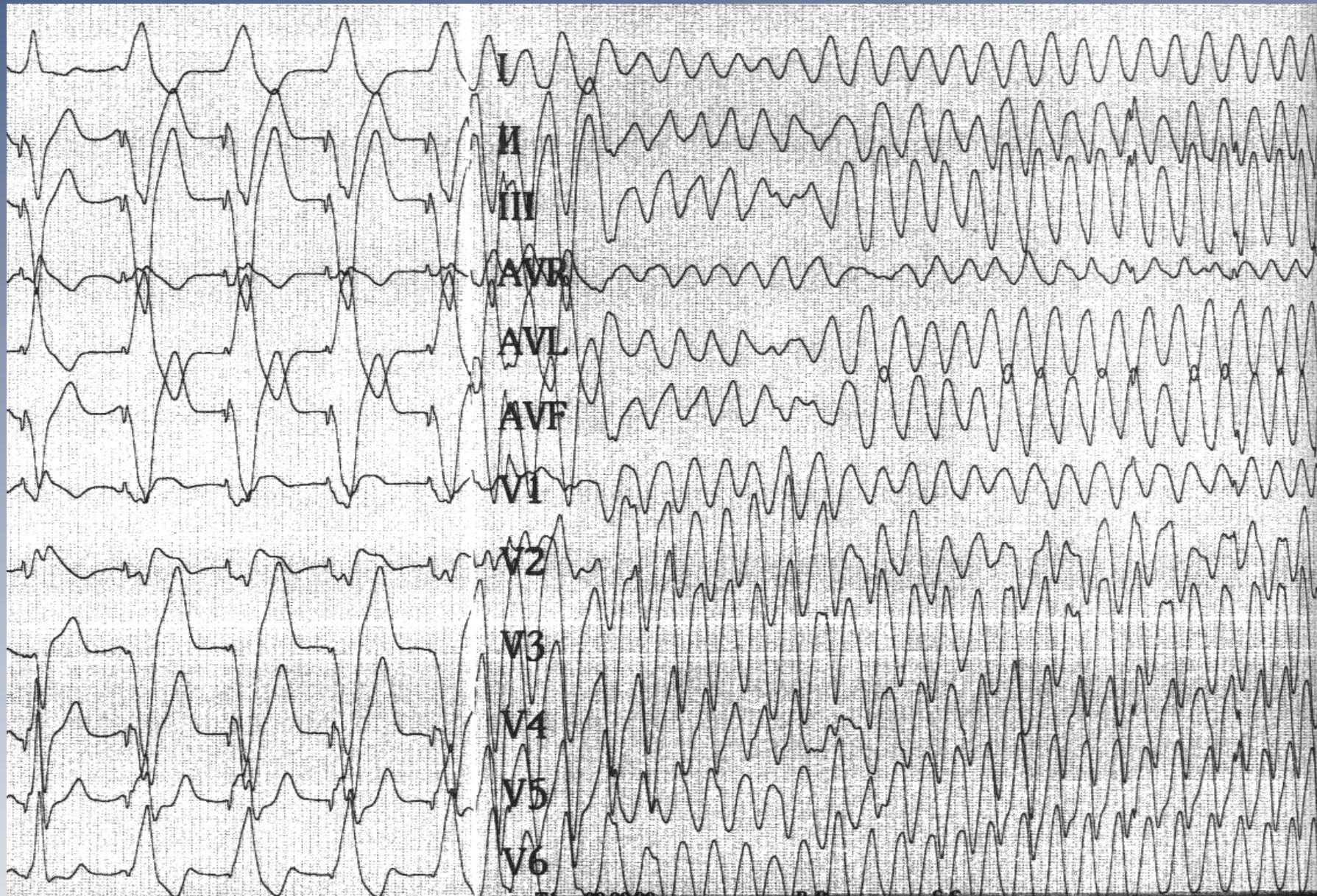
isoprénaline

ESV

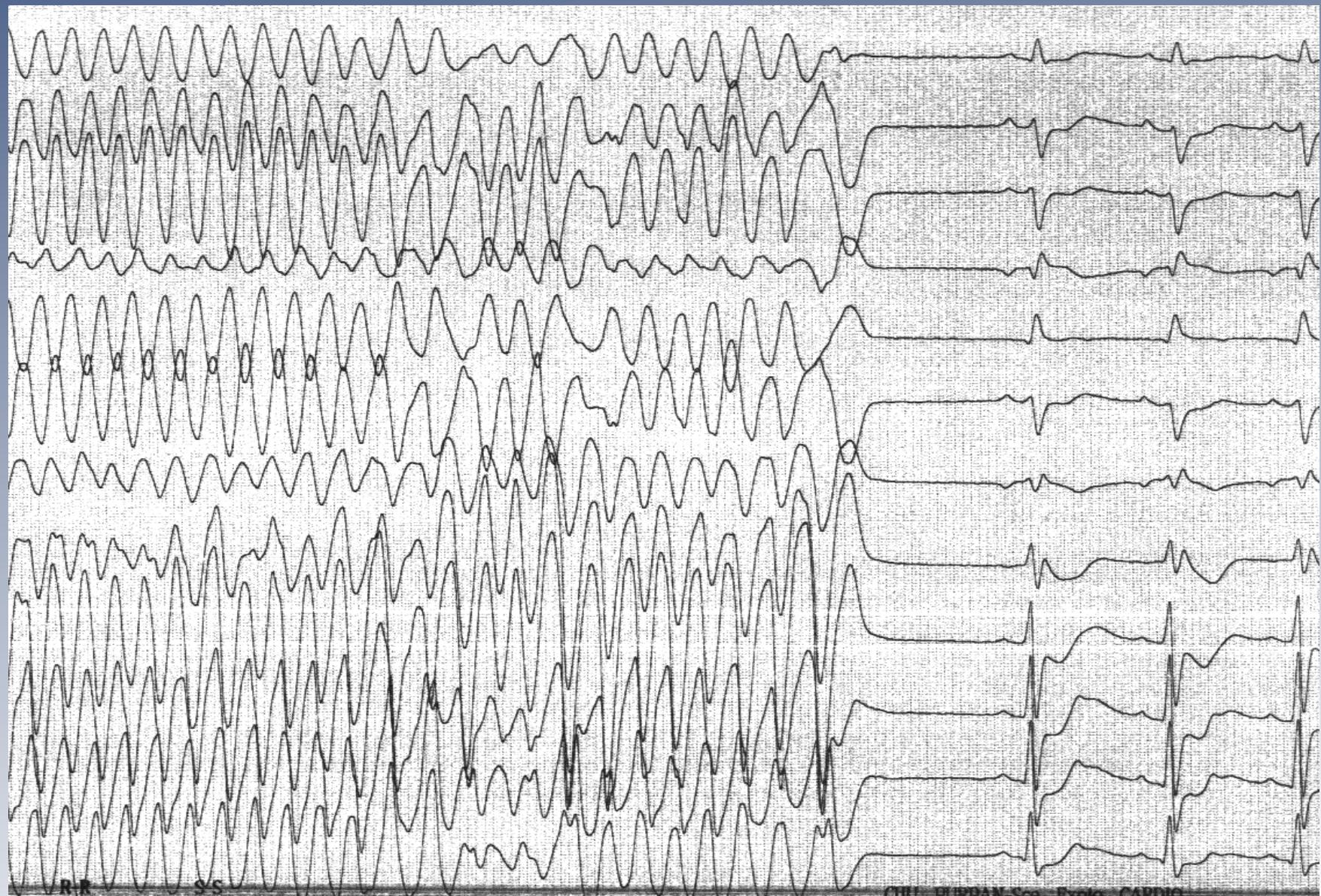
Couplage court ou long



Tachycardies ventriculaires polymorphes ou fibrillation ventriculaires spontanées ou déclenchables



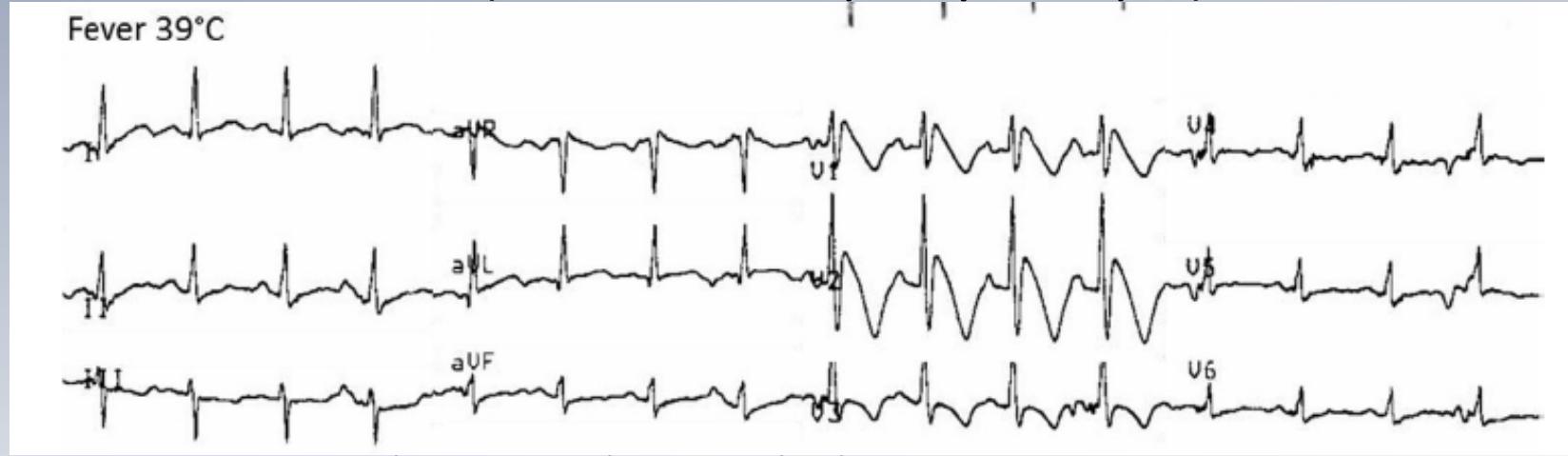
parfois spontanément réductibles ...



Brugada pédiatrique

106 Brugada < 19 ans

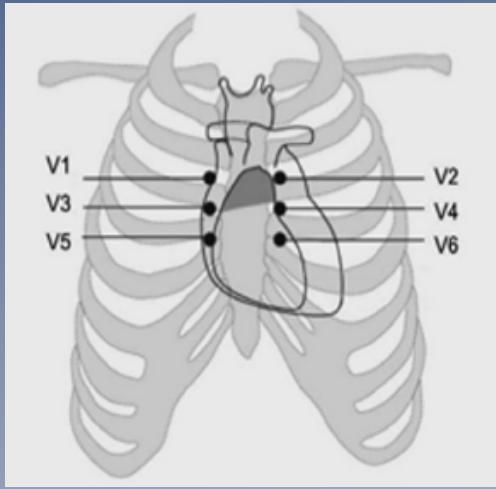
- 2/3 inapparent
- majorité asymptomatiques (screening familial)
- 9% arythmies malignes à 5 ans de suivi
(un quart pendant la fièvre)
- 6% syncopes
- 4% SVT
- 50% SCN5A (facteur de risque rythmique)



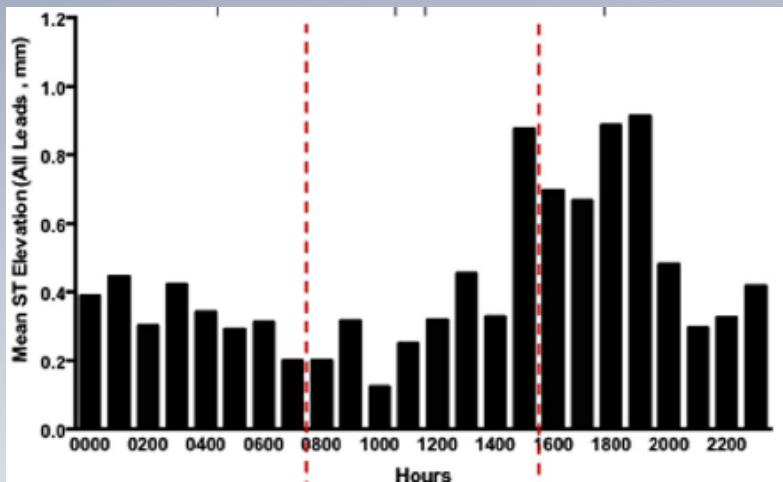
Andorin A, et al. Heart Rhythm. 2016;13:1274-82

ECG type 1 spontané chez enfant : facteur de risque ++++

Variabilité de l'aspect de type 1



54 Brugada (spontané ou non) avec Holter 12D et électrodes 4, 3 et 2 eic



1/3 des Brugada induits par medic ont un ST + type 1 au cours des 24 h

Twelve-lead ambulatory electrocardiographic monitoring in Brugada syndrome: Potential diagnostic and prognostic implications ◎ ↗

Belinda Gray, BSc(Med), MBBS, *†‡ Adrienne Kirby, MSc, †§ Peter Kabunga, MBChB, *
Saul B. Freedman, MBBS, PhD, †|| Laura Yeates, GDipGC, ‡ Ajita Kanthan, MBBS, PhD, #
Caroline Medi, B Med, PhD, *†‡ Anthony Keech, MBBS, PhD, *†§ Christopher Semsarian, MBBS, PhD, MPH, FFRS, *†‡ Raymond W. Sy, MBBS, PhD*†||

(Heart Rhythm 2017;14:866–874)

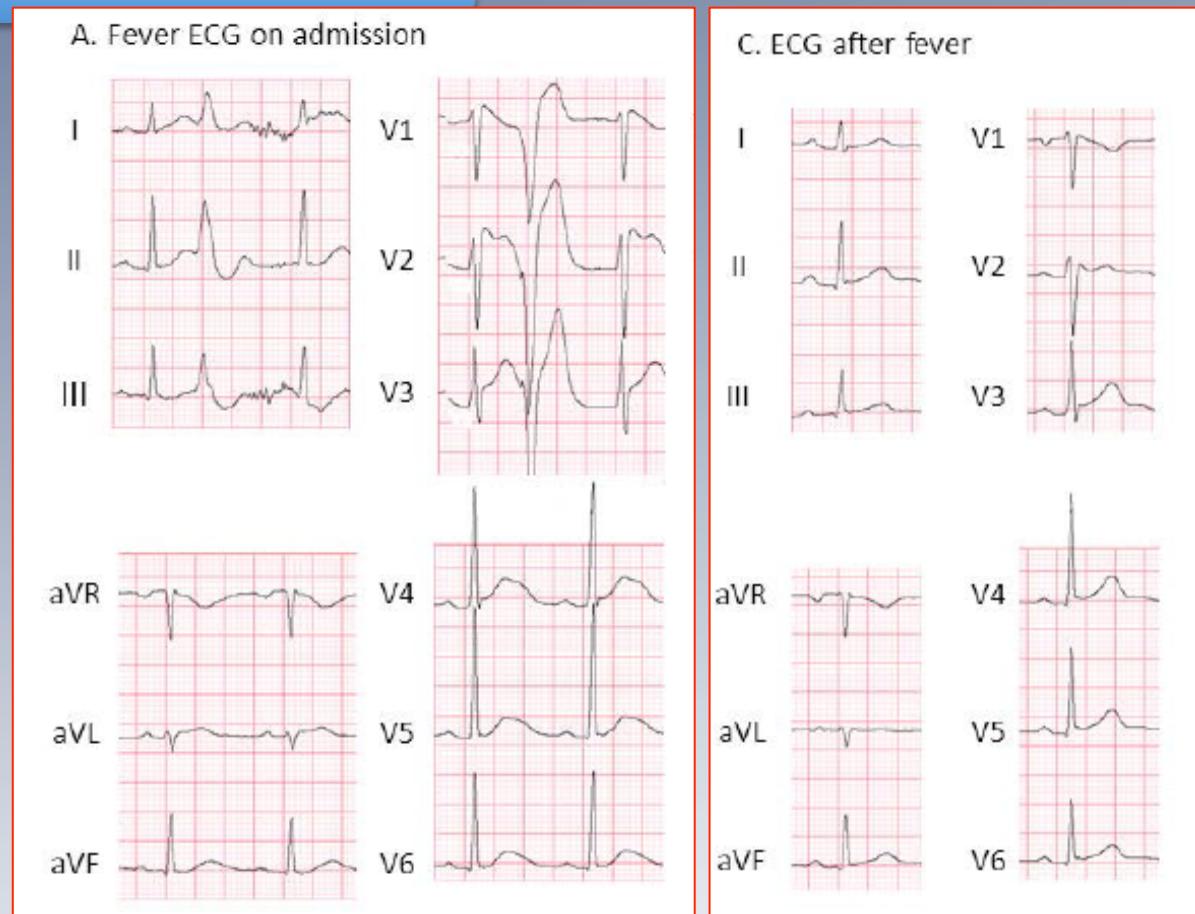
Variabilité de l'aspect de type 1

57 patients avec type 1 pendant hyperthermie

7 patients avec type 1 spontané
après normalisation t°

75% tests médicamenteux positifs

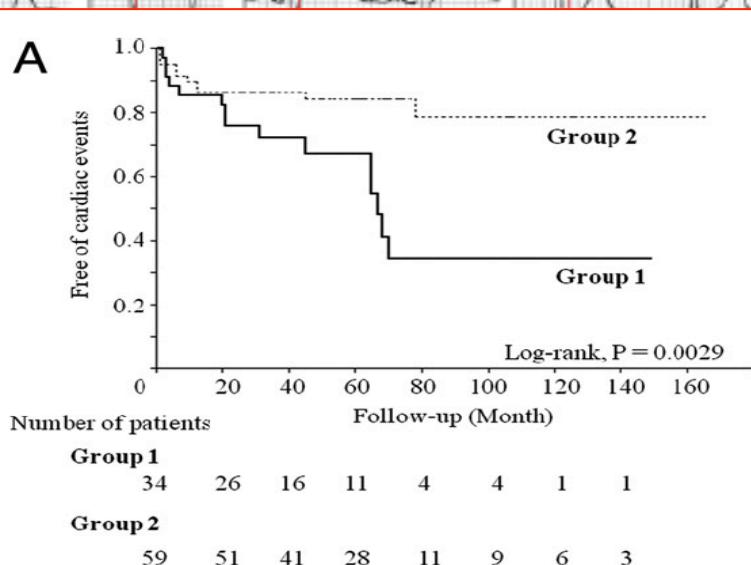
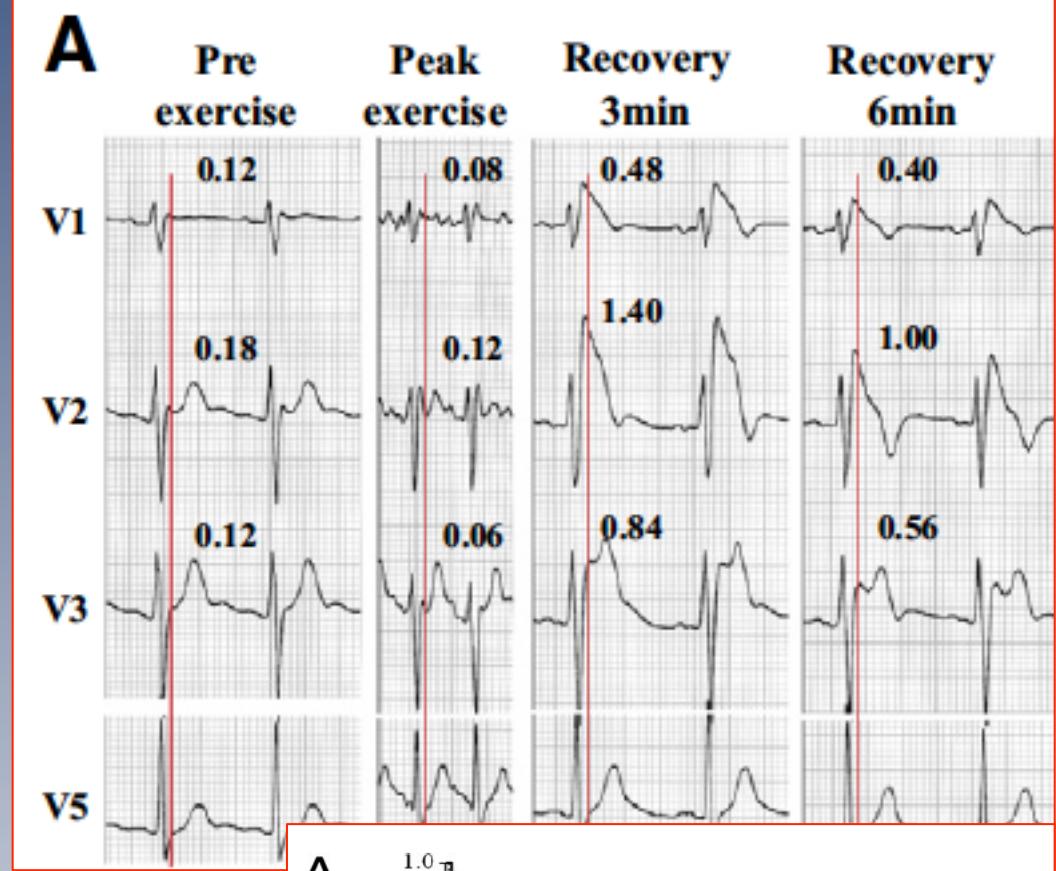
**Mortalité 1.5% / an
si type 1 fébrile
et absence type 1 spontané**



Epreuve effort

- 93 Brugada
(22 FV, 35 syncopes, 36 asymptom)
vs 102 contrôles
- épreuve d'effort
(ECG à chaque palier + récupération
1 à 4 min)

37% Brugada
élévation du ST >0.05 mV V1-V3
en récupération vs 0% témoins

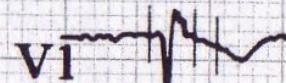


ST au repos

EFFORT

0:00

96 /min



V1

-0.70

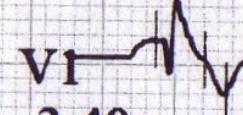
-1.13

ST max.

RECUP.

0:17

173 /min



V1

-3.40

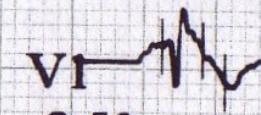
-3.64

charge max.

