Brugada syndrome:

30 years of progress.

Prof. Dr. Pedro Brugada.

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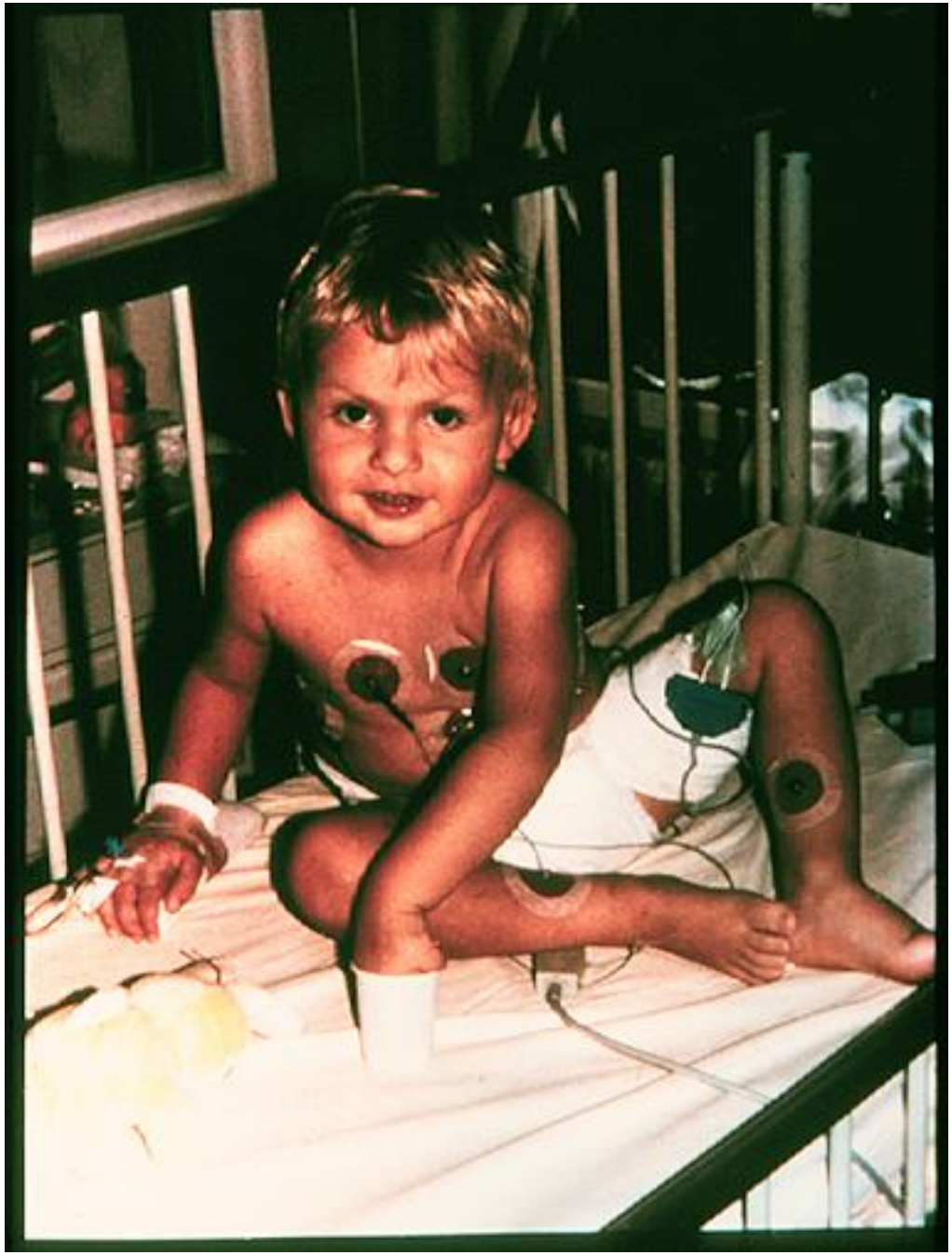
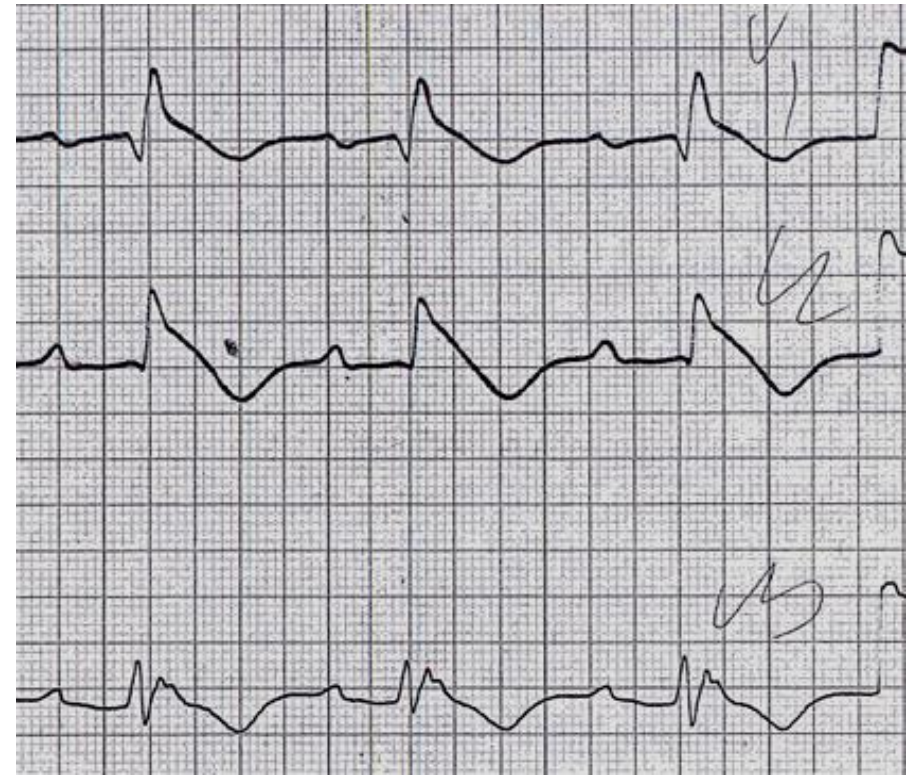
UZ Brussel-VUB, Brussels. Belgium.





Brugada P, Brugada J. **1992:**

„Right bundle-branch block, persistent ST-segment elevation in the right precordial leads and sudden cardiac death: a distinct clinical and electrocardiographic syndrome“

***J Am Coll Cardiol* 1992;20:1391**

„ECG abnormalities constitute the hallmark of Brugada syndrome.

They include repolarization and depolarization abnormalities

in the absence of identifiable structural cardiac abnormalities

or other conditions or agents known to lead to ST-segment elevation

in the right precordial leads“

Circulation 2002;106:2514

P wave duration ↑

PR prolongation

QRS prolongation,
RBBB and LFHB

SN dysfunction

Atrial arrhythmias

Late potentials (SAECG),

QRS fragmentation

Conduction defect and
depolarization abnormality

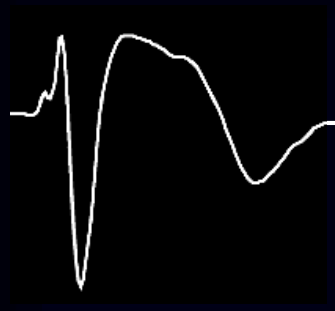
Repolarization
abnormality

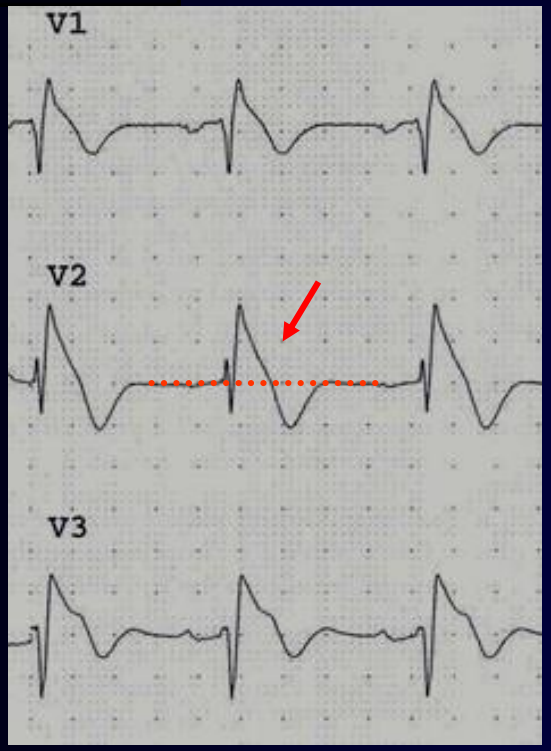
ST- segment elevation

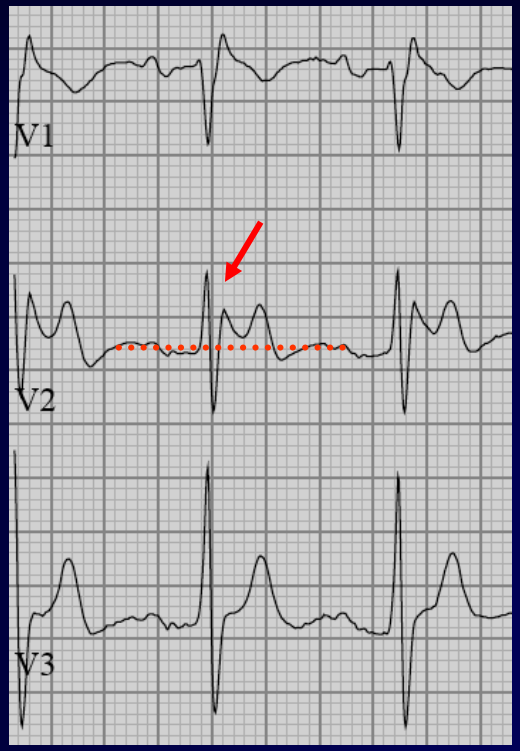
J wave accentuation

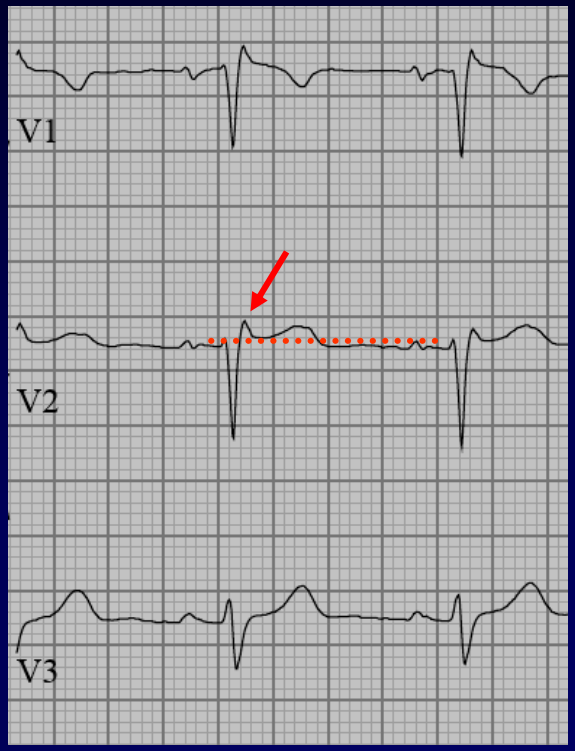
QT prolongation /
QT shortening.