EFFORT

7:20

179 /min



V1

-2.50

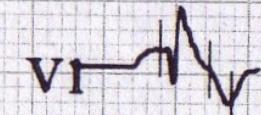
-4.28

Fin du test

RECUP.

0:17

173 /min



V1

-3.40

-3.64

ST au repos

EFFORT

0:01

66 /min



V1

2.40

-3.38

ST max.

EFFORT

2:00

81 /min



V1

2.00

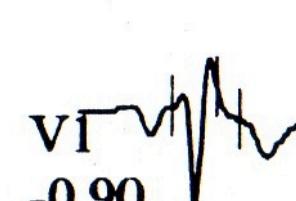
-3.44

charge max.

EFFORT

8:50

127 /min



V1

-0.90

-1.48

Fin du test

RECUP.

6:10

71 /min

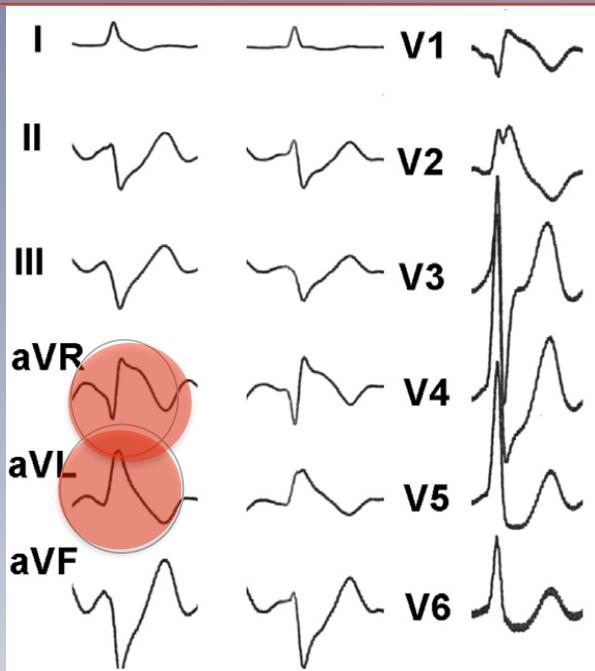


V1

1.80

-4.54

Type 1 dans les dérivation frontales



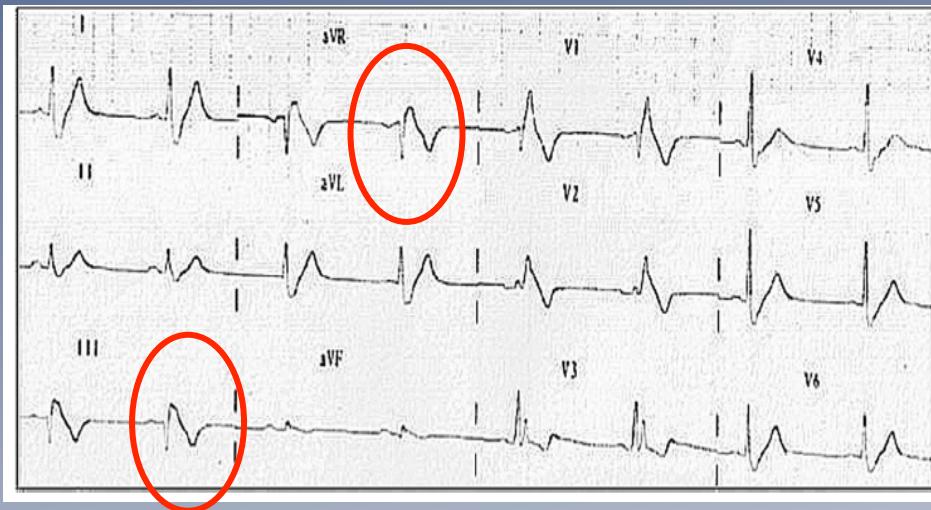
- 9% avec type 1 en dérivation frontales
- 22 pts en aVR
- 2 en inférieur
- 5 en aVR et inférieure
- 1 en aVR et aVL

Prevalence, characteristics, and prognosis role of type 1 ST elevation in the peripheral ECG leads in patients with Brugada syndrome [Heart Rhythm 2013;10:1012–1018](#)

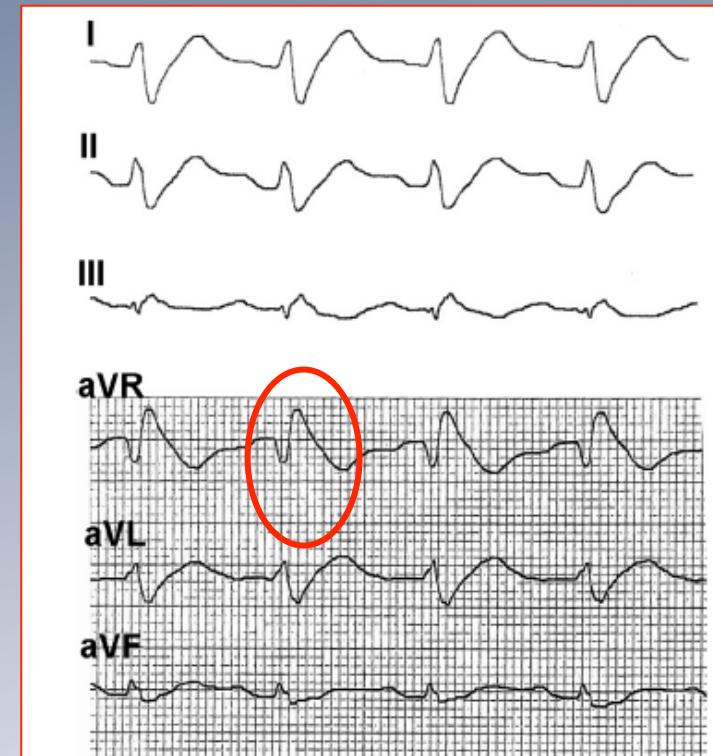
A. Rollin,^{*} F. Sacher,[†] J.B. Gourraud,[‡] J.L. Pasquié,[§] F. Raczka,[§] A. Duparc,^{*} P. Mondoly,^{*} C. Cardin,^{*} M. Delay,^{*} S. Chatel,[‡] N. Derval,[†] A. Denis,[†] M. Sadron,^{*} J.M. Davy,[§] M. Hocini,[†] P. Jaïs,[†] L. Jesel,[†] M. Haïssaguerre,[†] V. Probst,[†] P. Maury^{*}

325 Brugada

Type 1 dans les dérivations frontales



27% mort subite/thérapies appropriées
vs 6% ($p < .0001$)



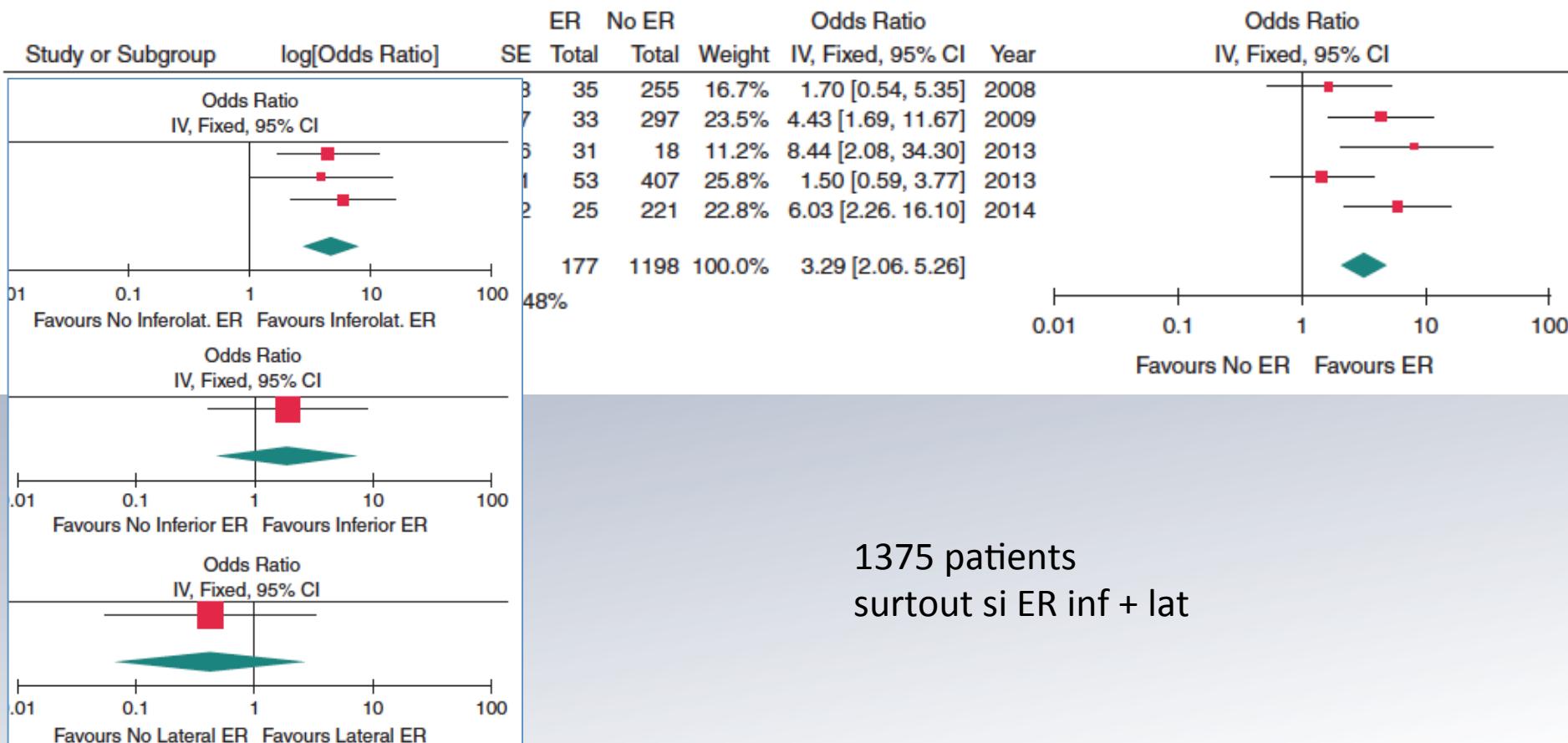
Multivariate analysis

Type 1 ST elevation in the peripheral leads	4.58 (1.70–12.32)	.0025
Spontaneous type 1 ST elevation	2.43 (1.01–5.84)	.047
Syncope	2.34 (0.99–5.50)	.051

Brugada + repolarisation précoce

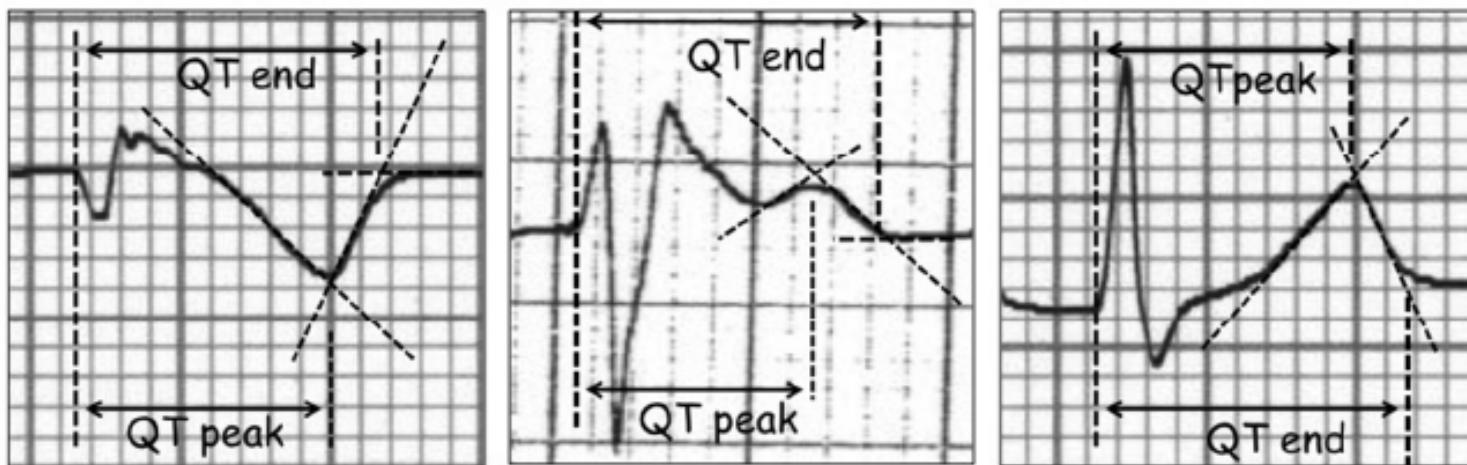
A meta-analysis on the prognostic significance of inferolateral early repolarization pattern in Brugada syndrome Europace (2018) 20, 134–139

Stamatis Georgopoulos¹, Konstantinos P. Letsas^{1*}, Tong Liu², Maria Kalafateli¹, Panagiotis Korantzopoulos³, Gerd Bürkle⁴, Konstantinos Vlachos¹, Georgios Giannopoulos⁵, Michael Efremidis¹, Spyridon Deftereos⁵, Antonios Sideris¹, Masahiko Takagi⁶, Gan-Xin Yan^{7,8}, and Joachim R. Ehrlich⁴



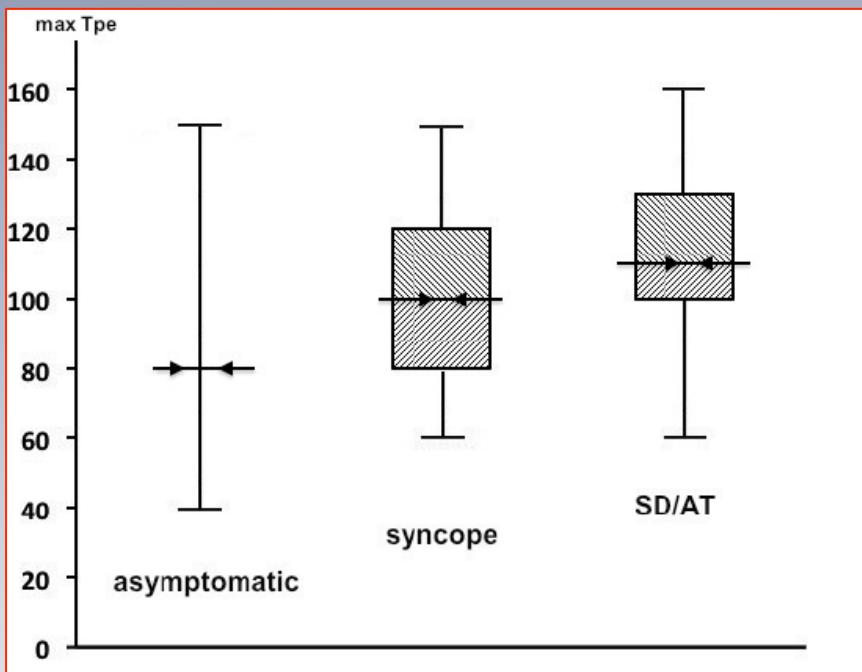
gradient transmural de repolarisation: Tpe

- Analyse rétrospective de 325 pts avec Brugada
- 70% asymptomatiques, 22% syncope, 8% FV
- Mesure de l'intervalle entre le pic et la fin de l'onde T (Tpe) V1-V6



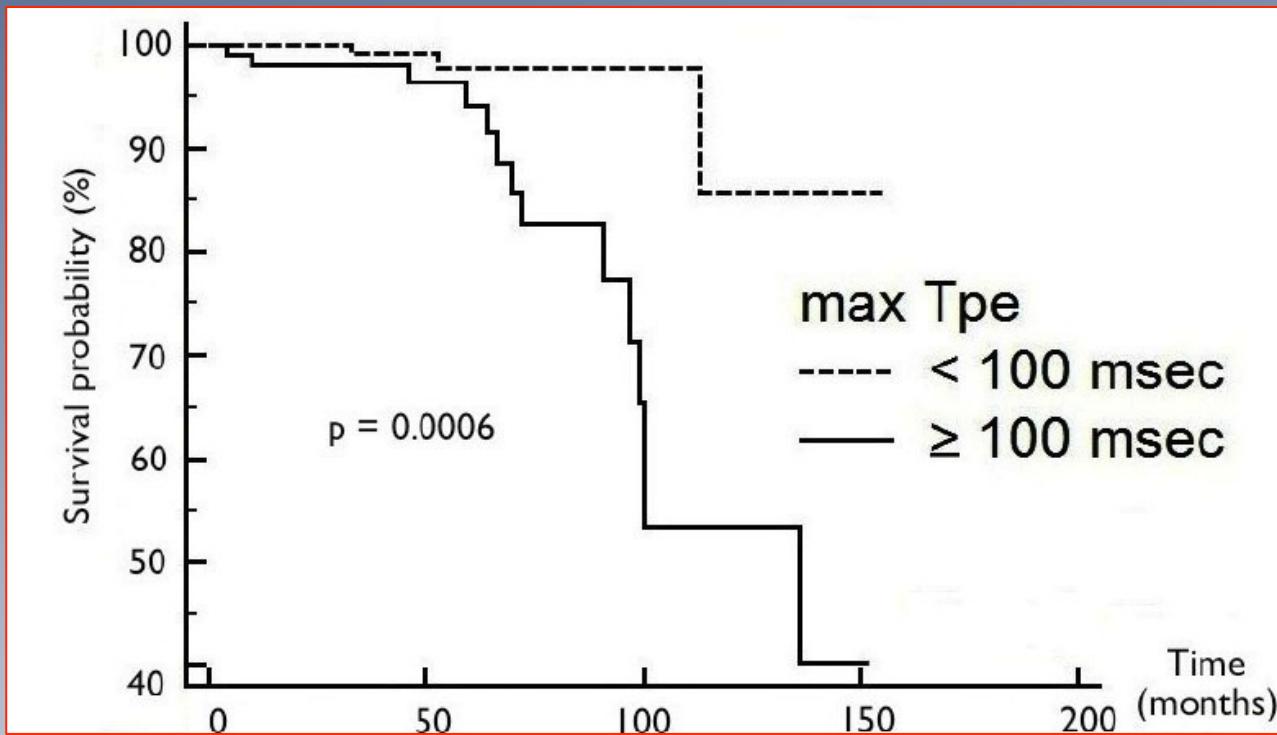
gradient transmural de repolarisation: Tpe

	Asymptomatic n = 226	Syncope n = 73	SD/AT n = 26	p value Asympt vs SD/AT	p value Asympt vs Syncope	p value Syncope vs SD/AT
Tpe V1 (ms)	63±18	73±18	84±27	<0.0001	<0.0001	0.17
Tpe V2 (ms)	67±22	83±24	85±18	<0.0001	<0.0001	0.6
Tpe V3 (ms)	72±21	83±25	92±22	<0.0001	0.0002	0.2
Tpe V4 (ms)	70±18	79±21	90±24	<0.0001	0.002	0.06
Tpe V5 (ms)	68±18	69±17	74±21	0,11	0,48	0.28
Tpe V6 (ms)	66±18	68±17	75±21	0,02	0,3	0.14
Max Tpe (ms)	81±18	101±18	110±23	<0.0001	<0.0001	0.07



Tpe V1-V4 et max Tpe plus long
si VF/th appropriées ou syncope
vs asymptomatiques

gradient transmural de repolarisation: Tpe



Multivariate analysis	OR (95%CI)	p =
Maximal Tp-e > 100 msec	9.61 (3.13-29.41)	< 0.0001
Type 1 ST + in peripheral leads	3.66 (1.37-9.8)	0.009

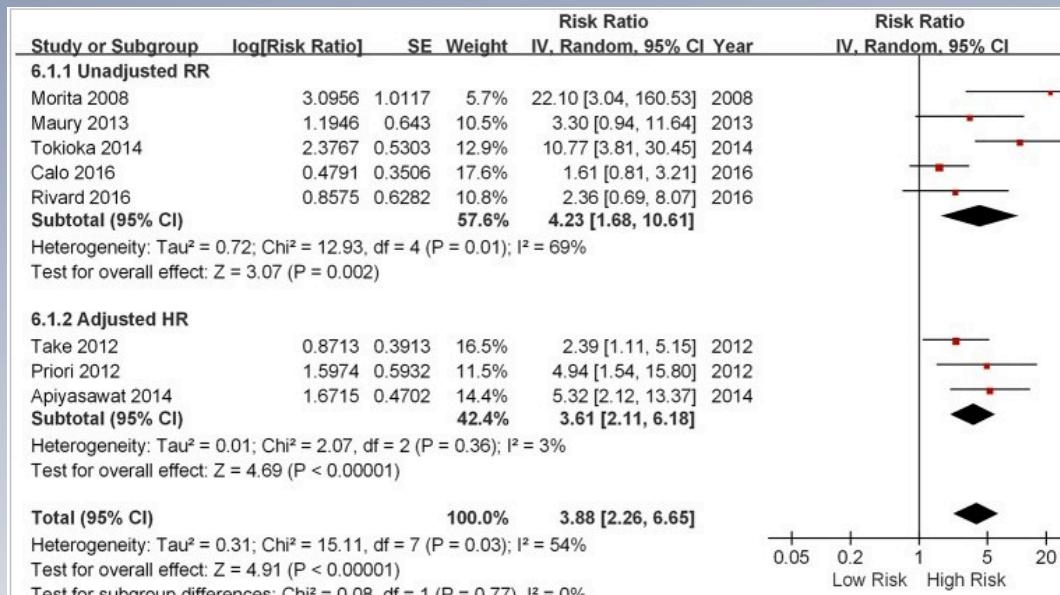
Facteur indépendant et puissant de survenue arythmies (VF et th appropriées)

gradient transmural de repolarisation: Tpe

The $T_{\text{peak}} - T_{\text{end}}$ interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: A systematic review and meta-analysis

Gary Tse, MBBS, PhD, FESC, FACC, FRCP (Glasg), *†‡ Mengqi Gong, MD, §
 Wing Tak Wong, MPhil, PhD, || Stamatis Georgopoulos, MD, ¶
 Konstantinos P. Letsas, MD, FESC, FEHRA, ¶
 Vassilios S. Vassiliou, MA, MBBS, MRCP, PhD, FHEA, FESC, #**
 Yat Sun Chan, MBBS, FRCP, FACC, * Bryan P. Yan, MBBS, FRCP, FACC, *
 Sunny Hei Wong, MBChB, DPhil, MRCP, *† William K. K. Wu, MMedSc, MPhil, PhD, FRCPath, †††
 Ana Ciobanu, MD, PhD, ‡‡ Guangping Li, MD, PhD, § Jayaprakash Shenthal, MD, §§§
 Ardan M. Saguner, MD, |||| Sadeq Ali-Hasan-Al-Saegh, MD, ¶¶ Aishwarya Bhardwaj, MD, ##
 Abhishek C. Sawant, MD, MPH, ## Paula Whittaker, MBChB, MPH, MMed, MRCGP, †
 Yunlong Xia, MD, PhD, *** Gan-Xin Yan, MD, PhD, ††††† Tong Liu, MD, PhD §