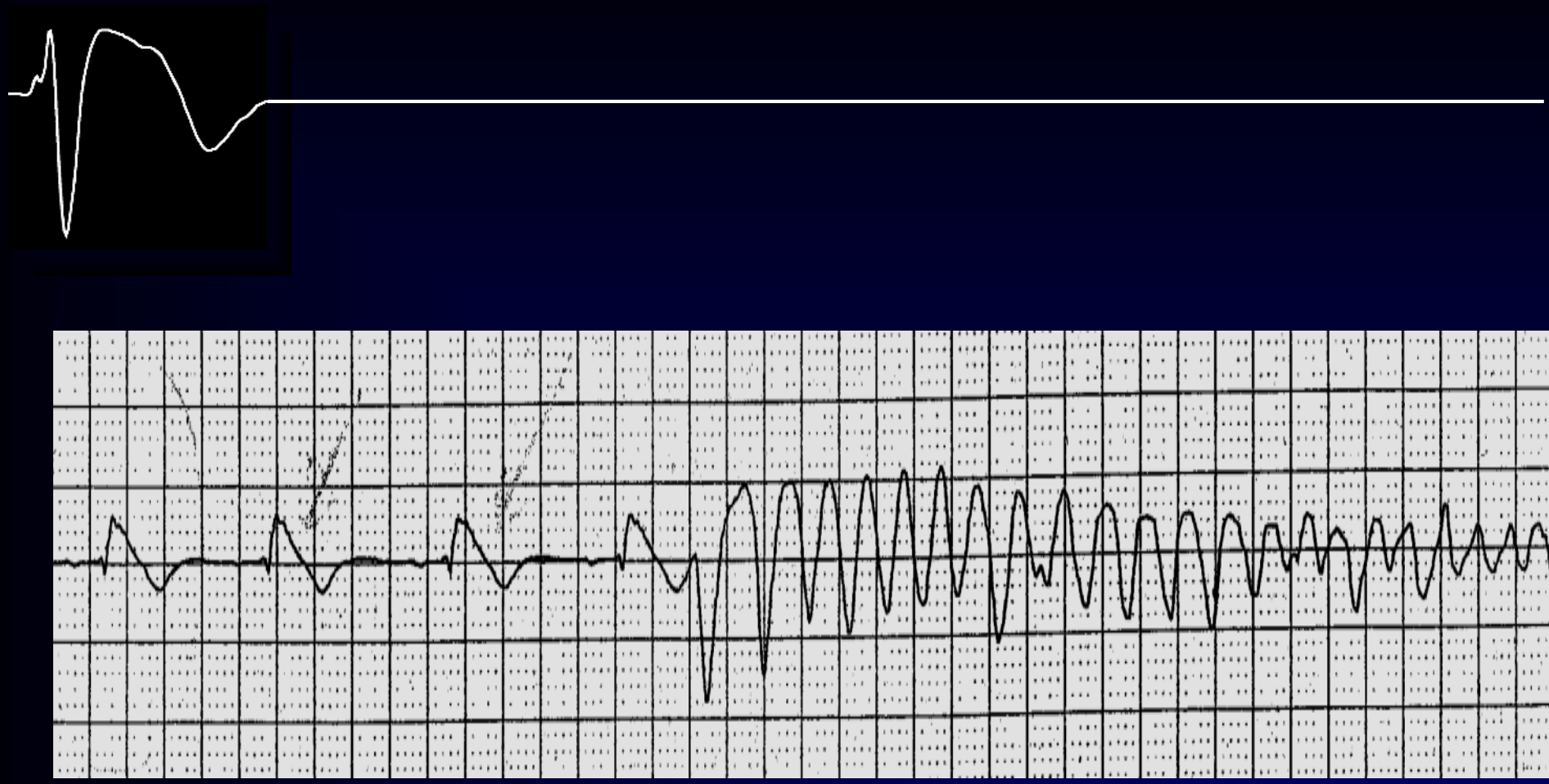
Ventricular arrhythmias




V1
V2
V3

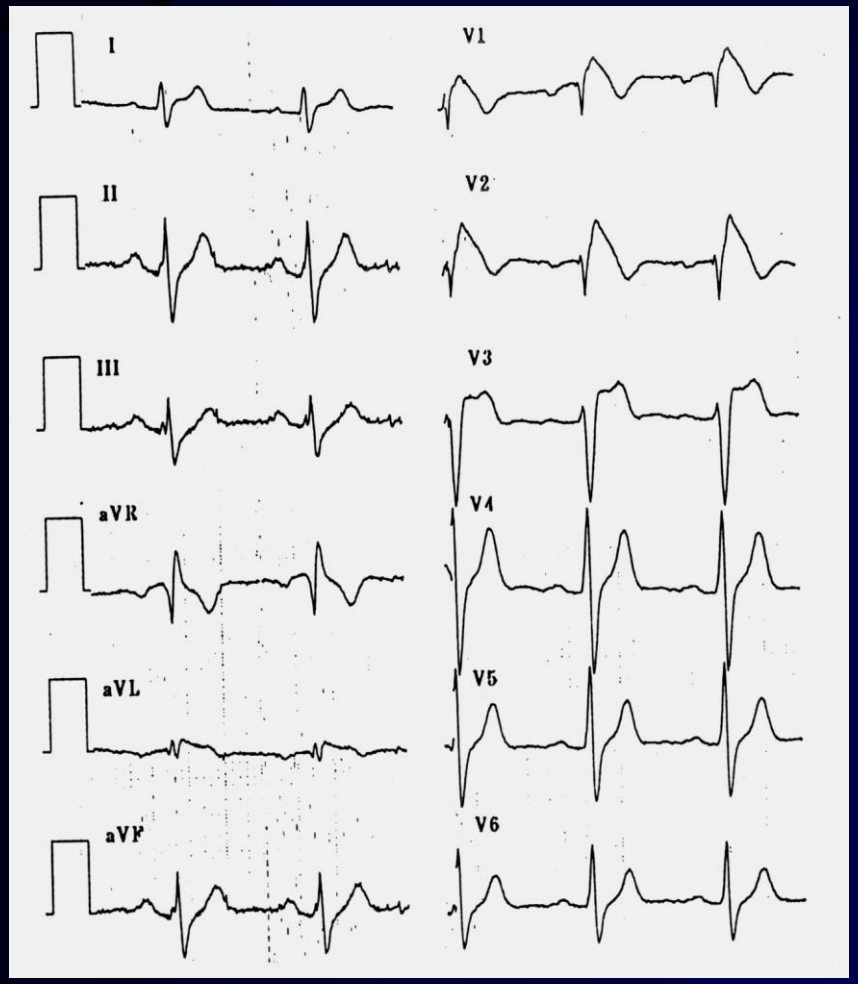

V1
V2
V3

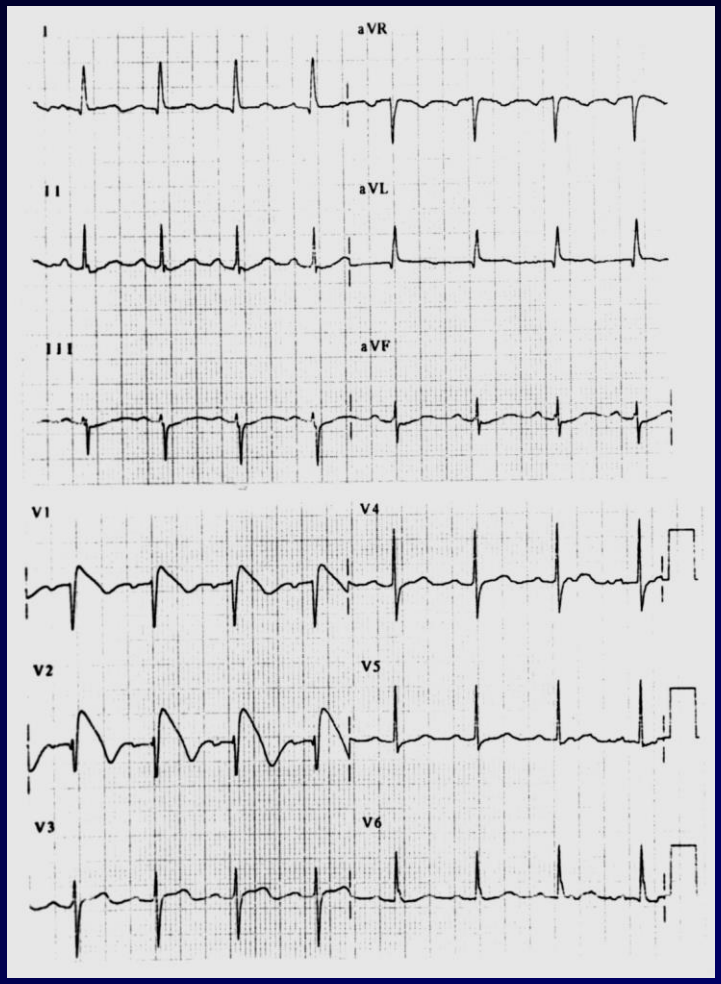

V1
V2
V3