(Heart Rhythm 2017;14:1131–1137)

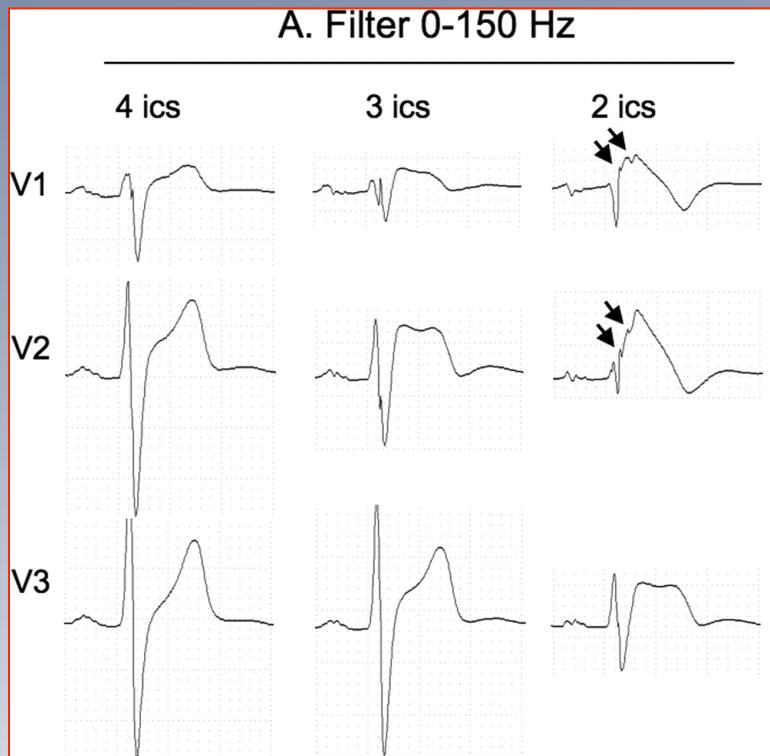


risk of VT/VF or death was highest for Brugada syndrome
 (OR 5.68; 95% CI 1.57-20.53; $P < .01$)

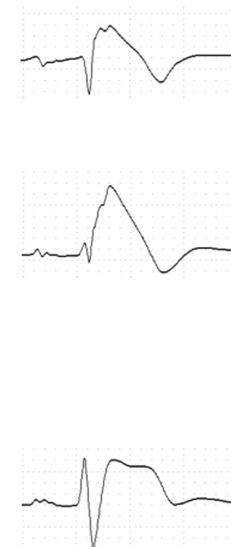
QRS fragmentés

115 Brugada
13 FV, 28 syncope, 74 asymptomatiques

QRS fragmentés de V1 à V3 :
> 4 spikes sur 1 dérivation ou > 8 en tout



B. Filter 0-25 Hz



Recommendations
0.05-0.5 Hz
150 Hz
(250 Hz enfants)



Attention aux filtres...

parfois que 3/2ème espace intercostal

Morita H, et al. Circulation 2008

QRS fragmentés

Risk Stratification in Brugada Syndrome : Results of the PRELUDE (PRegressed
EElectrical stimUlation preDicitive valuE) Registry

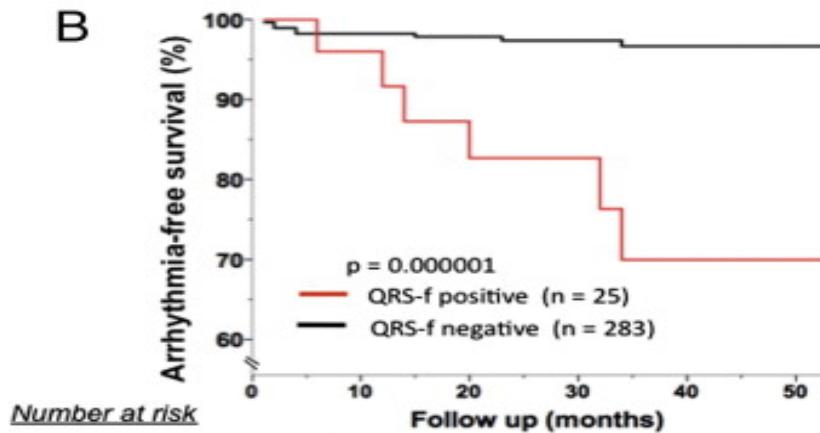


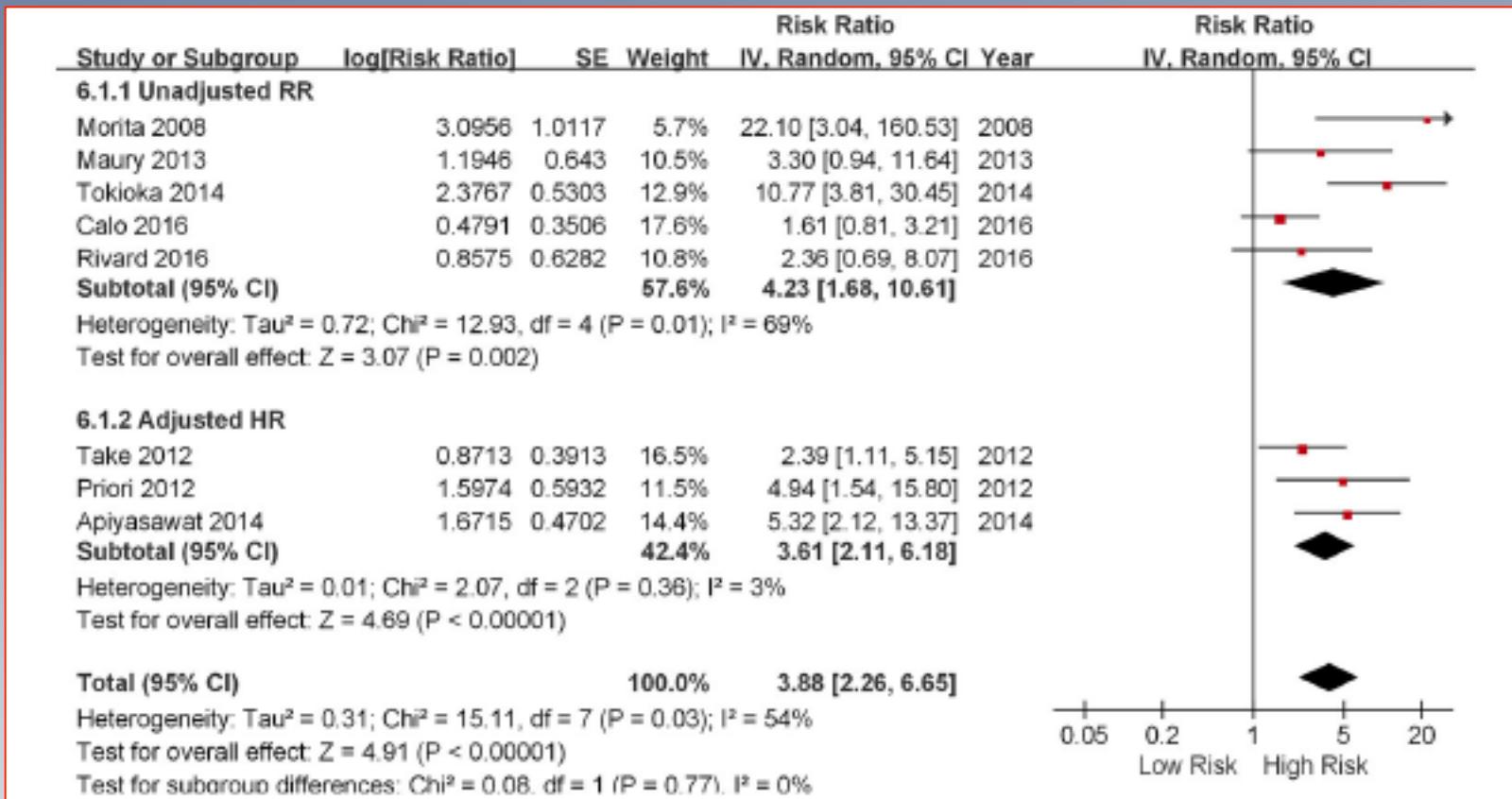
Figure 5 Survival According QRS-f Kaplan-Meier survivorship analysis of arrhythmic event-free survival according to presence or absence of QRS fragmentation (QRS-f).

	p Value	HR	95% CI	
			Lower	Upper
QRS-fragmentation	0.000	8.898	3.040	26.038

Priori S
Prelude

2.5 % QRS fragmentés dans notre série de 325 pts
VF 25% vs 3% (p=0.001)
Maury P, et al. Am J Cardiol 2013

QRS fragmentés

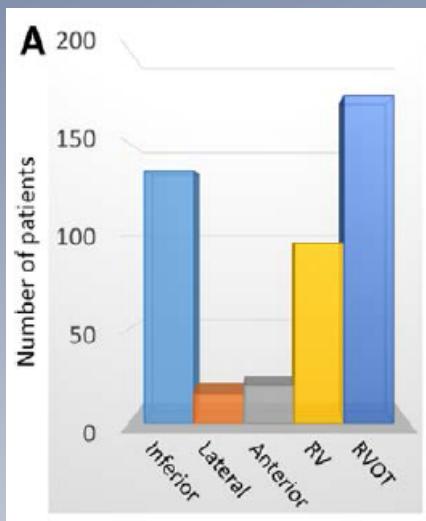


QRS fragmentés

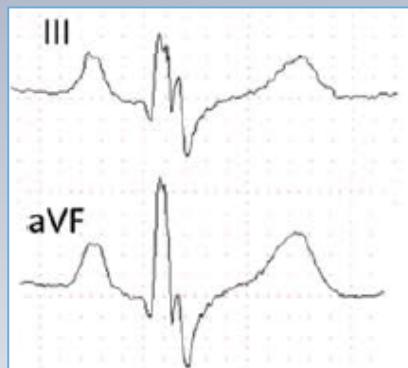
Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome

Hiroshi Morita, MD, PhD; Atsuyuki Watanabe, MD, PhD; Yoshimasa Morimoto, MD;
Satoshi Kawada, MD; Motomi Tachibana, MD; Koji Nakagawa, MD, PhD;
Nobuhiro Nishii, MD, PhD; Hiroshi Ito, MD, PhD

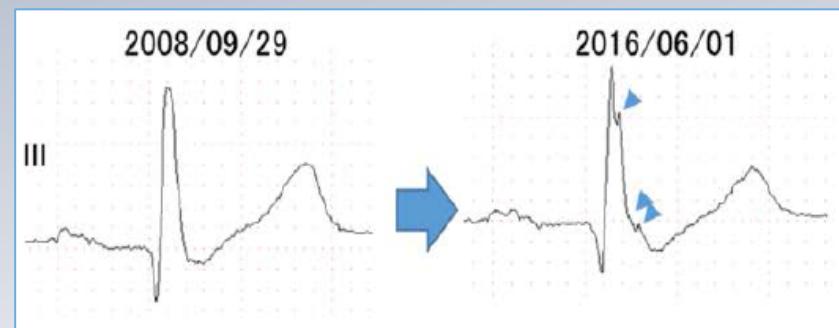
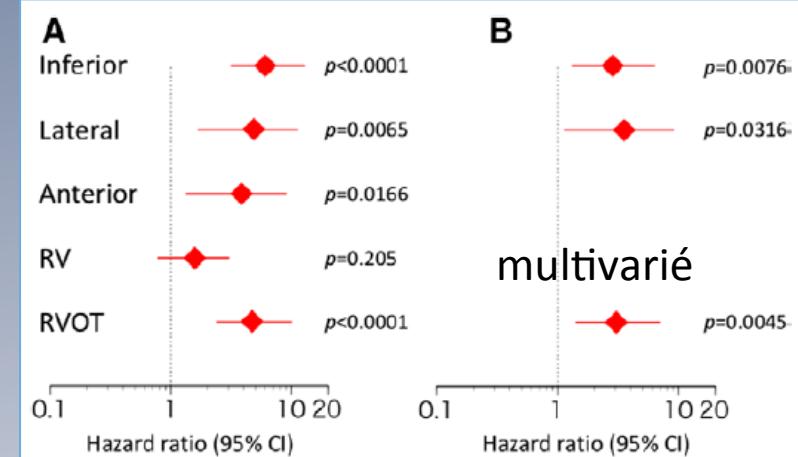
Circ Arrhythm Electrophysiol. 2017;10:e004765.



464 patients
32% QRS fragmentés
Associé à l'inductibilité
Pas avec SCN5A



0-150 Hz filter



troubles conductifs

Prevalence and Prognostic Role of Various Conduction Disturbances in Patients With the Brugada Syndrome

Philippe Maury, MD^{a,*}, Anne Rollin, MD^a, Frédéric Sacher, MD^b, Jean-Baptiste Gourraud, MD^c, Franck Raczka, MD^d, Jean-Luc Pasquié, MD^d, Alexandre Duparc, MD^a, Pierre Mondoly, MD^a, Christelle Cardin, MD^a, Marc Delay, MD^a, Nicolas Derval, MD^b, Stéphanie Chatel, PhD^c, Vanina Bongard, MD, PhD^a, Marie Sadron, MD^a, Arnaud Denis, MD^b, Jean-Marc Davy, MD^d, Mélèze Hocini, MD^b, Pierre Jaïs, MD^b, Laurence Jesel, MD^b, Michel Haïssaguerre, MD^b, and Vincent Probst, MD^c

Am J Cardiol 2013;112:1384–1389

- 40% durée de l'onde P \geq 120 ms
- 35% bloc AV du premier degré
- 28% bloc de branche droit
- 16% bloc fasciculaire

9 %
10 %
1-5%
1-5 %

} pop normale

survenue arythmies V maligne

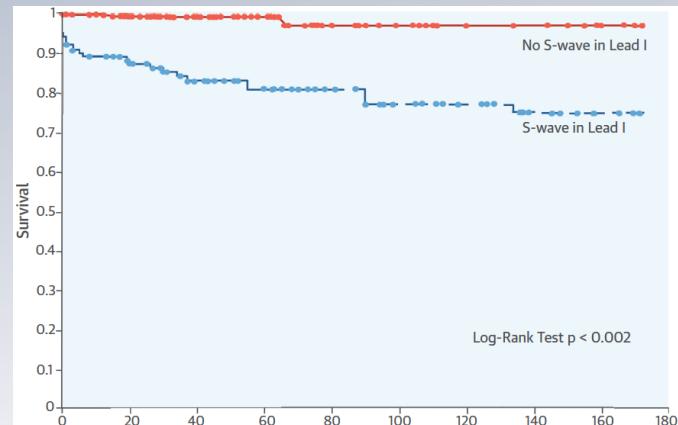
Multivariate

Spontaneous type 1 ST elevation	2.74	1.11–6.75	0.028
First degree AVB	2.41	1.01–5.73	0.046
Syncope	2.38	1.00–6.63	0.048

A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome

The S-Wave in Lead I

Calo L, et al (J Am Coll Cardiol 2016;67:1427–40)

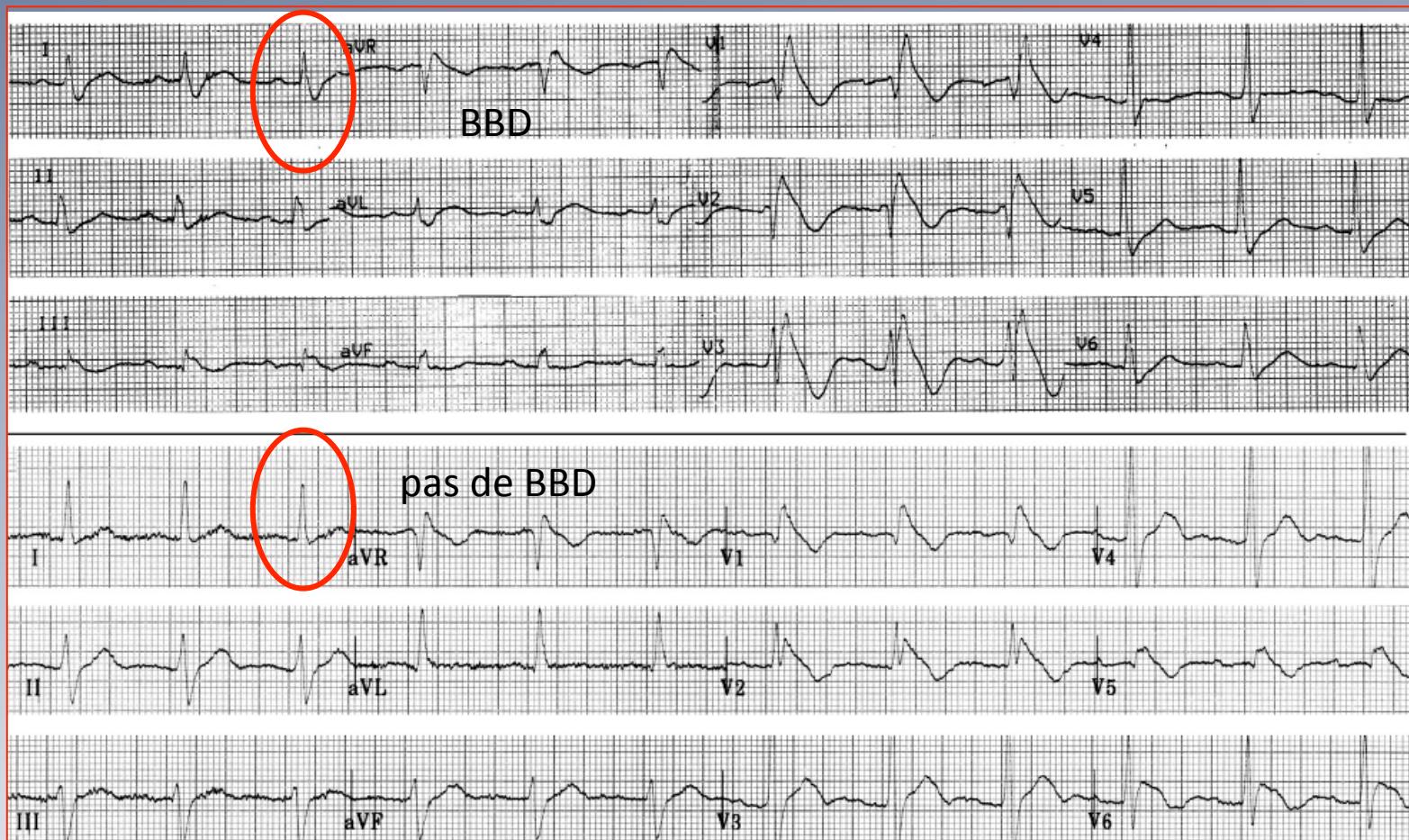


troubles conductifs

Prevalence and Prognostic Role of Various Conduction Disturbances in Patients With the Brugada Syndrome

Philippe Maury, MD^{a,*}, Anne Rollin, MD^a, Frédéric Sacher, MD^b, Jean-Baptiste Gourraud, MD^c, Franck Raczka, MD^d, Jean-Luc Pasquié, MD^d, Alexandre Duparc, MD^a, Pierre Mondoly, MD^a, Christelle Cardin, MD^a, Marc Delay, MD^a, Nicolas Derval, MD^b, Stéphanie Chatel, PhD^c, Vanina Bongard, MD, PhD^a, Marie Sadron, MD^a, Arnaud Denis, MD^b, Jean-Marc Davy, MD^d, Mélèze Hocini, MD^b, Pierre Jaïs, MD^b, Laurence Jesel, MD^b, Michel Haïssaguerre, MD^b, and Vincent Probst, MD^c

Am J Cardiol 2013;112:1384–1389



syndrome de Brugada type 3 et 4

(Antzelevitch C et al., Circulation 2007)

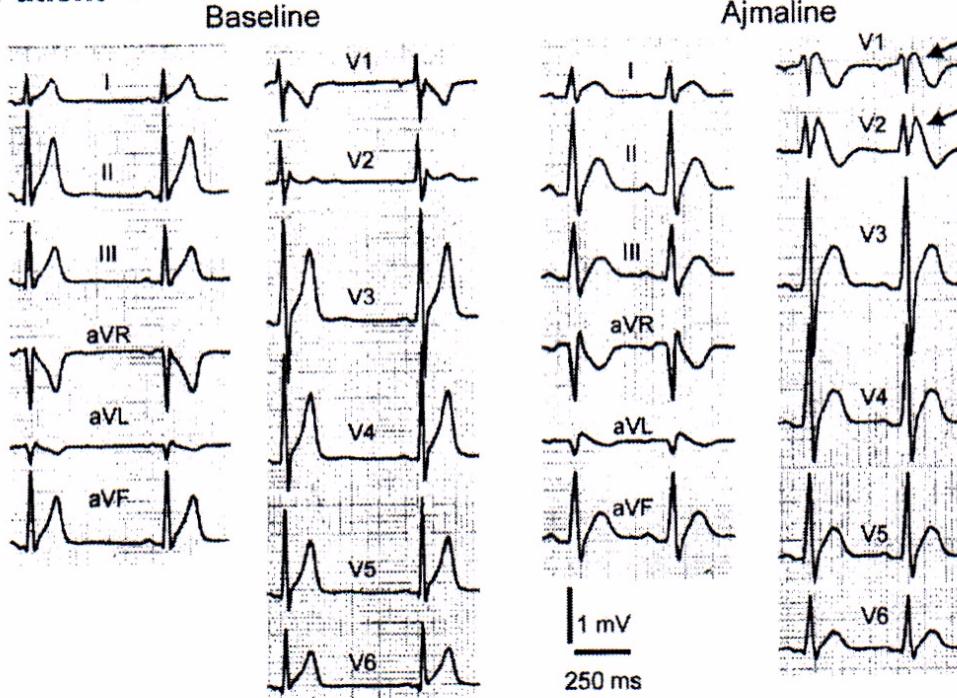
CACNA 1C (sous-unité alpha I_{CaL} Cav 1.2)

CACNB 2B (sous-unité beta I_{CaL} $Ca_{v\beta 2b-}$)

(2007 : 2 mutations)

8.5 % d'un registre de 82 Brugada dont la moitié avec $QTc \leq 360$ ms

A Patient 1



Antzelevitch et al. , Circulation 2007

Perte de fonction ou défaut d'assemblage membranaire de I_{CaL}

Syndromes cliniques associés « overlap syndromes »

(2006 : 18 mutations)

Associations Brugada et LQT 3
pour diverses mutations SCN5A

Brugada et troubles conductifs progressifs familiaux
pour même mutation SCN5A

Brugada et dysfonction sinusale ou paralysie atriale

... pas de cardiopathie structurelle...

SCN5A + Brugada : dimensions VD et VG > Brugada non SCN5A ou témoins
FE plus basses que Brugada non SCN5A ou témoins

Van Hoorn F, et al. PLoS One. 2012;7:e42037

Rudic C, et al. Europace. 2016;18:1411-9

CT scan 26 Brugada: anomalies contraction locale (hypokinesie ou akinesie) 81%
localisées au site ESV ou ST + (RVOT ou paroi inf)
Takagi M, et al. Eur Heart J. 2001;22:1032-1041

CT scan 13 Brugada with AA1 drug challenge: aggrav_anomalies contraction locale 62%
lié a l'allongement QRS
Takagi M, et al. Heart. 2003;89:169-174

IRM 20 Brugada: dimensions RVOT > témoins

Papavassiliu T, et al. J Cardiovasc Electrophysiol. 2004;15:1133-8.

IRM 30 Brugada: dimensions inflow tract et tr cinétiques mineurs VD (50%) > témoins
Catalano O, et al. Eur Heart J. 2009;30:2241-8

... pas de cardiopathie structurelle...

Late gadolinium enhancement in Brugada syndrome: A marker for subtle underlying cardiomyopathy?

Rachel Bastiaenen, PhD,^{*†} Andrew T. Cox, MRCP,^{*†} Silvia Castelletti, MD,[‡]
Yanushi D. Wijeyeratne, MRCP,^{*†} Nicholas Colbeck, MBBS,^{*} Nadia Pakroo, MBBS,^{*}
Hammad Ahmed, MBBS,^{*} Nick Bunce, MD,[†] Lisa Anderson, MD,^{*†} James C. Moon, MD,[§]
Sanjay Prasad, MD,^{||} Sanjay Sharma, MD,^{*†} Elijah R. Behr, MD^{*†}

(Heart Rhythm 2017;14:583–589)

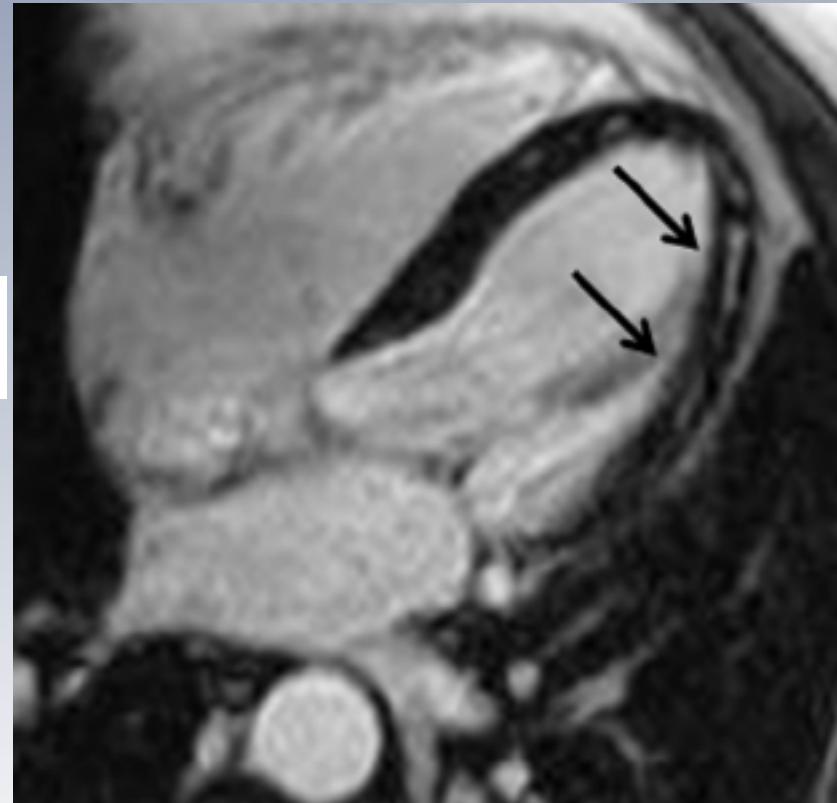
	Patients with Brugada syndrome (n = 78)	Healthy controls (n = 78)	
RVESV (mL/m ²)	31 ± 10	28 ± 6	.038
RVEF (%)	61 ± 8	64 ± 5	.004
LGE presence	6 (8%)	0 (0%)	.028

8% avec rehaussement tardif VG

Nb MS familiales

1 avec mutation DSP

1 avec T negatives diffuses

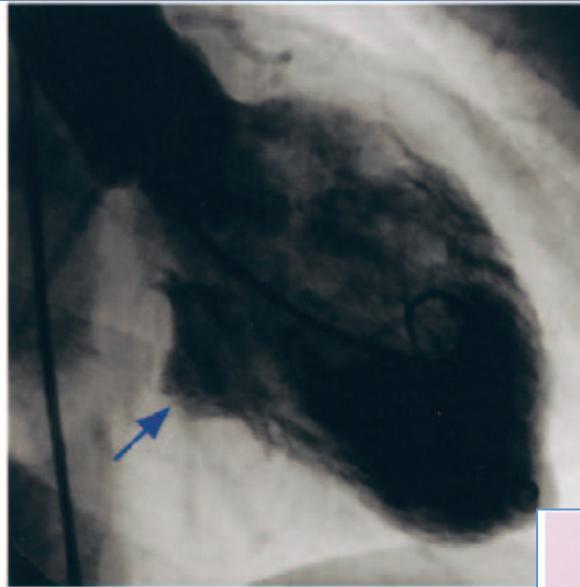


Cardiac Histological Substrate in Patients With Clinical Phenotype of Brugada Syndrome

Andrea Frustaci, MD*; Silvia G. Priori, MD, PhD*; Maurizio Pieroni, MD, PhD;
Cristina Chimenti, MD, PhD; Carlo Napolitano, MD, PhD; Ilaria Rivolta, PhD; Tommaso Sanna, MD;
Fulvio Bellocchi, MD; Matteo Antonio Russo, MD

(*Circulation*. 2005;112:3680-3687.)

18 patients avec investigations invasives



38%

micro anévrismes VD +/- VG

28 % ADN viral

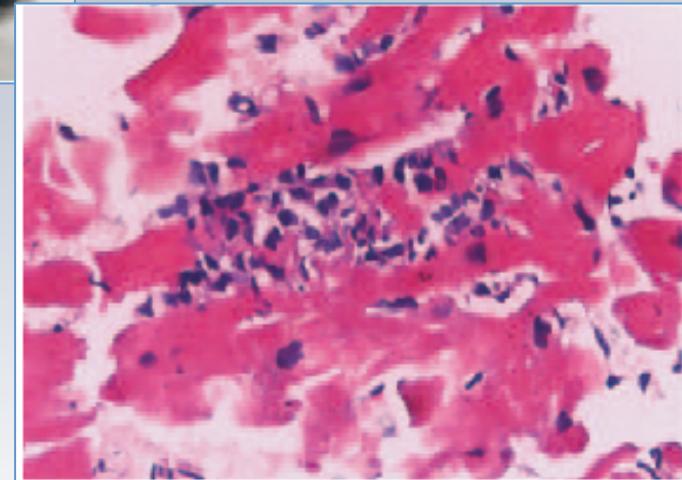
78% myocardite lymphocytaire VD ou VG

(ST + transitoire 2/3 cas)

6 % DVDA (SCN5A sans mutation DVDA)

16 % cardiomyopathie (SCN5A tous)

Apoptose plus marquée si SCN5A



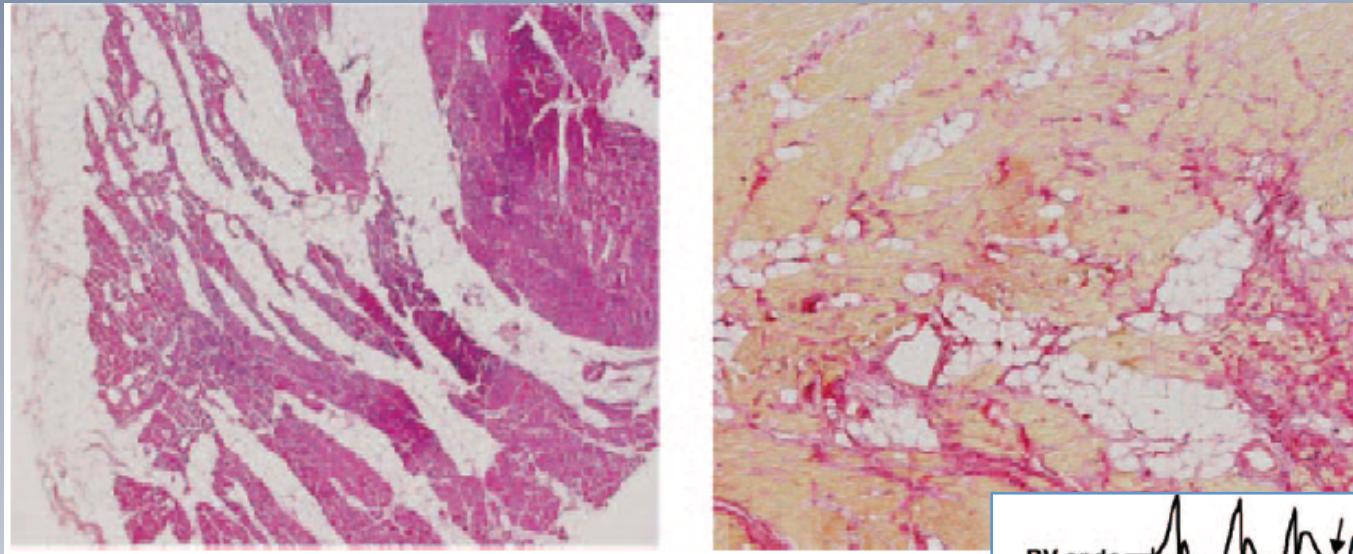
Right Ventricular Fibrosis and Conduction Delay in a Patient With Clinical Signs of Brugada Syndrome

A Combined Electrophysiological, Genetic, Histopathologic, and Computational Study

Ruben Coronel, MD, PhD; Simona Casini, MSc; Tamara T. Koopmann, BSc; Francien J.G. Wilms-Schopman, RA; Arie O. Verkerk, PhD; Joris R. de Groot, MD, PhD; Zahurul Bhuiyan, MD, PhD; Connie R. Bezzina, PhD; Marieke W. Veldkamp, PhD; André C. Linnenbank, PhD; Allard C. van der Wal, MD, PhD; Hanno L. Tan, MD, PhD; Pedro Brugada, MD, PhD; Arthur A.M. Wilde, MD, PhD; Jacques M.T. de Bakker, PhD

Circulation. 2005;112:2769-2777

Autopsie de cœur de Brugada (diagnostiquée 10 ans plus tôt) avec orage VF:
infiltration fibreuse et graisseuse RVOT + mutation SCN5A

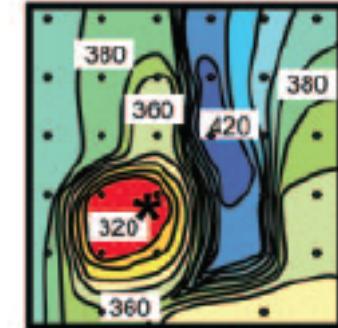
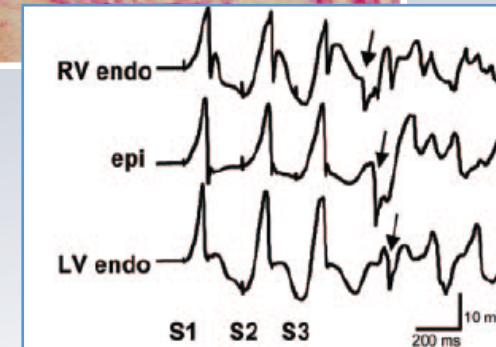


Pas de gradient de repolarisation MAP endo/epi

Anomalie restitution de conduction VD

Tr conduction basal VD endo et épi

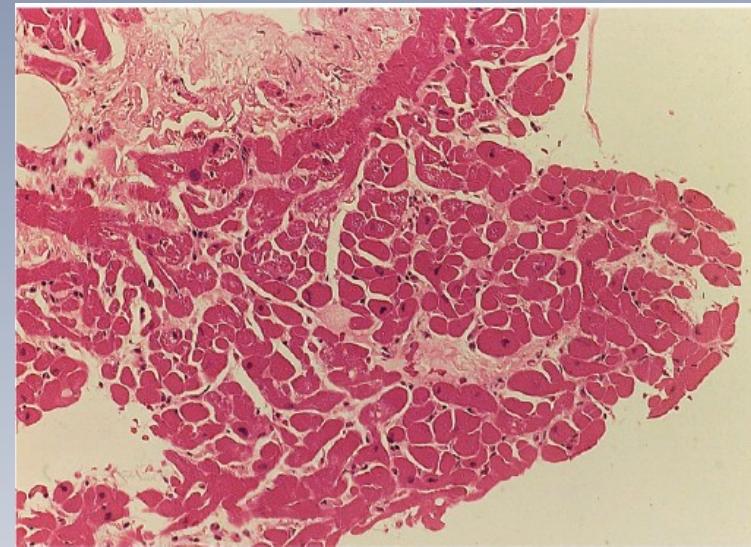
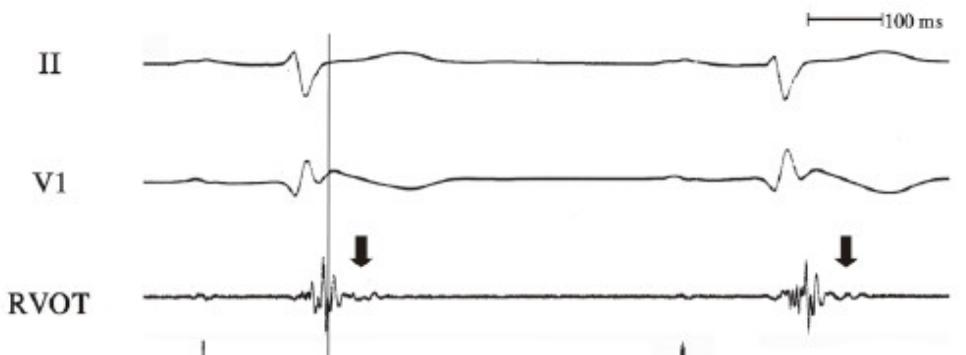
Declenchement VF par reentrée endocardique



Right Ventricular Histological Substrate and Conduction Delay in Patients With Brugada Syndrome

Kimie OHKUBO,¹ MD, Ichiro WATANABE,¹ MD, Yasuo OKUMURA,¹ MD, Yasuhiro TAKAGI,¹ MD, Sonoko ASHINO,¹ MD, Masayoshi KOFUNE,¹ MD, Hidezou SUGIMURA,¹ MD, Toshiko NAKAI,¹ MD, Yuji KASAMAKI,¹ MD, Atsushi HIRAYAMA,¹ MD, and Shin-Ichiro MORIMOTO,² MD

Int Heart J 2010;51:17-23



24 Brugada avec VF

72 % avec pot fragmentés tardifs RVOT endo

54 % avec anomalies biopsie (septum VD)

(CM hypertrophie et degenerescence, fibrose intersticielle, infiltrat graisseux, lymphocytes, désorganisation fibrillaire)

Right ventricular outflow tract high-density endocardial unipolar voltage mapping in patients with Brugada syndrome: evidence for electroanatomical abnormalities

Konstantinos P. Letsas^{1*}, Michael Efremidis¹, Konstantinos Vlachos¹, Stamatis Georgopoulos¹, Nikolaos Karamichalakis¹, Dimitrios Asvestas¹, Kosmas Valkanas¹, Panagiotis Korantzopoulos², Tong Liu³, and Antonios Sideris¹

Europace (2017) 0, 1–7

Mapping endo 10 Brugada

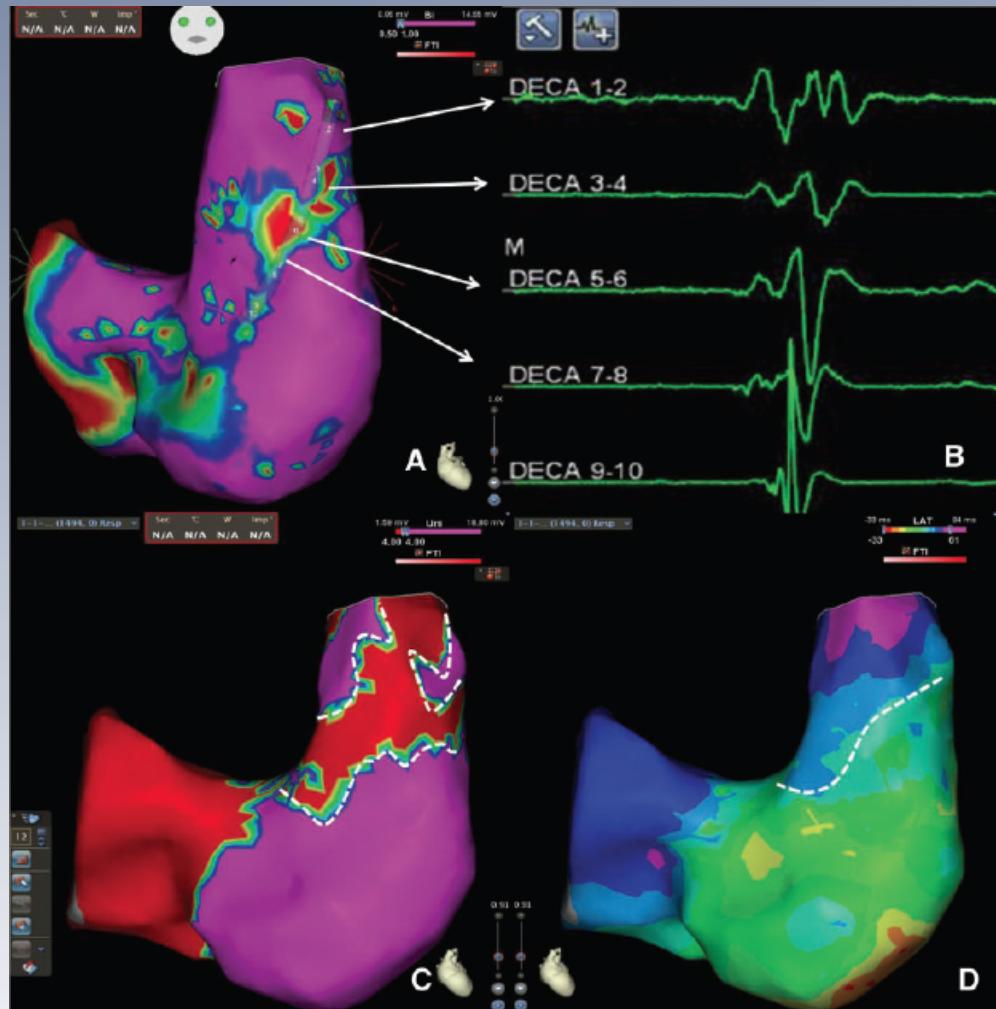
Bipolaire < 1 mV $3.4 \pm 1.7 \text{ cm}^2$

Unipolaire < 4 mV $12.6 \pm 4.6 \text{ cm}^2$

Paroi libre RVOT (sinon para tric)
Liés à l'inductibilité

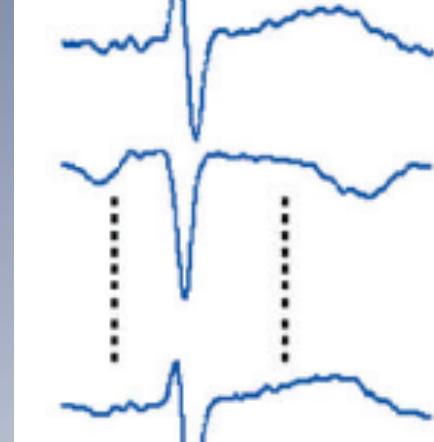
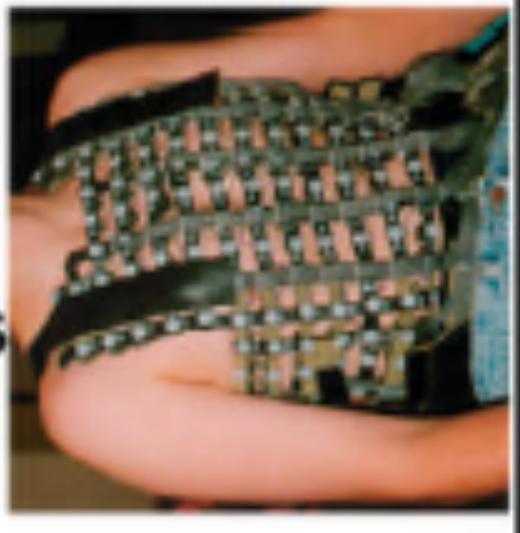
Pot fractionnés 100% patients

Durée activation VD > témoins

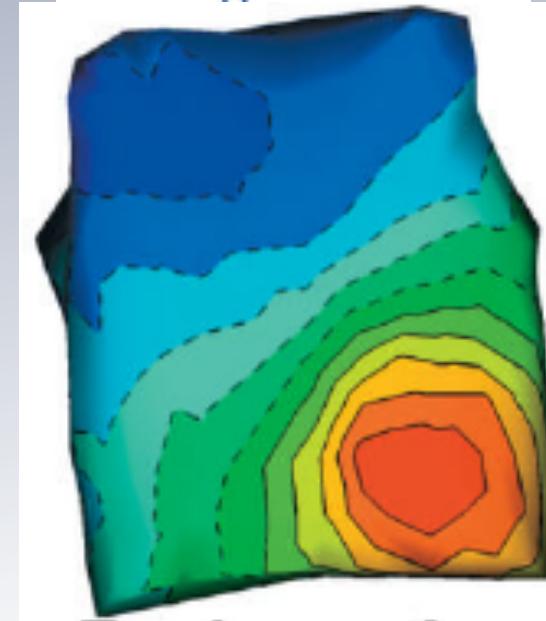


The Cardiac Electrophysiologic Substrate Underlying the ECG Phenotype and Electrogram Abnormalities In Brugada Syndrome Patients *Circulation*. 2015 June 2; 131(22): 1950–1959.