→ **„Spontaneous coved ST-segment elevation is a marker of malignant ventricular arrhythmias and sudden cardiac death“**

→ **Right bundle-branch block**





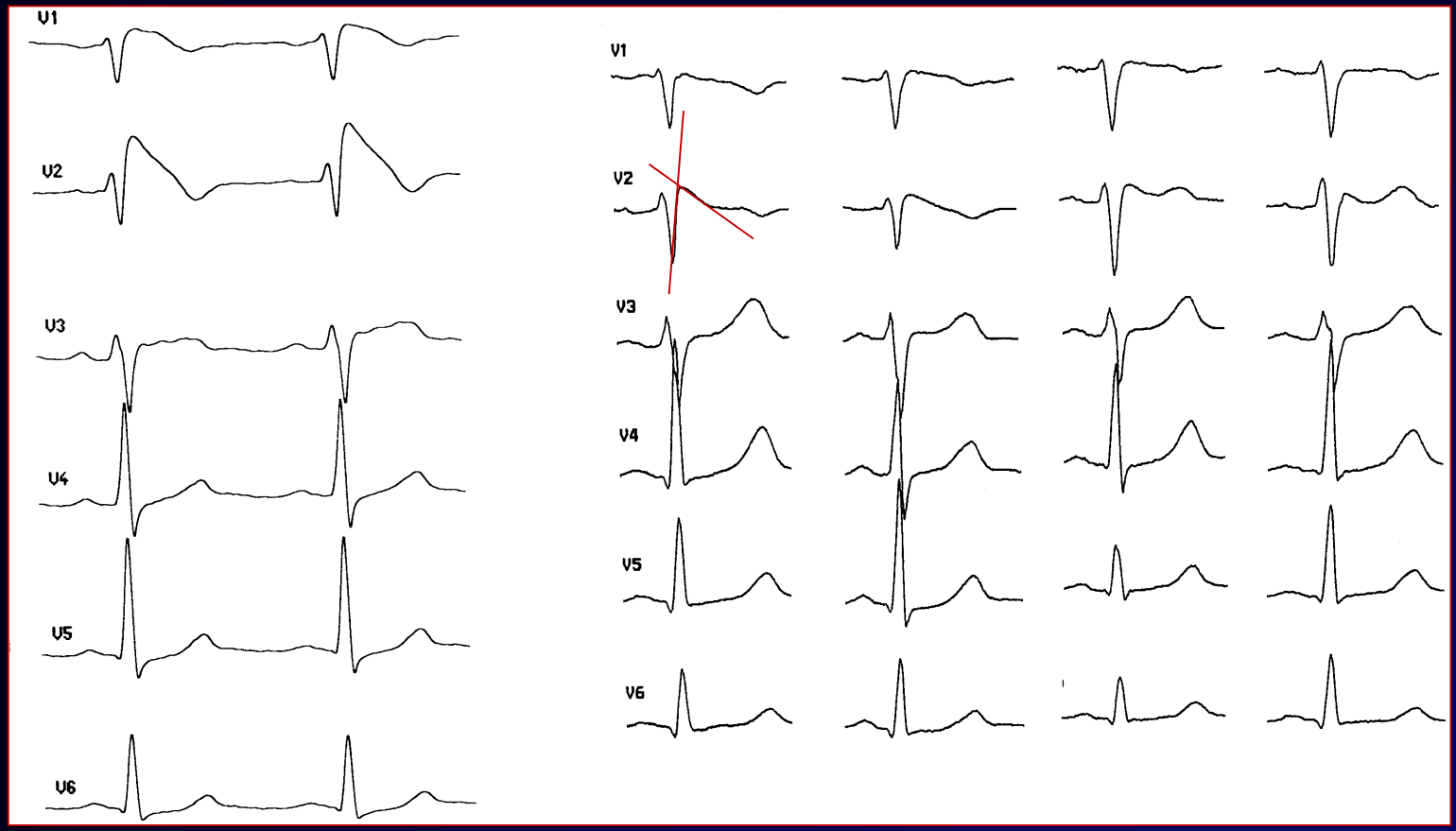
→ Persistent ST segment elevation:

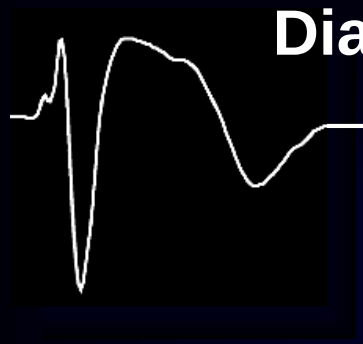
Variability of the diagnostic ECG pattern

- → Transient normalization and/or conversion to saddleback-type pattern occur in > 95% of the patients during long-term follow-up
- → 35% of patients diagnosed with Brugada syndrome do not reveal a spontaneous coved-type ECG during 4-years follow-up
- → Only every 4th ECG is spontaneously diagnostic and every 2nd ECG does not display any Brugada-type ST elevation

Eur Heart J 2006;27:593

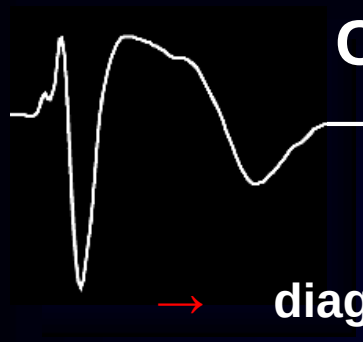
Feb5 Feb7 Feb13





Diagnostic tools to unmask a type I ECG pattern

- → Administration of a class I sodium channel blocker
- → Superior placement of the right precordial leads
- → ECG monitoring during recovery phase of exercise



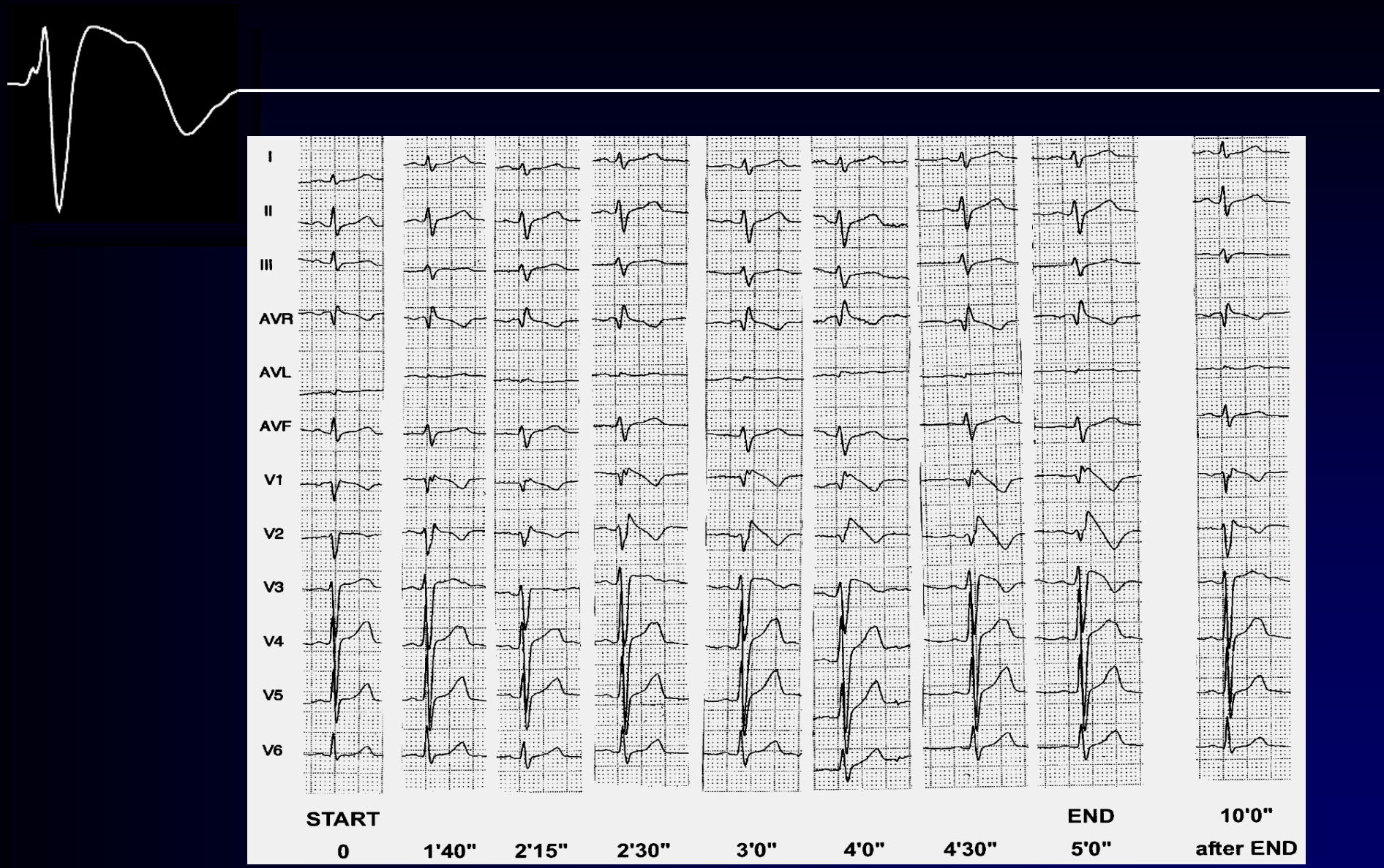
Class I drugs to unmask Brugada syndrome

→ diagnosis of individuals with normalized or non-diagnostic ECG

→ identification of family members at risk for the diseas

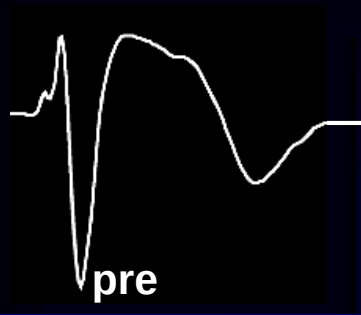
→ diagnosis in suspected BrS (syncope, atrial fibrillation)

Class I drug	Dosage
Ajmaline	1 mg/kg over 5 min, IV
Flecainide	2 mg/kg over 10 min, IV
Procainamide	10 mg/kg over 10 min, IV
Pilsicainide	1 mg/kg over 10 min, IV