Junjie Zhang, BS^{1,2}, Frédéric Sacher, MD³, Kurt Hoffmayer, MD⁴, Thomas O'Hara, PhD⁵, Maria Strom, PhD⁶, Phillip Cuculich, MD^{1,7}, Jennifer Silva, MD^{1,7}, Daniel Cooper, MD^{1,7}, Mitchell Faddis, MD^{1,7}, Méléze Hocini, MD³, Michel Haïssaguerre, MD³, Melvin Scheinman, MD⁸, and Yoram Rudy, PhD^{1,2,7}

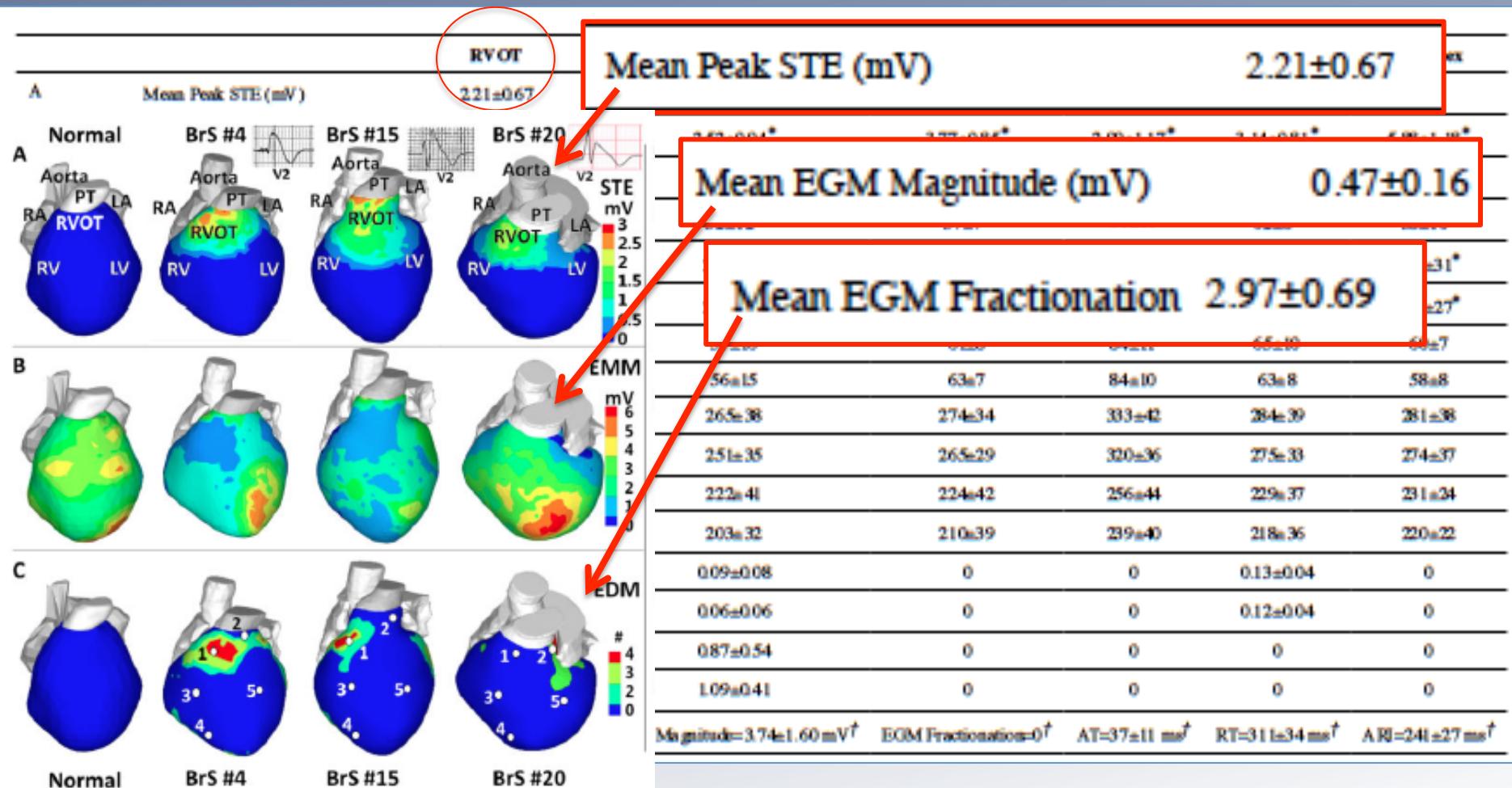


Etude panoramique épicarde



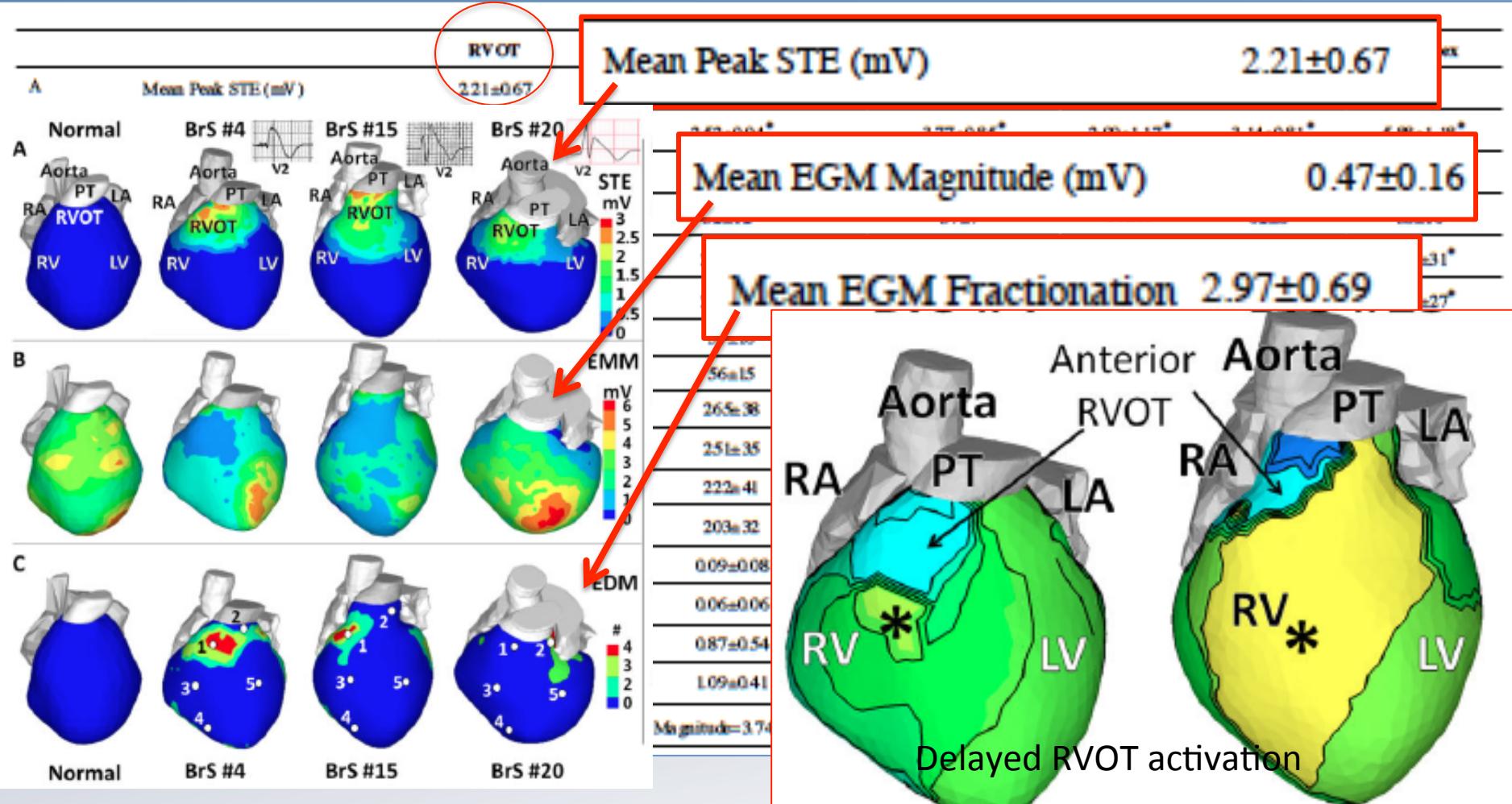
The Cardiac Electrophysiologic Substrate Underlying the ECG Phenotype and Electrogram Abnormalities In Brugada Syndrome Patients *Circulation*. 2015 June 2; 131(22): 1950–1959.

Junjie Zhang, BS^{1,2}, Frédéric Sacher, MD³, Kurt Hoffmayer, MD⁴, Thomas O'Hara, PhD⁵, Maria Strom, PhD⁶, Phillip Cuculich, MD^{1,7}, Jennifer Silva, MD^{1,7}, Daniel Cooper, MD^{1,7}, Mitchell Faddis, MD^{1,7}, Mélèze Hocini, MD³, Michel Haïssaguerre, MD³, Melvin Scheinman, MD⁸, and Yoram Rudy, PhD^{1,2,7}



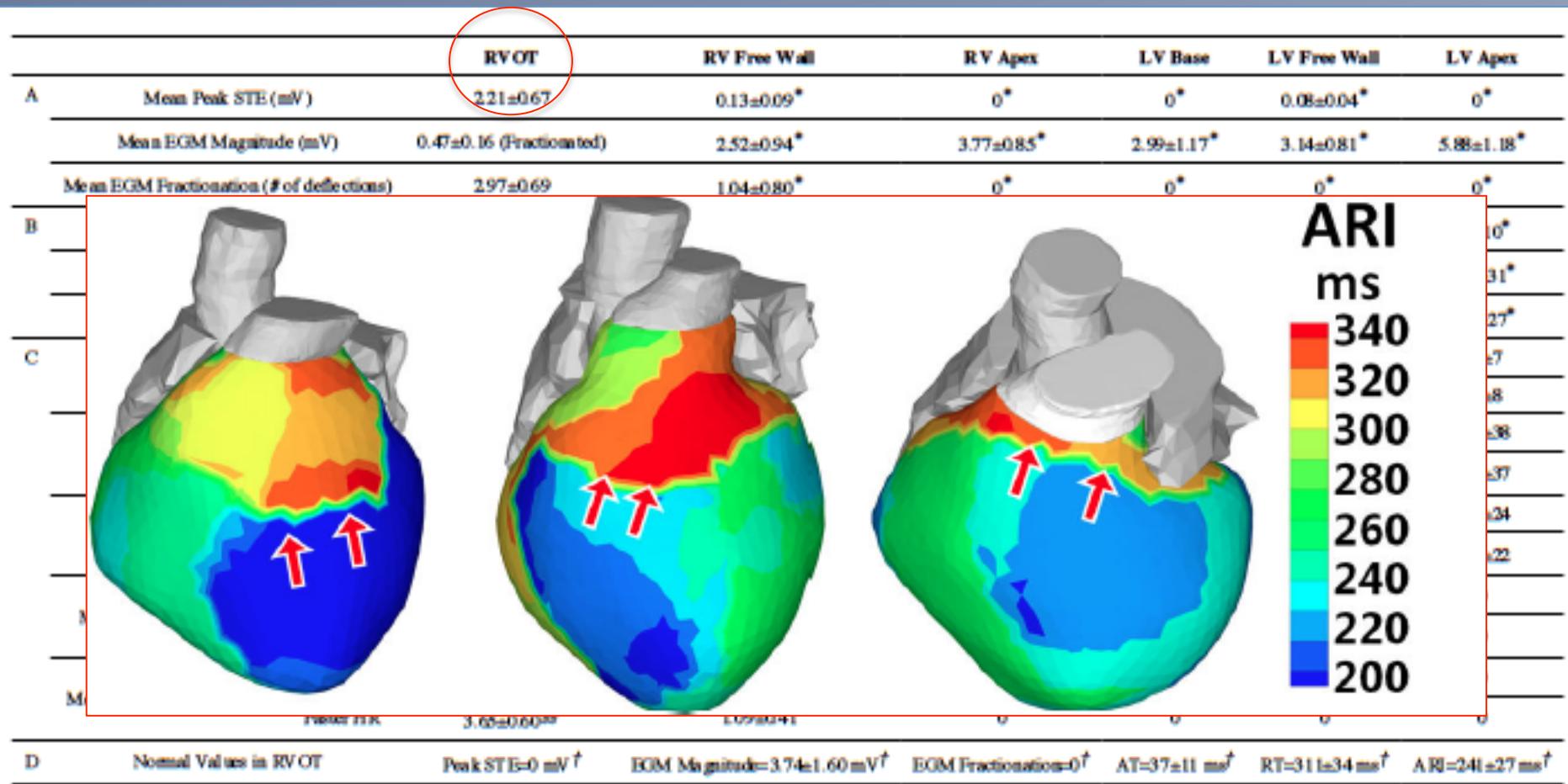
The Cardiac Electrophysiologic Substrate Underlying the ECG Phenotype and Electrogram Abnormalities In Brugada Syndrome Patients *Circulation*. 2015 June 2; 131(22): 1950–1959.

Junjie Zhang, BS^{1,2}, Frédéric Sacher, MD³, Kurt Hoffmayer, MD⁴, Thomas O'Hara, PhD⁵, Maria Strom, PhD⁶, Phillip Cuculich, MD^{1,7}, Jennifer Silva, MD^{1,7}, Daniel Cooper, MD^{1,7}, Mitchell Faddis, MD^{1,7}, Mélèze Hocini, MD³, Michel Haïssaguerre, MD³, Melvin Scheinman, MD⁸, and Yoram Rudy, PhD^{1,2,7}

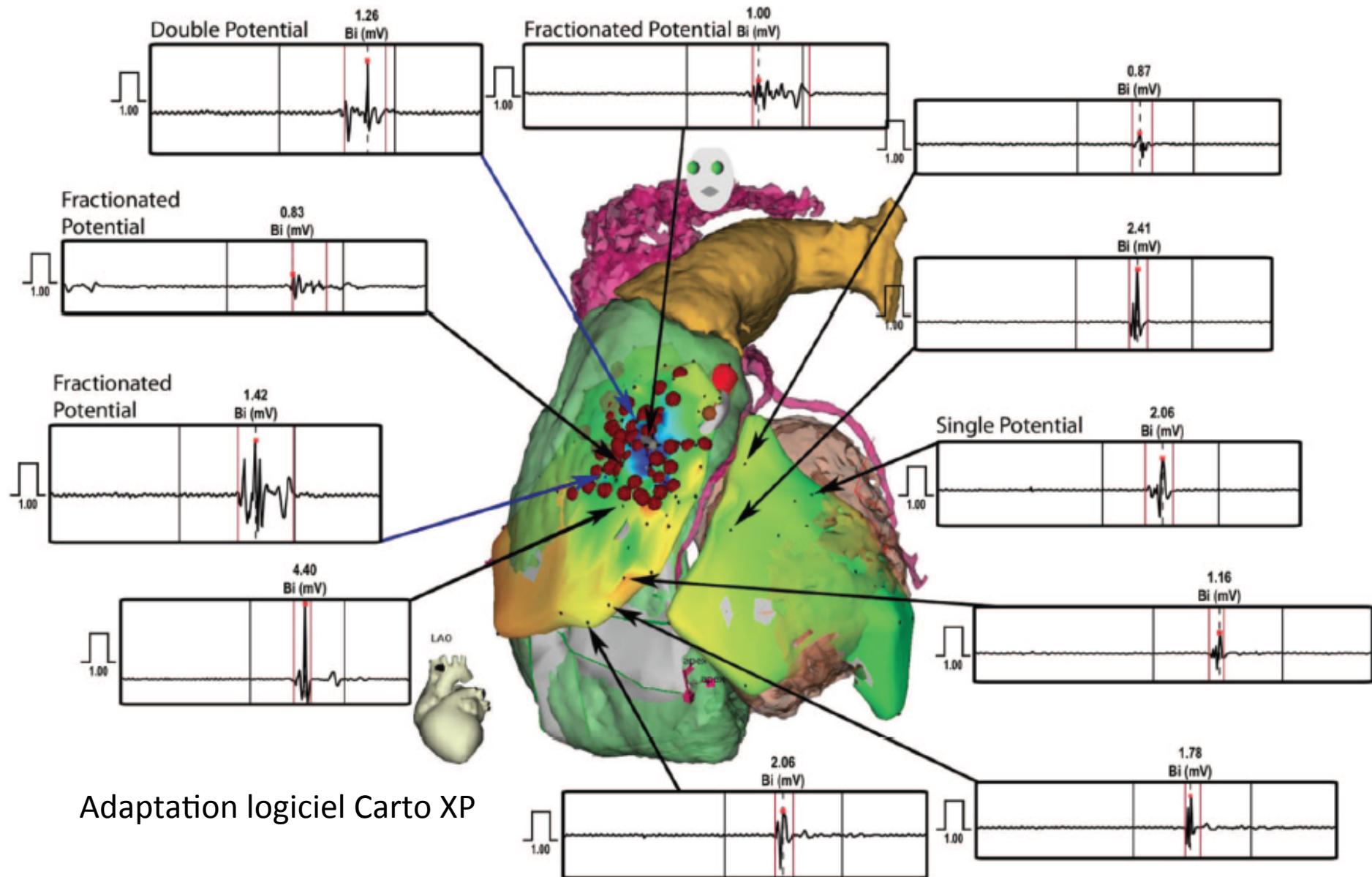


The Cardiac Electrophysiologic Substrate Underlying the ECG Phenotype and Electrogram Abnormalities In Brugada Syndrome Patients *Circulation*. 2015 June 2; 131(22): 1950–1959.

Junjie Zhang, BS^{1,2}, Frédéric Sacher, MD³, Kurt Hoffmayer, MD⁴, Thomas O'Hara, PhD⁵, Maria Strom, PhD⁶, Phillip Cuculich, MD^{1,7}, Jennifer Silva, MD^{1,7}, Daniel Cooper, MD^{1,7}, Mitchell Faddis, MD^{1,7}, Mélèze Hocini, MD³, Michel Haïssaguerre, MD³, Melvin Scheinman, MD⁸, and Yoram Rudy, PhD^{1,2,7}



Gradients ARI bruts RVOT mais diminuent si fréquence rapide. Durée ARI plus longue RVOT



Argument en faveur de la théorie de la dépolarisation

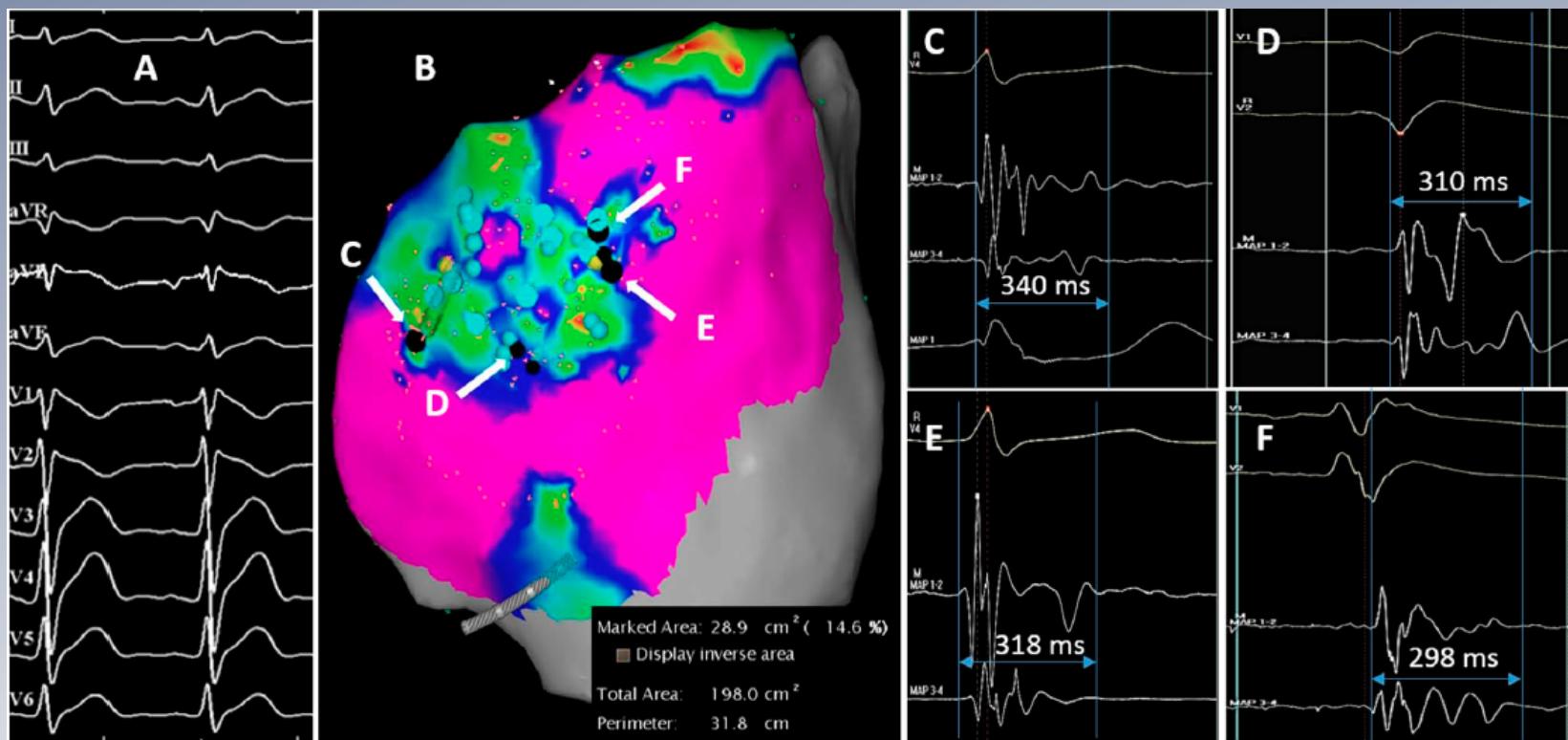
Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation

Josep Brugada, MD*; Carlo Pappone, MD, PhD*; Antonio Berruezo, MD, PhD;
Gabriele Vicedomini, MD; Francesco Manguso, MD, PhD; Giuseppe Ciccone, MD;
Luigi Giannelli, MD; Vincenzo Santinelli, MD

(*Circ Arrhythm Electrophysiol.* 2015;8:1373-1381)

14 Brugada inductibles, symptomatiques et implantés ICD

Zones bas voltage épi < 1.5 mV - pot > 80 ms - > 3 deflections ou post QRS



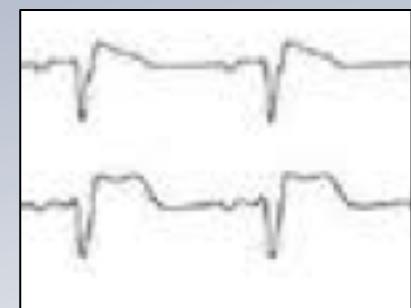
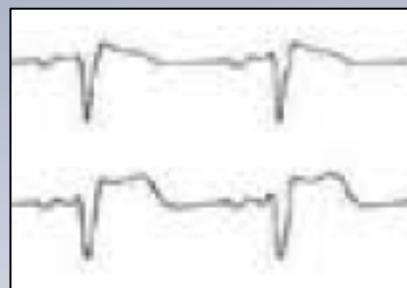
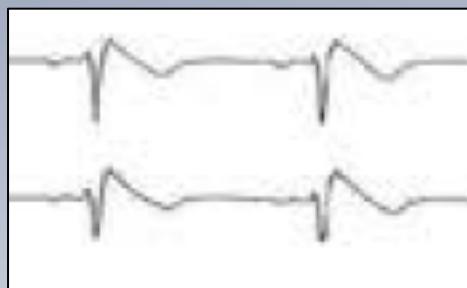
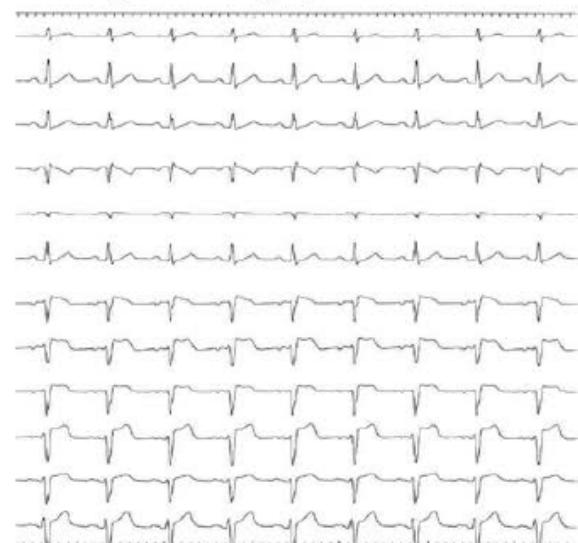
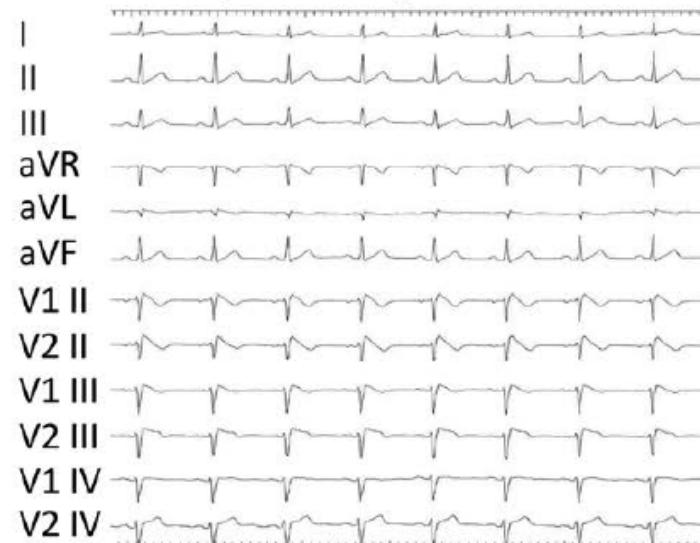
Map endocardiques sans scar significative

ACUTE ABLATION RESULTS

Spontaneous Type 1 ECG Pattern

After Ablation

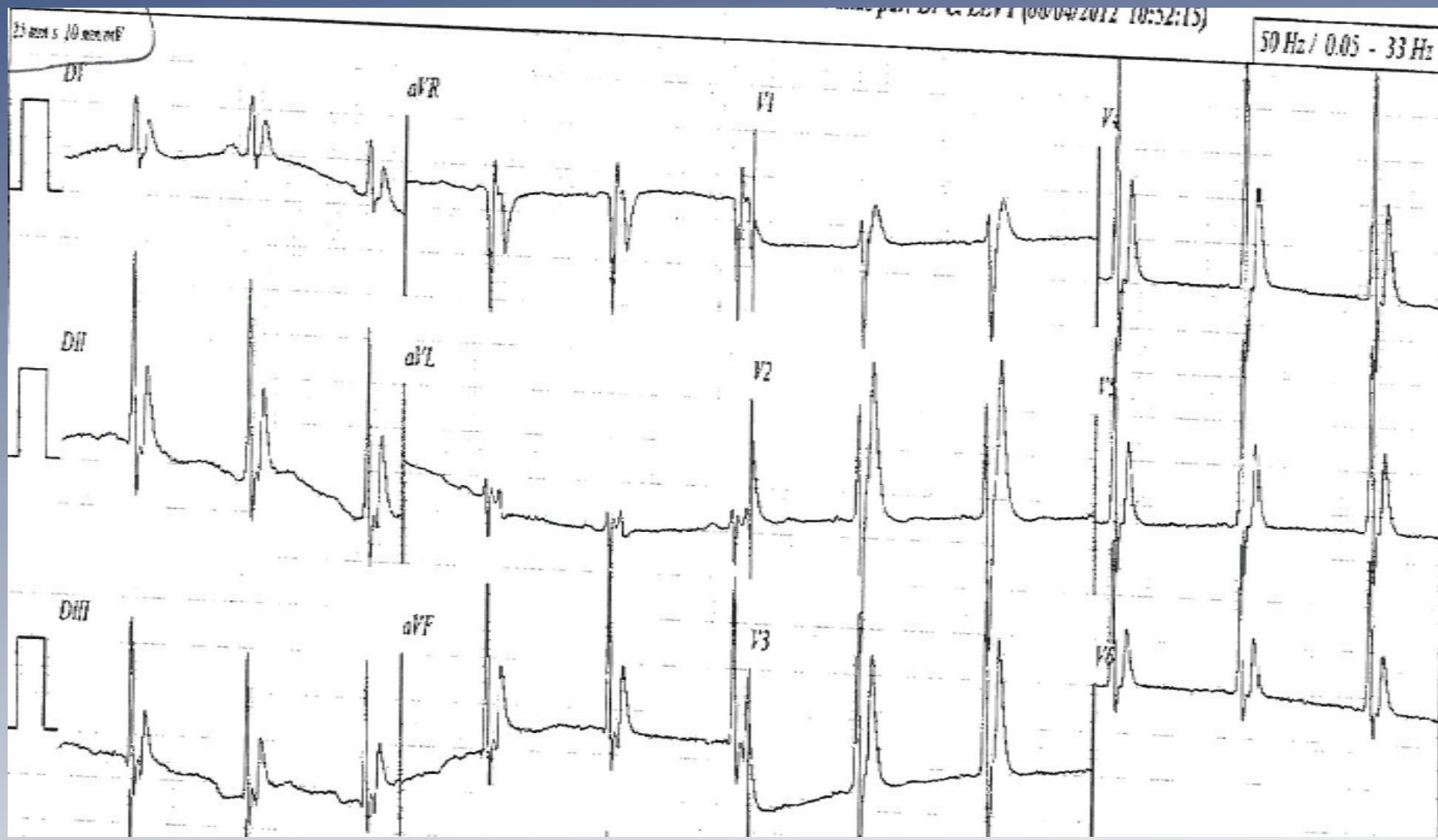
Ajmaline 1 mg/kg after Ablation

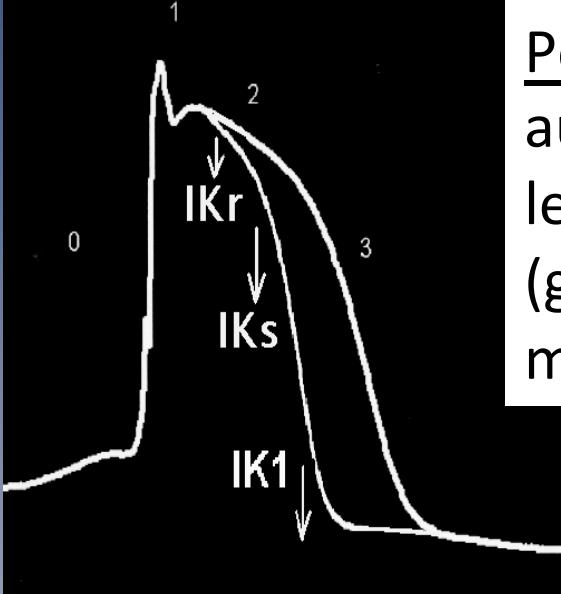


Modifications du ST dès RF (chaleur ?) qui devient concave
pas de modification du voltage local

QT court







Pour ce que l'on connaît:
autosomique dominant
le plus souvent HeRG
(gain de fonction)
mais 80% inconnu

SQTs « 1 »

Gain fonction IK_R (HERG ou KCNH2)

3 familles, 10 pts, MS, FA (Brugada, Circ 2004)
déjà impliqué dans LQT 2 (perte fct)

SQTs « 2 »

Gain fonction IK_S (KCNQ1)

3 cas (sporadiques), MS, FA
(Bellooeg, Circ 2004, Hong, Cardiovasc Res 2005)
déjà impliqué dans LQT 1 (perte fct)
ou FA familiale (gain fct)

SQTs « 3 »

Gain fonction IK_1 (KCNJ2)

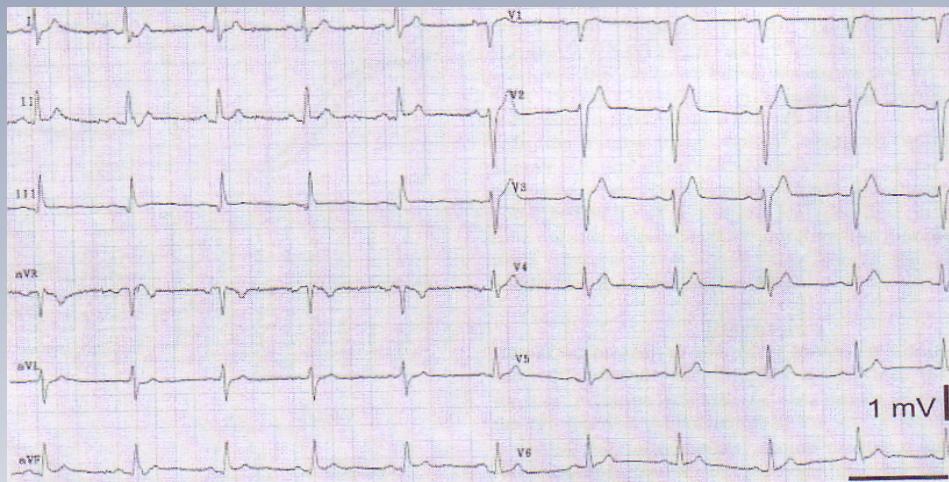
1 famille (2 pts) (Priori, Circ Res 2005)
déjà impliqué dans syndrome Andersen
« LQT » 7) (perte fct)

forme	gene	chromosome	transmission
SQT1	HeRG	7	dominant
SQT2	KCNQ1	11	dominant
SQT3	KCNJ2	17	dominant
SQT4	CACNA1C	12	dominant
SQT5	CACNB2B	10	dominant
SQT6	CACNA2D1	7	dominant
SQT7	SCN5A	3	dominant
SQT8	SLC4A3	2	dominant

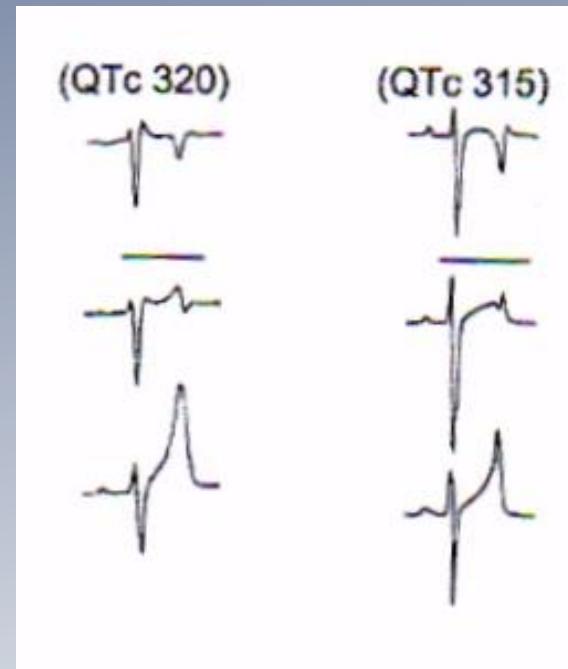
QT court



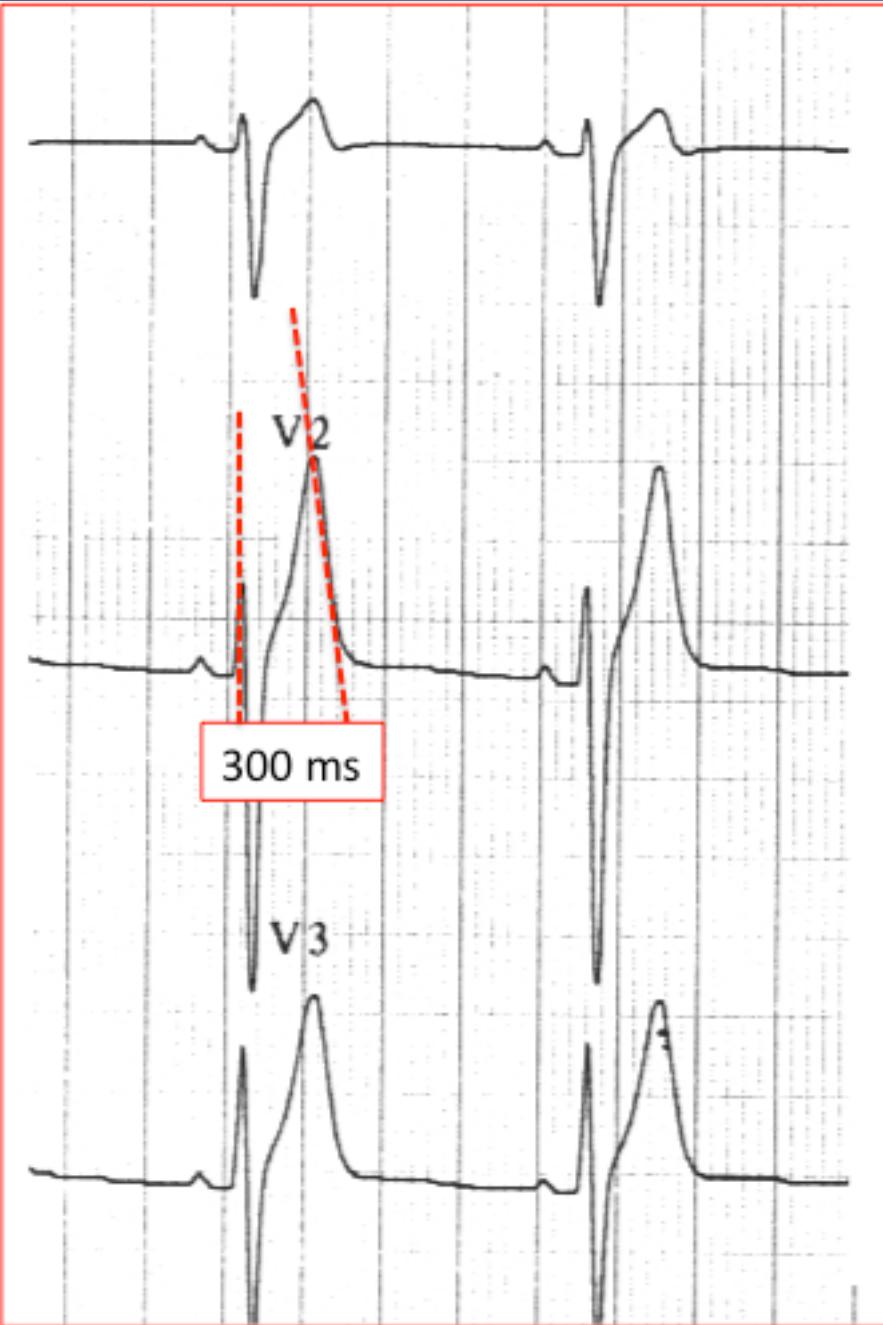
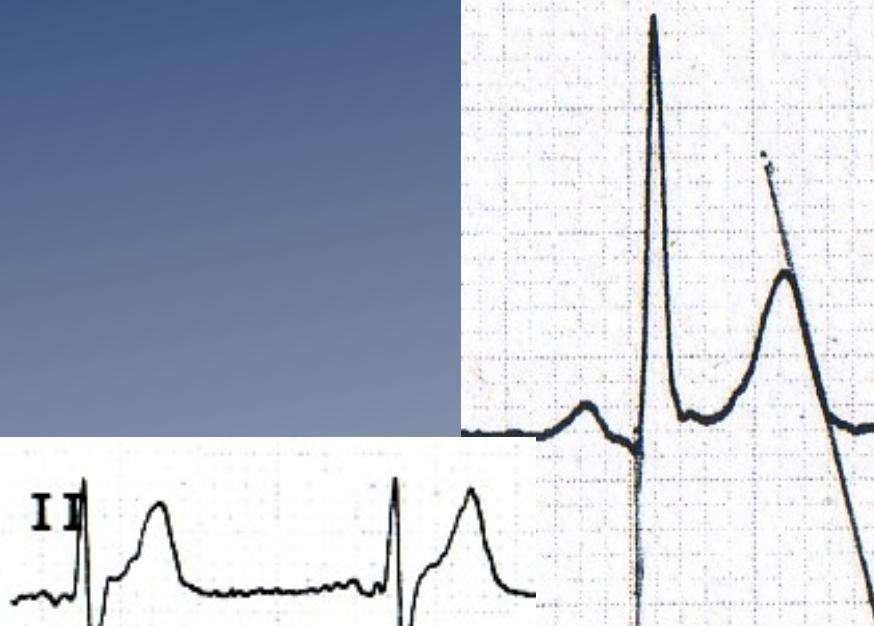
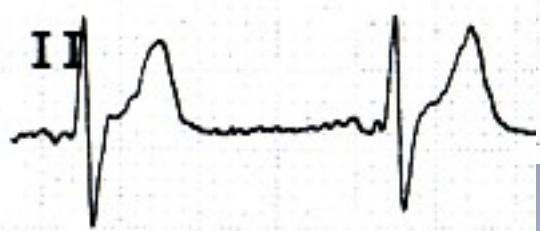
SQTS « 1 »



SQTS « 2 »



SQTS « 3 »



pas de segment ST

Table 1 Lower boundaries of the QT interval in the normal population, and successive cutoffs used to define a short QT.