I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
START
0
1'40"
2'15"
2'30"
3'0"
4'0"
4'30"
END
5'0"
10'0"
after END

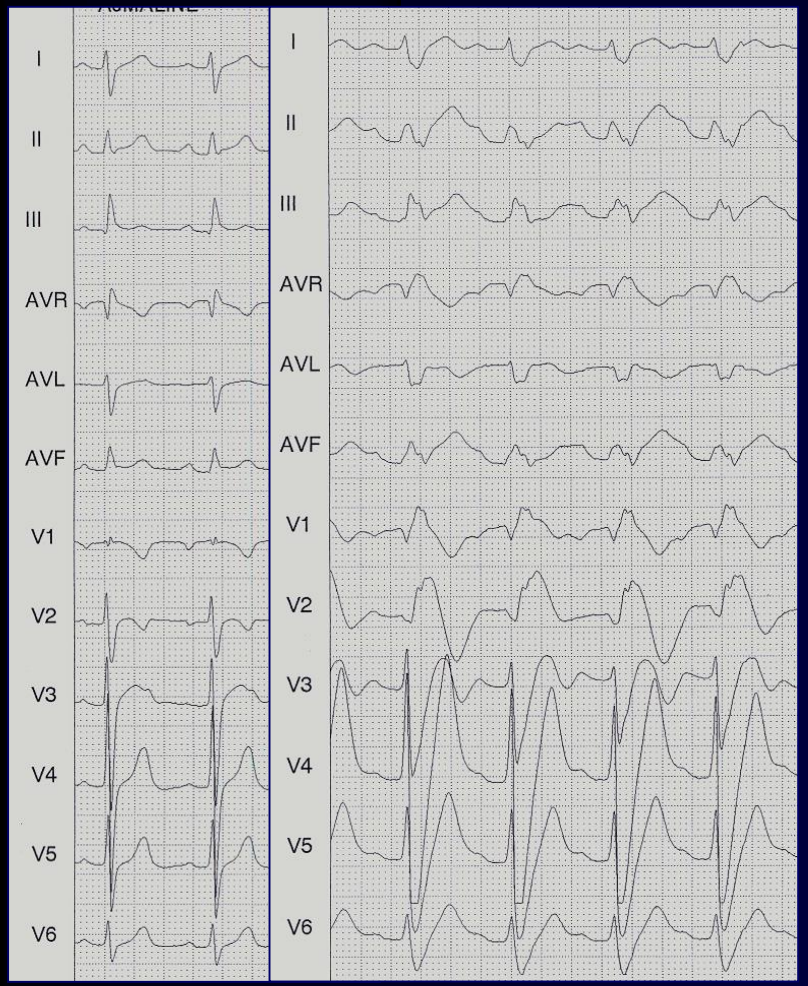
ajmaline IV

Ajmaline test in children



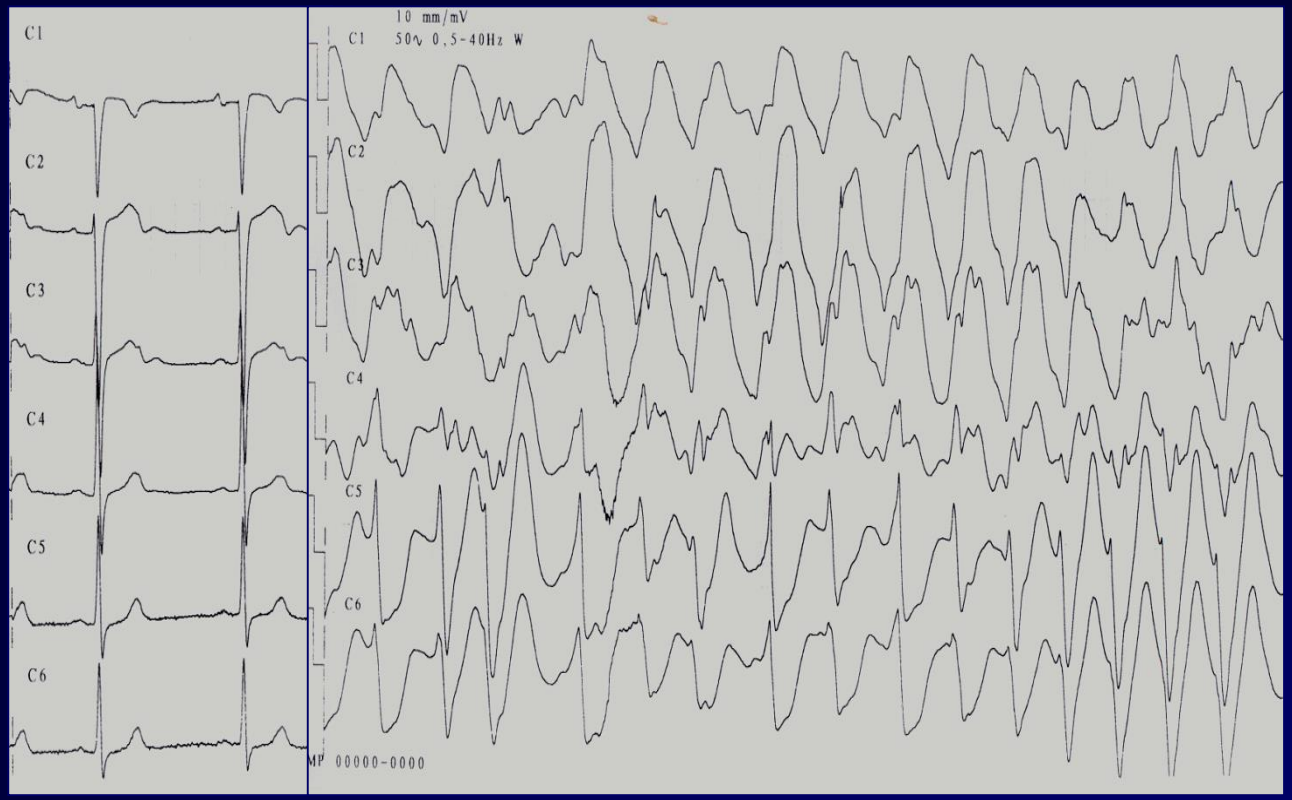
pre

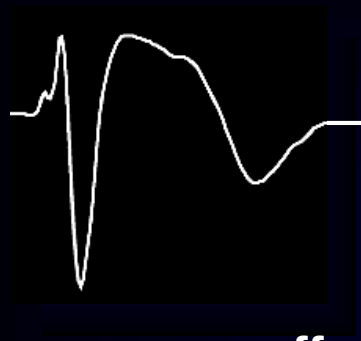
post



pre

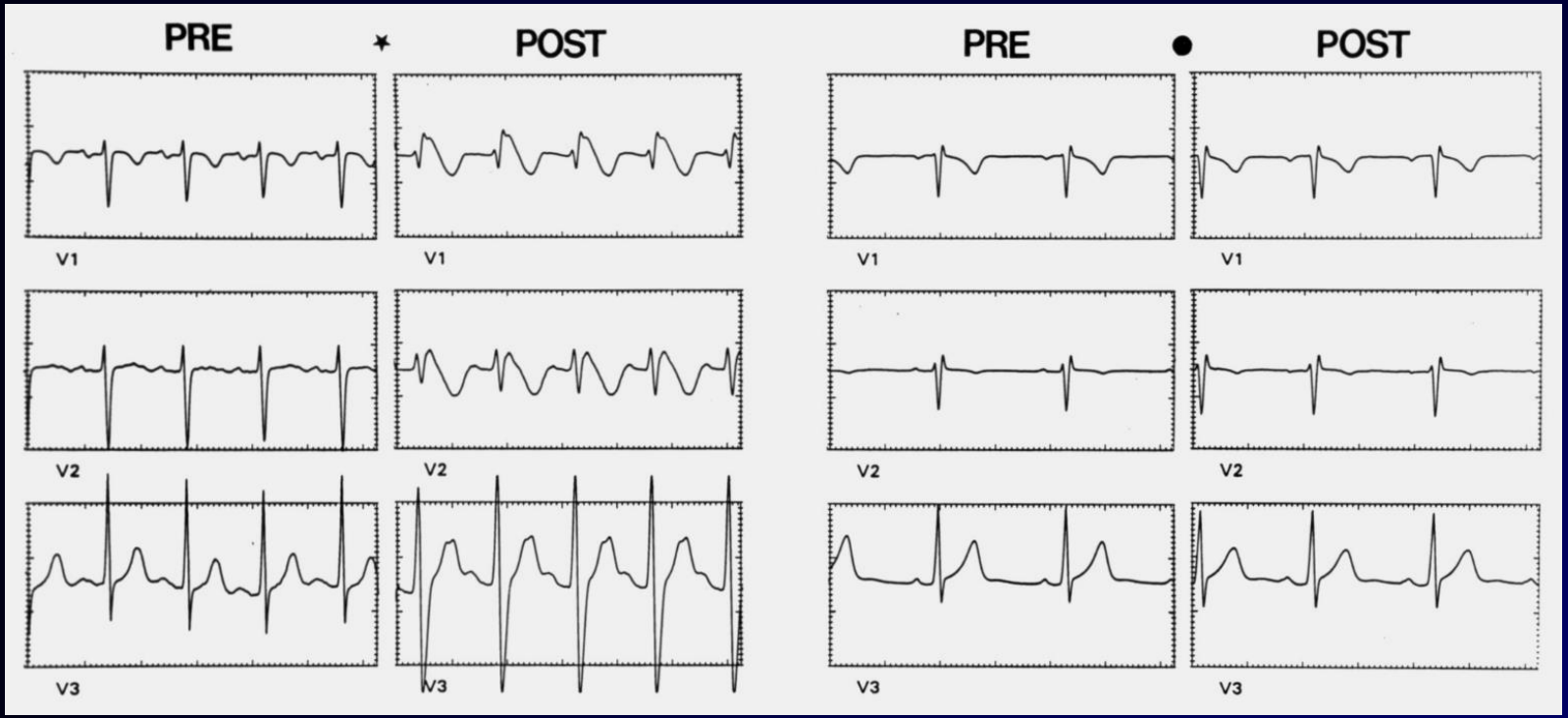
post





affected family member

non-affected family member



Sens 95.2%