	QT interval	QT _C interval
<i>Lower normal limit of the QT interval</i>		
Moss AJ, 1993 [19], Luo S 1994 [20]	330 ms (children 310 ms)	360-380 ms
Vincent GM, 1992 [22]		360 ms (M) – 370 ms (F)
<i>Definition of "short QT"</i>		
Gussak I, 2000 [5], Gaita F, 2003 [7]	<300 ms	<300 ms
Schimpf R, 2005 [18]	<320 ms	<320 ms
Giustetto C, 2006 [16]		<340 ms

pas de segment ST

Recommendations	Class ^a	Level ^b	Ref. ^c
SQTS is diagnosed in the presence of a QTc \leq 340 ms.	I	C	This panel of experts
SQTS should be considered in the presence of a QTc \leq 360 ms and one or more of the following: (a) A confirmed pathogenic mutation (b) A family history of SQTS (c) A family history of sudden death at age <40 years (d) Survival from a VT/VF episode in the absence of heart disease.	IIa	C	This panel of experts

Diagnostic

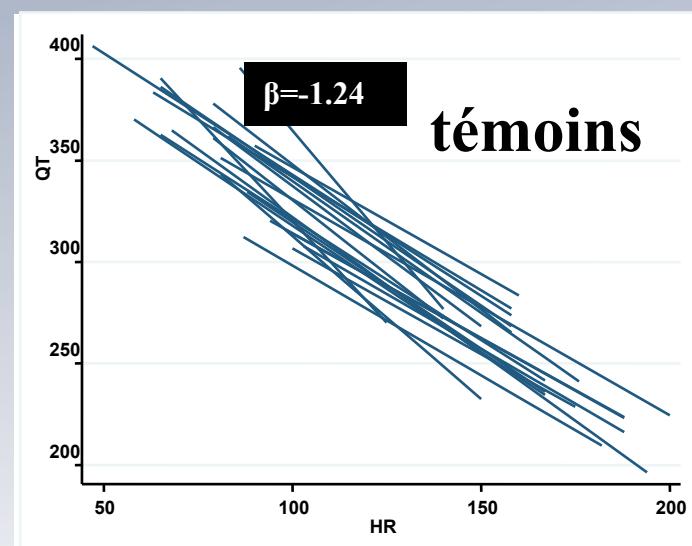
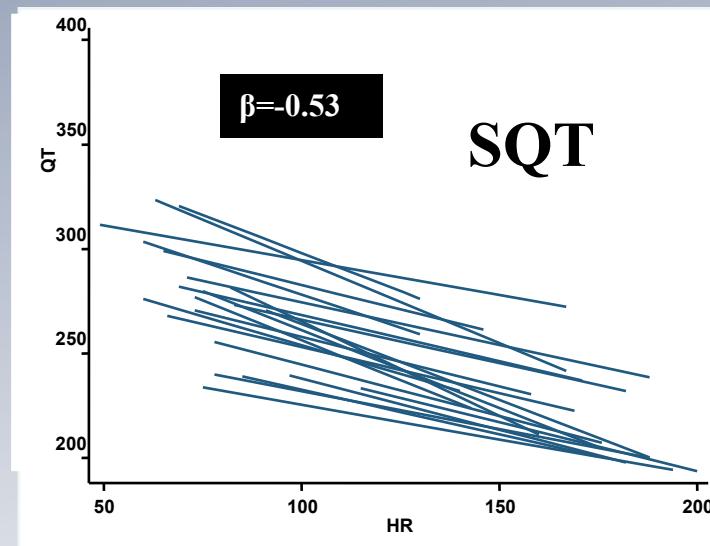
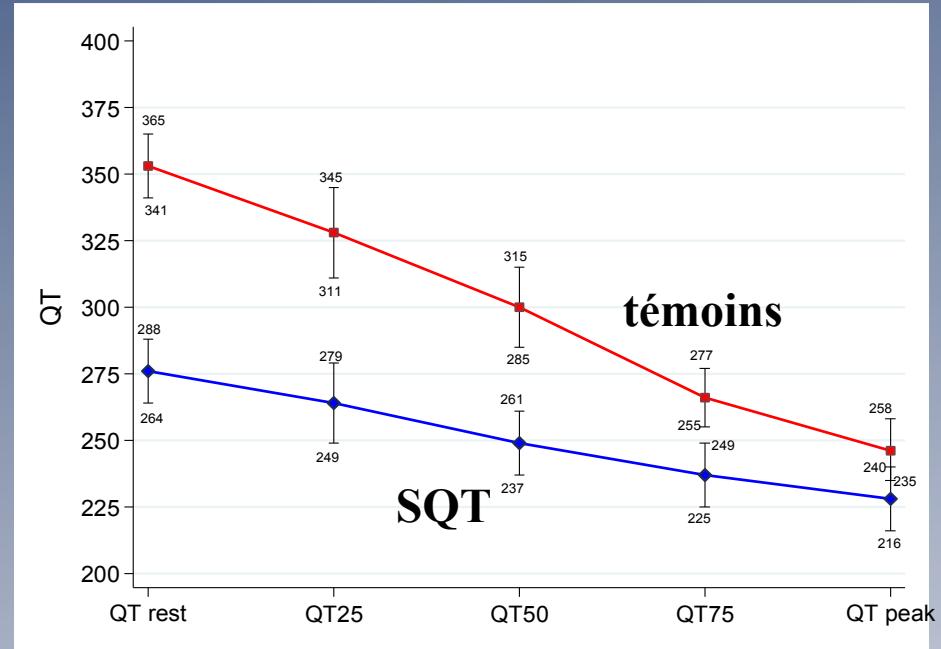
Nouvelles pistes

Holter

Épreuve effort

*pente de la droite QT/RR > - 1
chez témoins*

SQT: < - 0.9

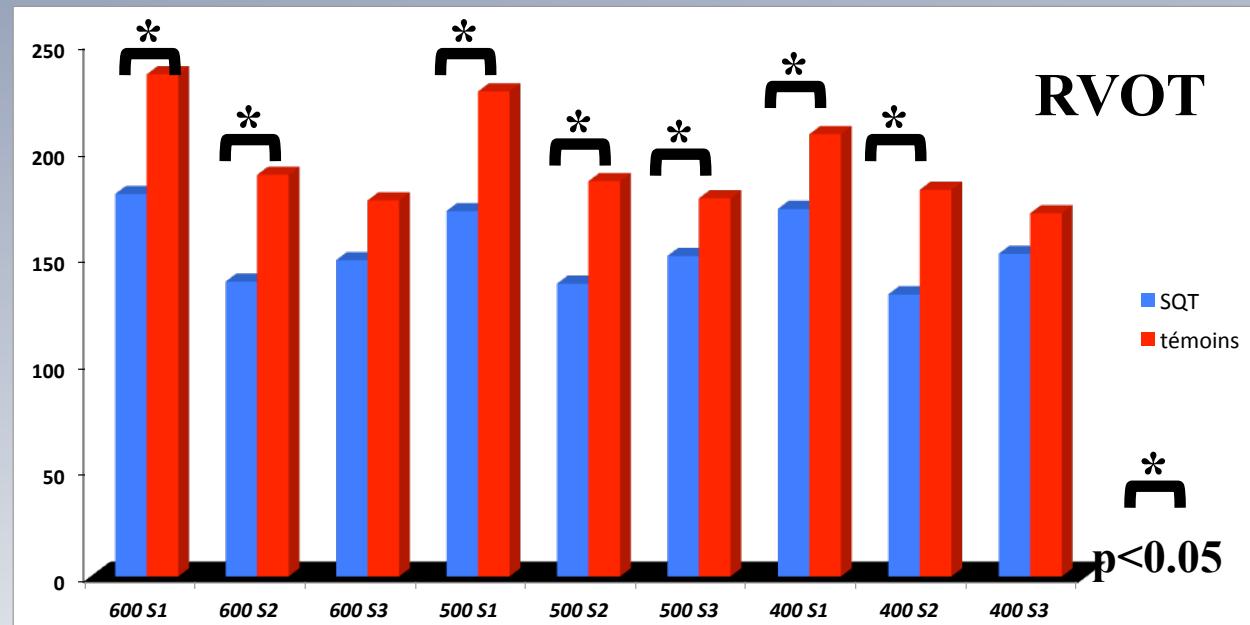
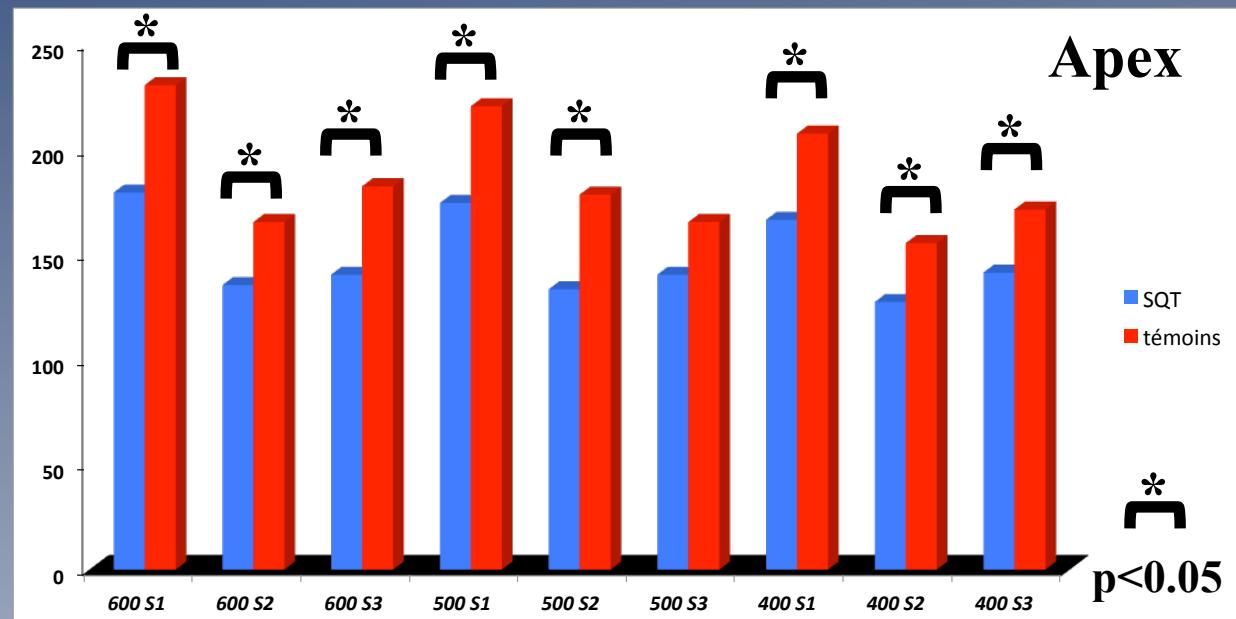


Diagnostic

Nouvelles pistes

Les périodes
réfractaires

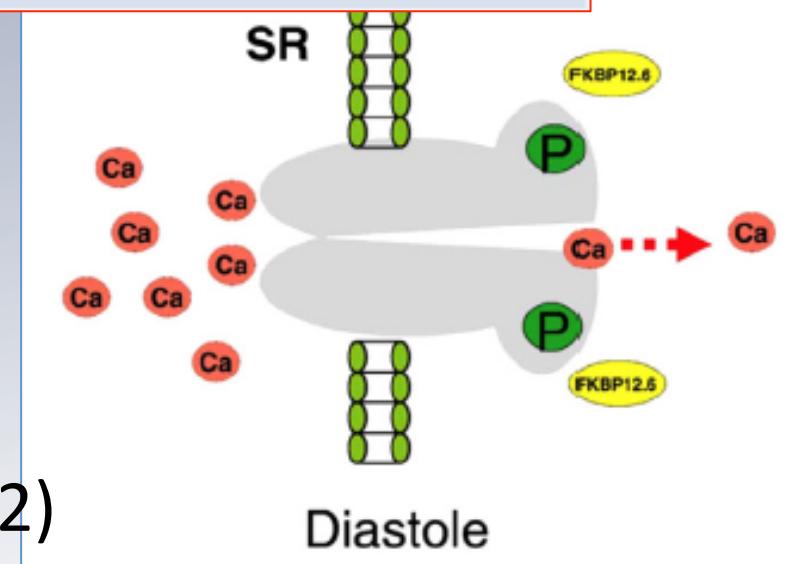
200 ms
valeur cut off
de base



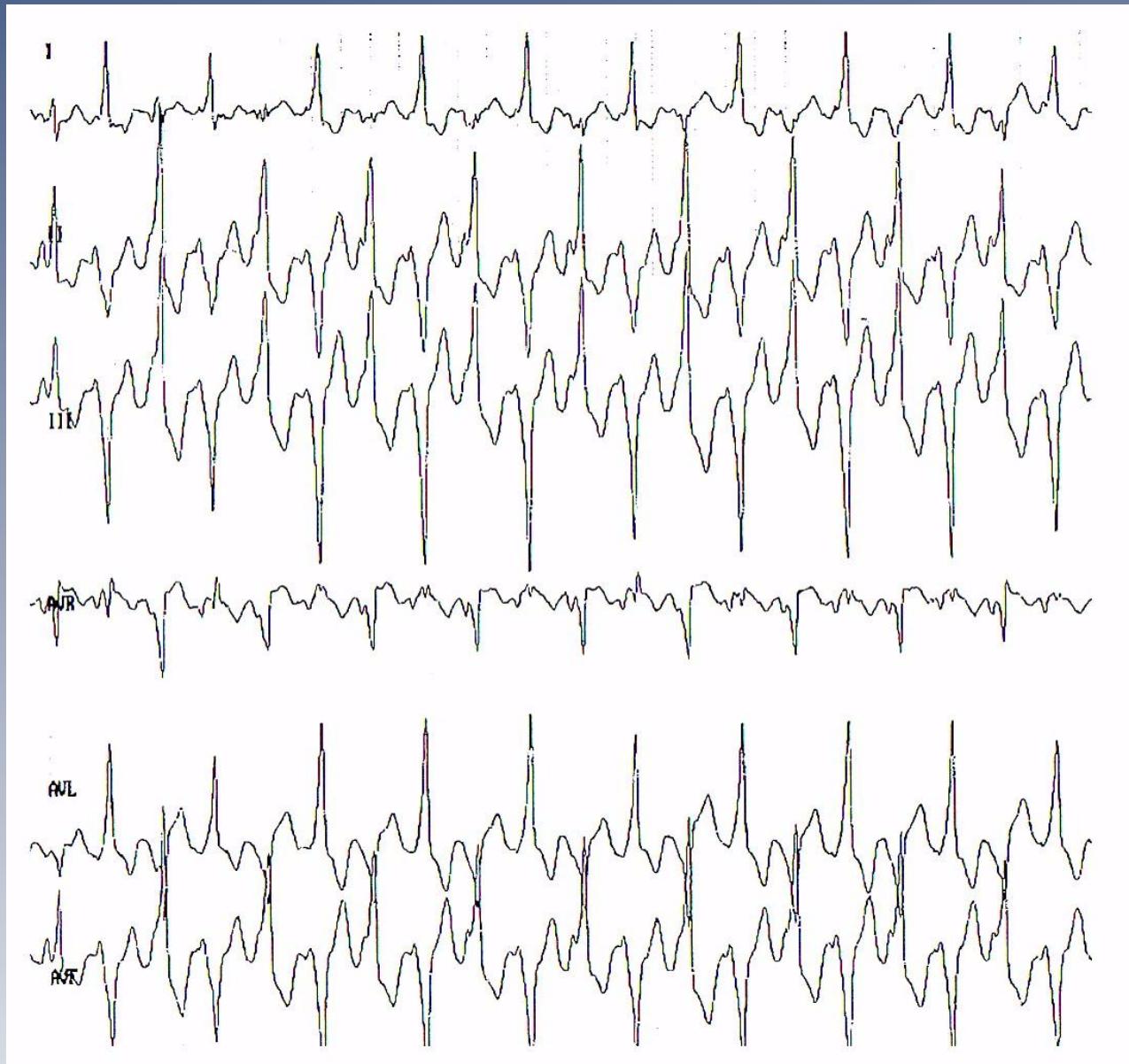
TV catécholergiques polymorphes

forme	gene	chromosome	transmission
CPVT 1	RYR2	1	dominant
CPVT 2	CASQ2	1	récessif ou dominant
CPVT 3	TECRL (?)	7 ou 4 ?	récessif
CPVT 4	CALM1	4	dominant
CPVT 5	TRDN	6	récessif
Forme apparentée	ANK2	4	dominant
Forme apparentée	KCNJ2	17	dominant

- QT normal, onde U
- Bradycardie sinusale (RYR2)



MS récupérée lors d' un bain en piscine



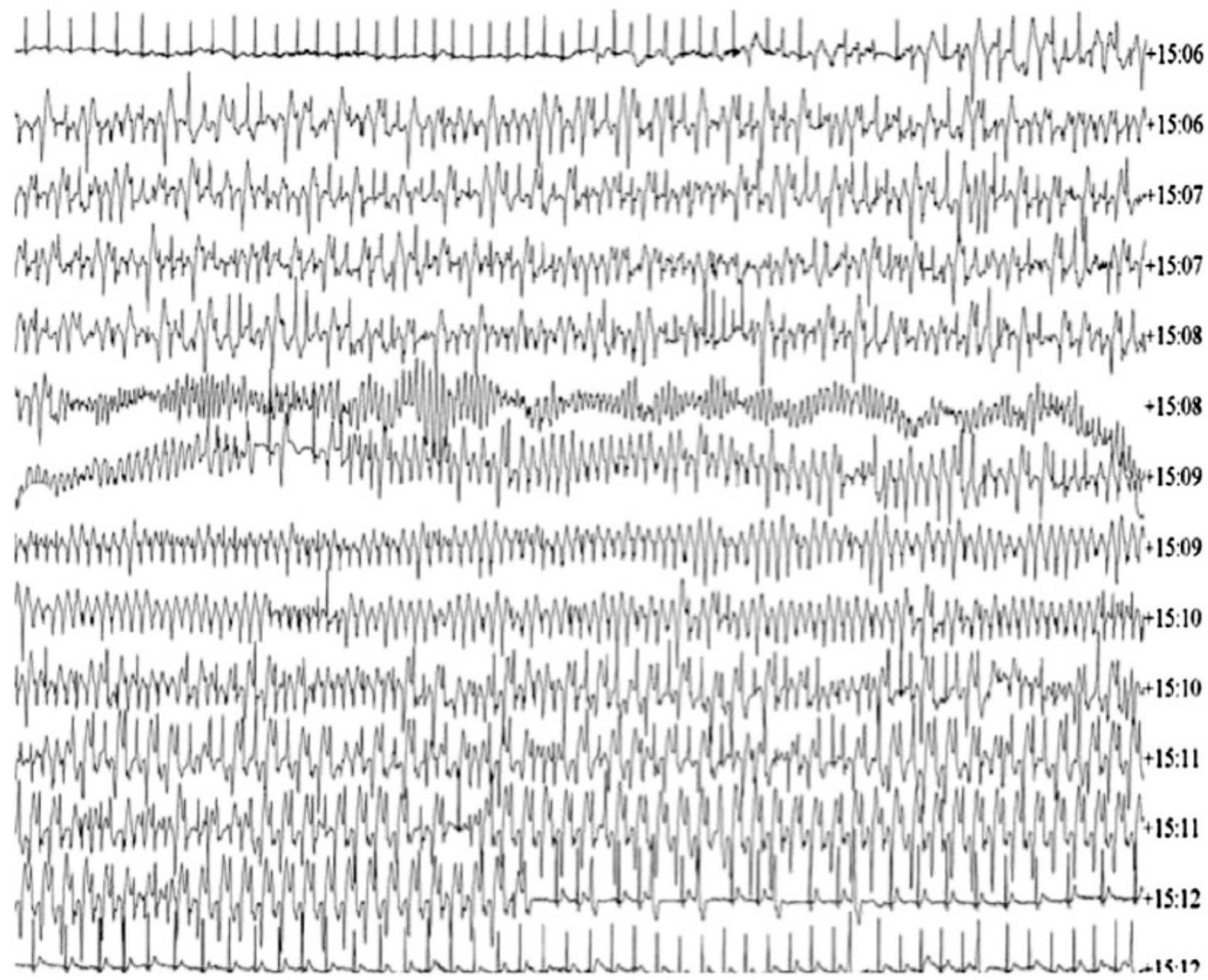
Exercise >>>

1 sec

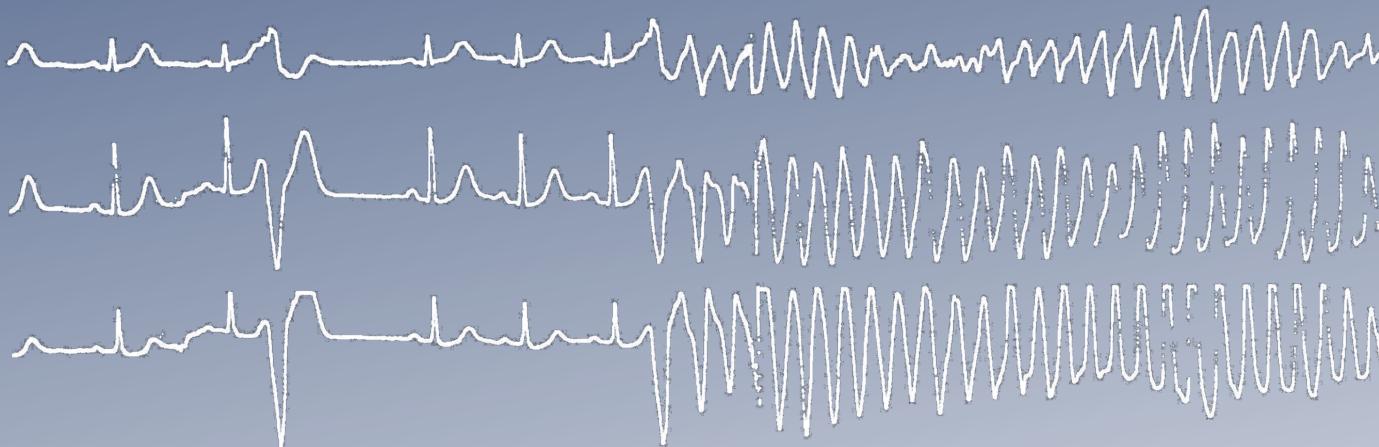




isoprénaline



Repolarisation précoce "maligne" et bénigne >>



- “Slurring” (delta inversée) ou “notching” fin QRS
 - J point $> 0.1 \text{ mV}$ (1mm) in ≥ 2 leads
 - Dérivations inferieures and/or latérales

Expert Consensus

Expert Consensus Recommendations on Early Repolarization Diagnosis

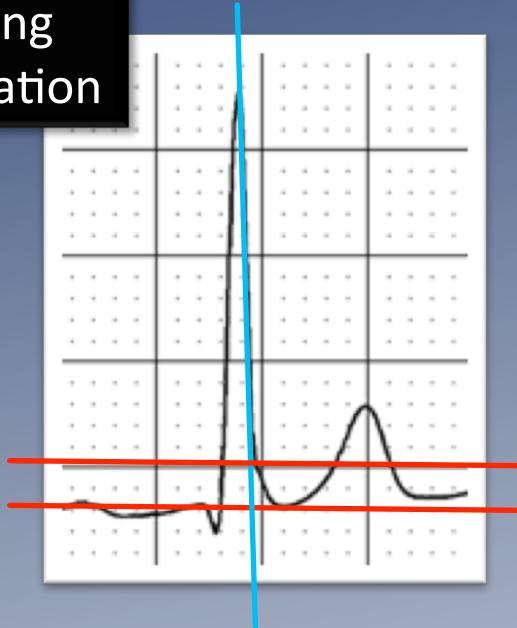
1. ER **syndrome is diagnosed** in the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/ Polymorphic VT
2. ER syndrome **can be diagnosed** in a SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
3. ER pattern **can be diagnosed** in the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

Pour ce que l'on connaît:

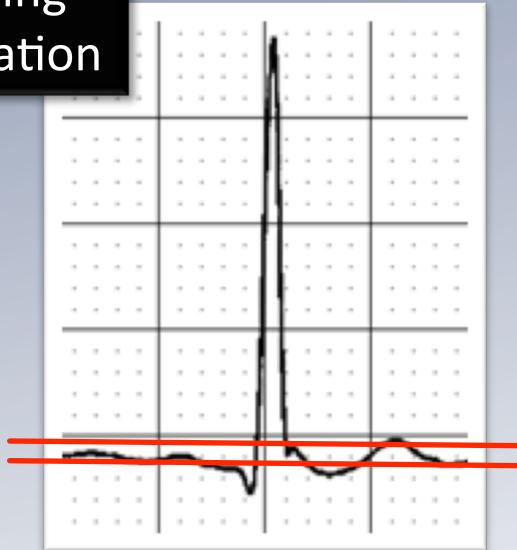
- autosomique dominant
- pénétrance inconnue
- % de ces formes inconnu

forme	gene	chromosome	canal
ERS1	KCNJ8	12	IK _{ATP}
ERS2	CACNA1C	12	ICaL
ERS3	CACNb2B	10	ICaL
ERS4	CACNA2D1	7	ICaL
ERS5	ABCC9	12	IK _{ATP}
ERS6	SCN5A	3	INa
ERS7	SCN10A	3	INa

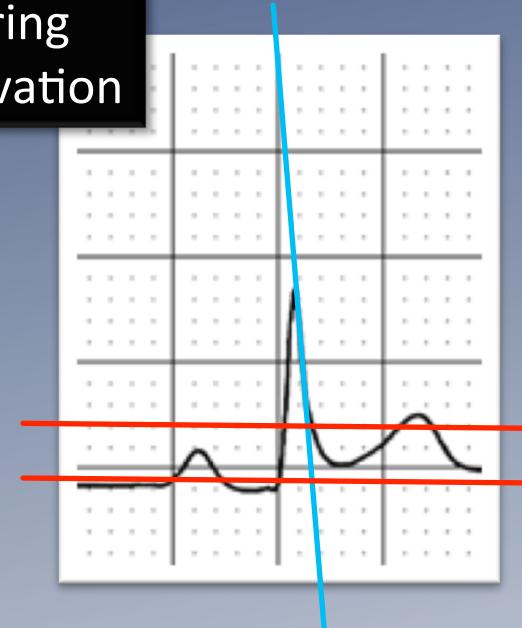
QRS slurring
w/o ST elevation



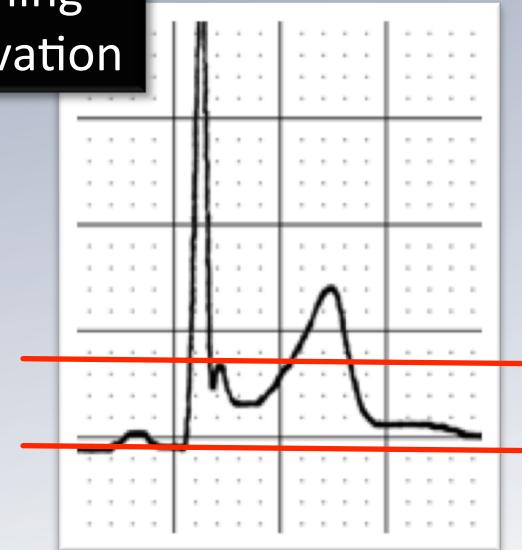
QRS notching
w/o ST elevation



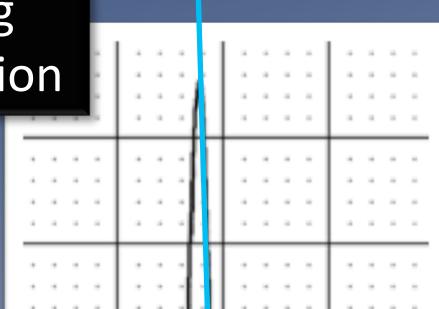
QRS slurring
with ST elevation



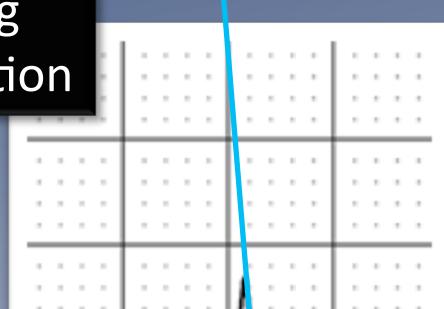
QRS notching
with ST elevation



QRS slurring
w/o ST elevation



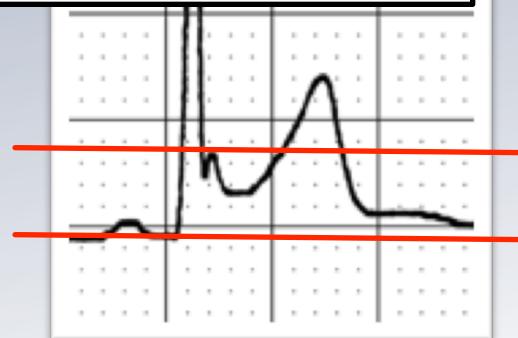
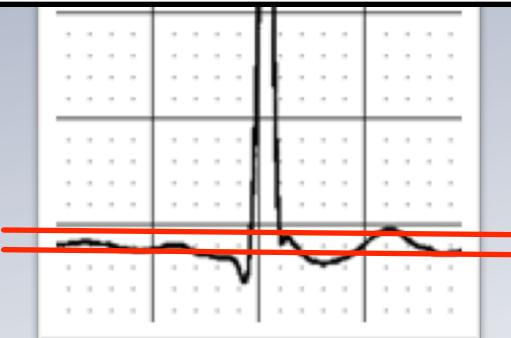
QRS slurring
with ST elevation



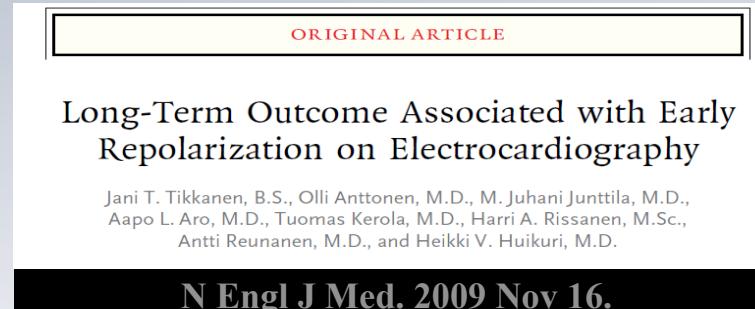
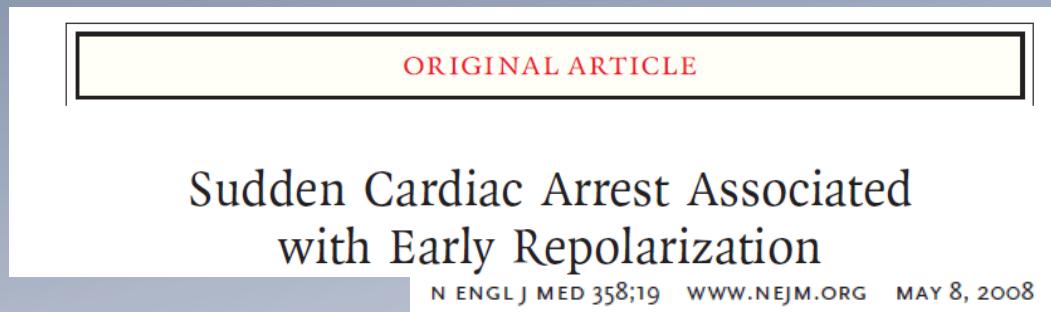
**ST segment elevation is not sufficient
for the diagnosis.**

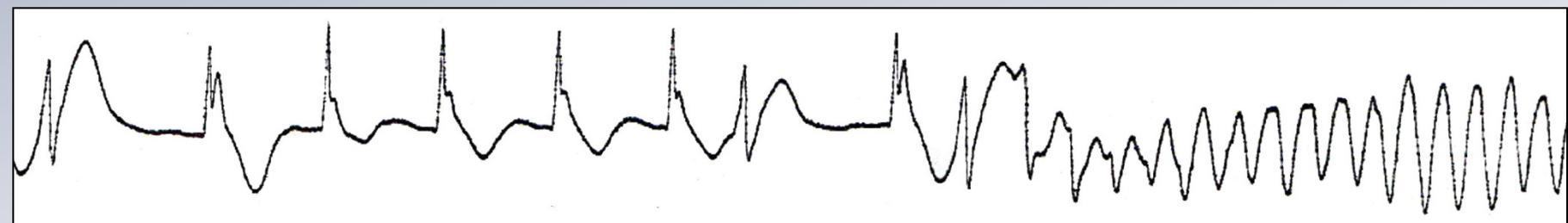
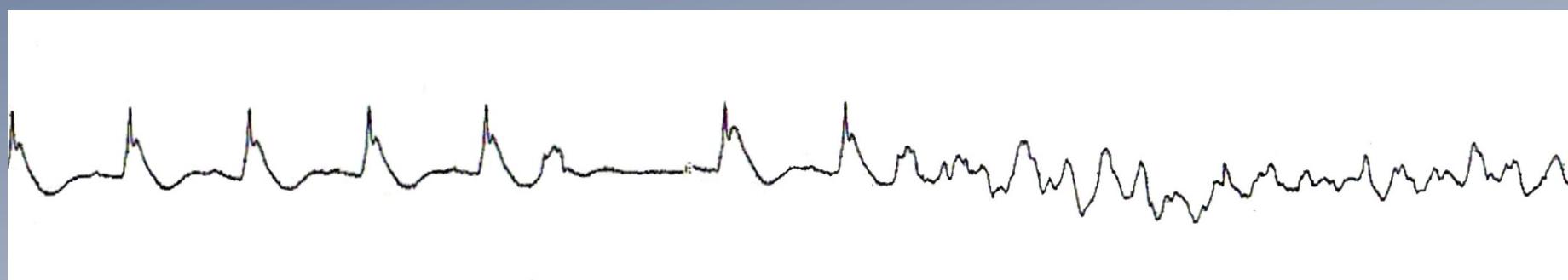
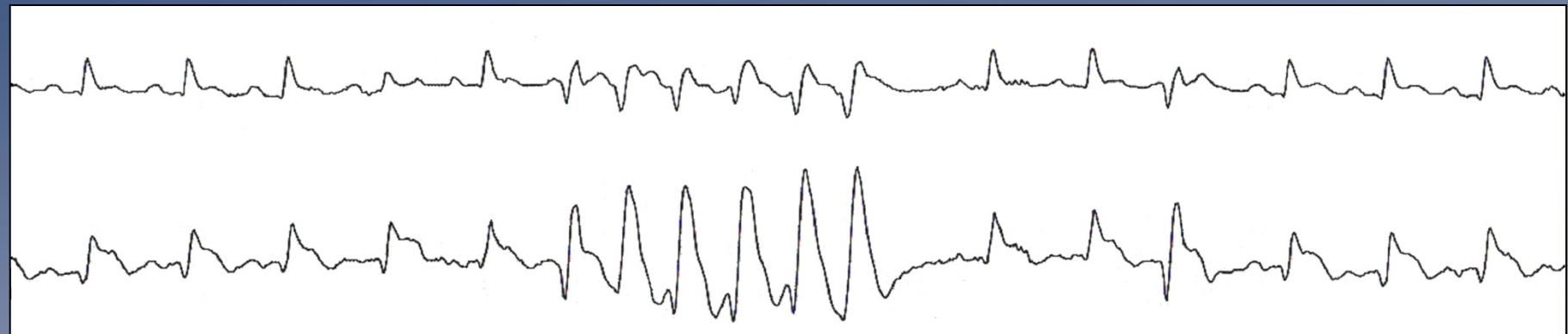
J-wave/point elevation is necessary !!

QRS not
w/o ST el



- ER pattern très fréquent pop générale (1 à 13 %)
- Early Repolarization *Pattern* Vs. Early Repolarization *Syndrome*
- Data suggest: J point elevation in a young adult increase risk of SCD





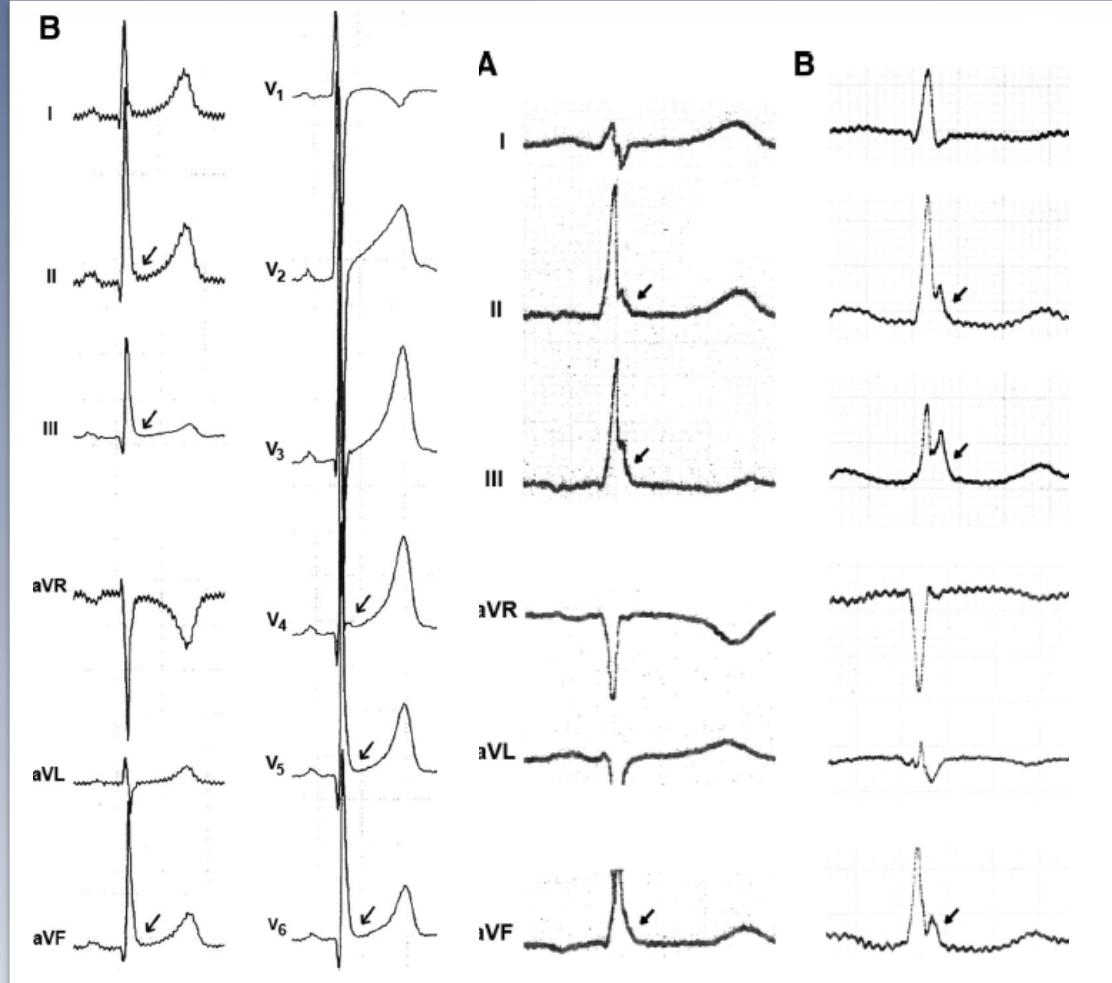
Formes à risque ? mais risque infime ...

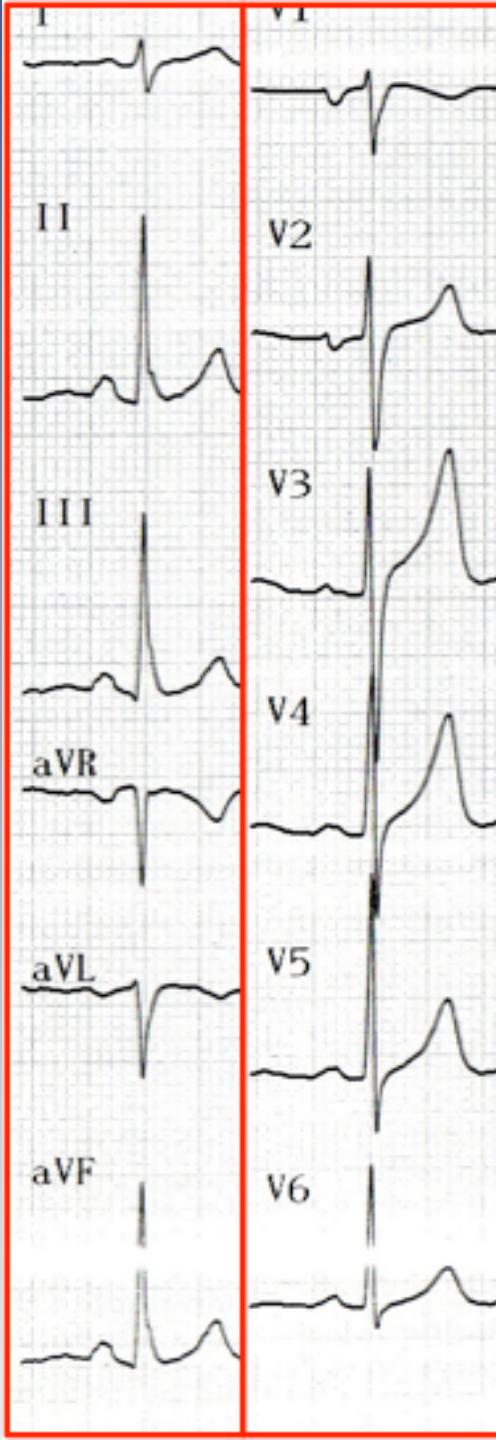
Ascending ST segment
→ benin

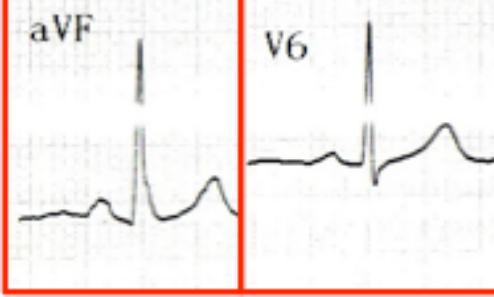
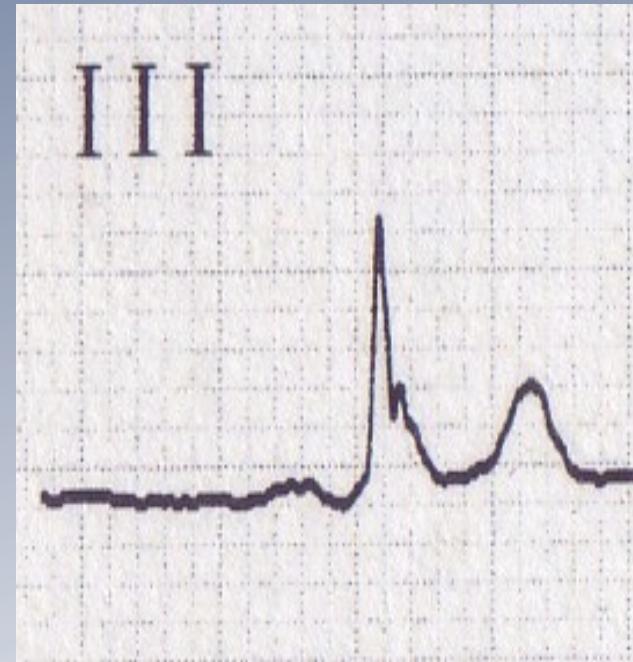
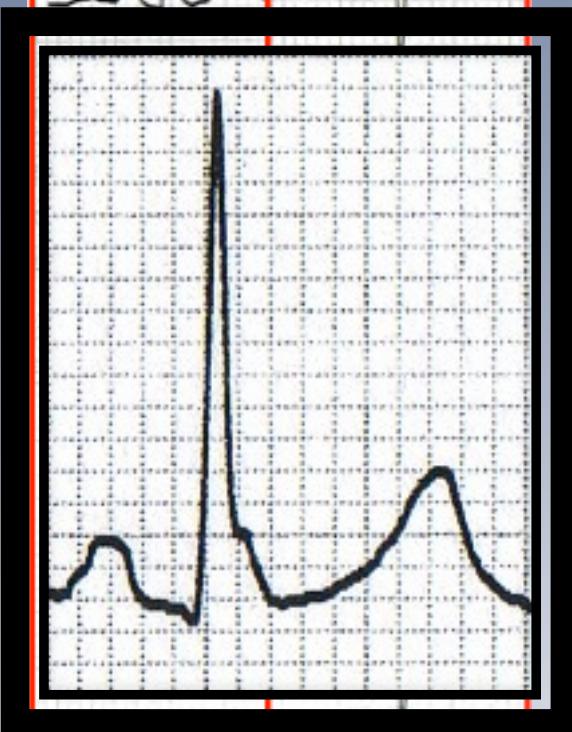
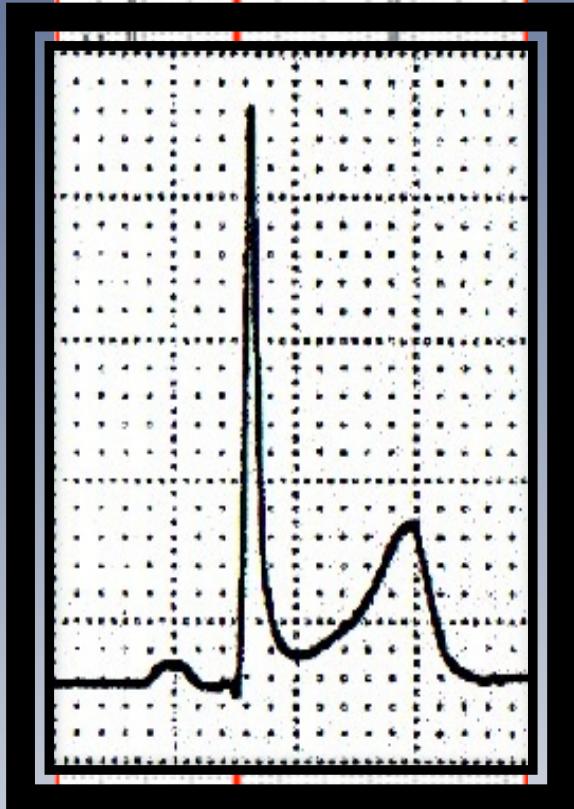
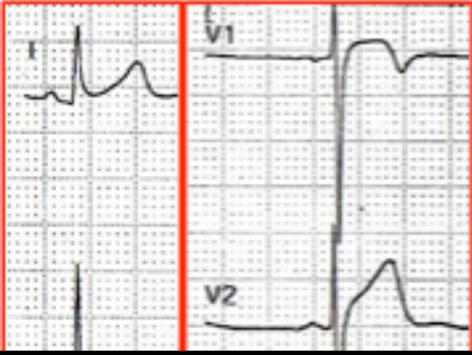
Horizontal/descending ST segment
→ malin

Diffus vs localisé
Amplitude > 2 mm

Inférieur vs latéral ?
Notch vs slurring ?







Ventricular fibrillation in loop recorder memories in a patient with early repolarization syndrome

doi:10.1093/europace/eur264

Philippe Maury^{1*}, Frederic Sacher², Anne Rollin¹, Alexandre Duparc¹, Pierre Mondoly², and Vincent Probst³