Spec 94.4%

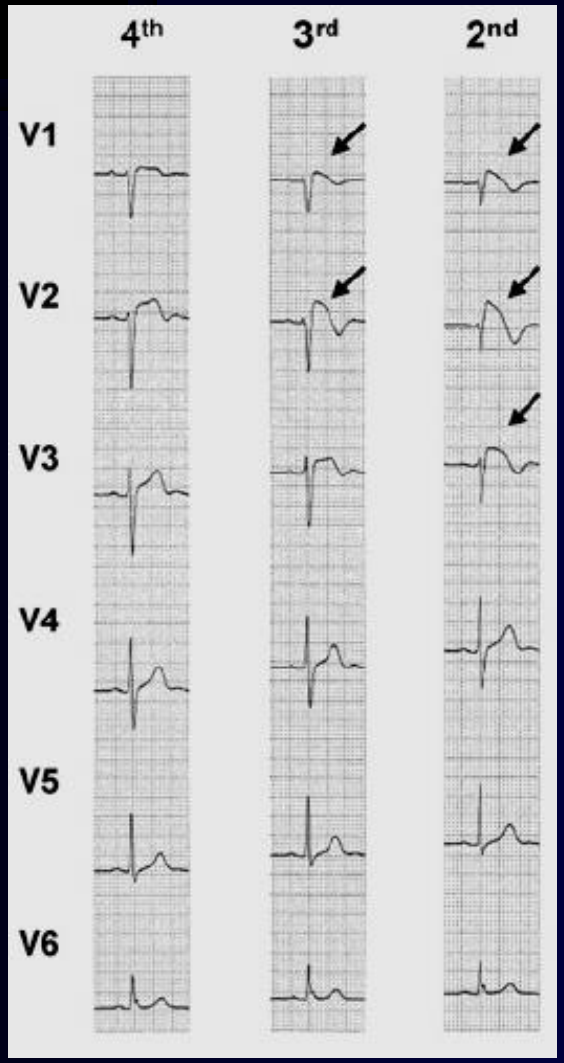
PPV 93.3%

NPV 94.9%

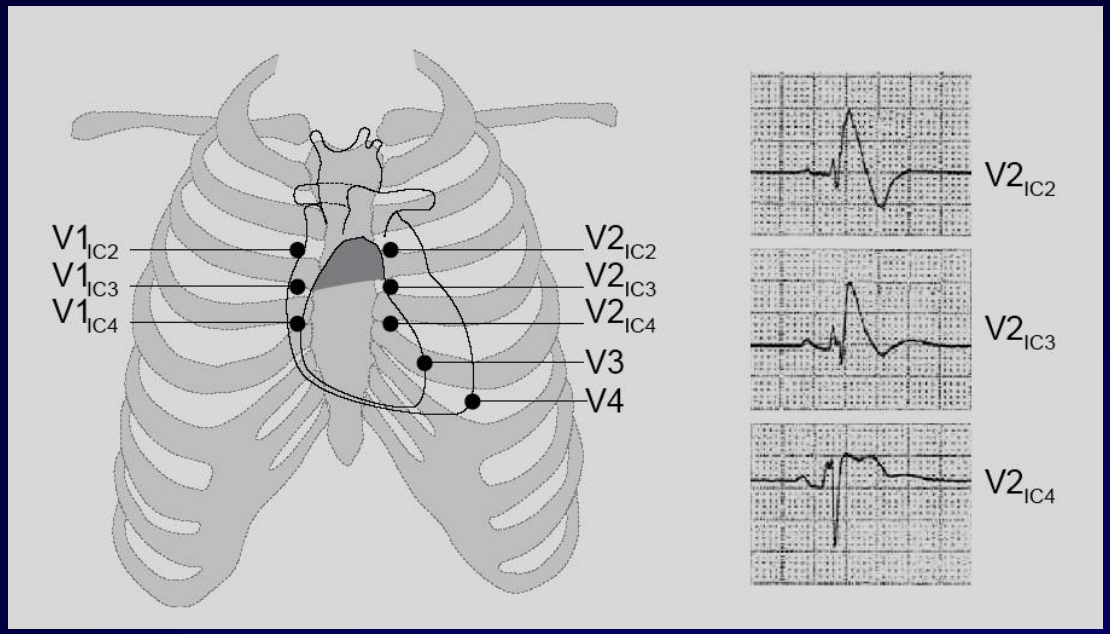
SCN5A*mt*

SCN5A*wt*

Higher right precordial leads.

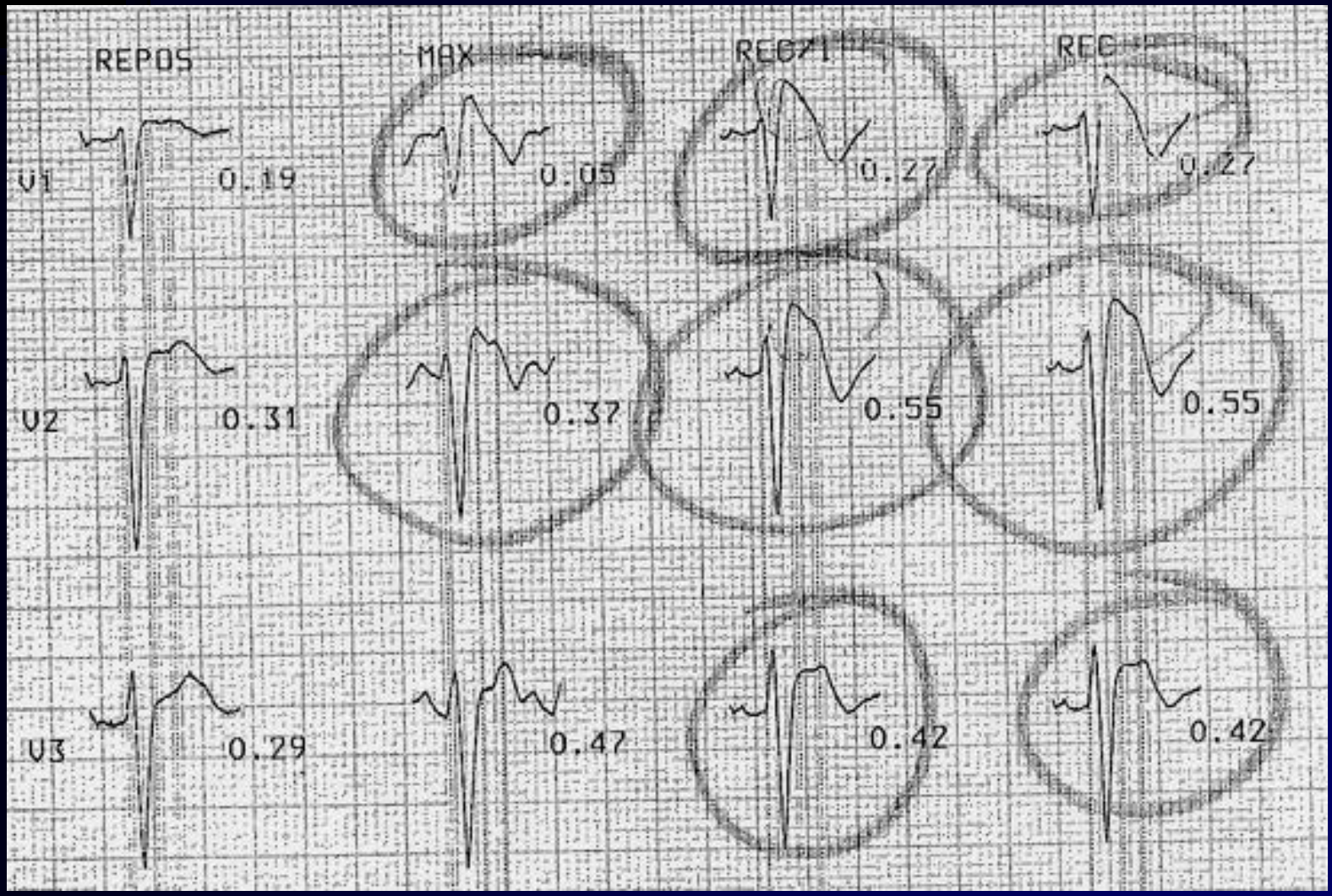


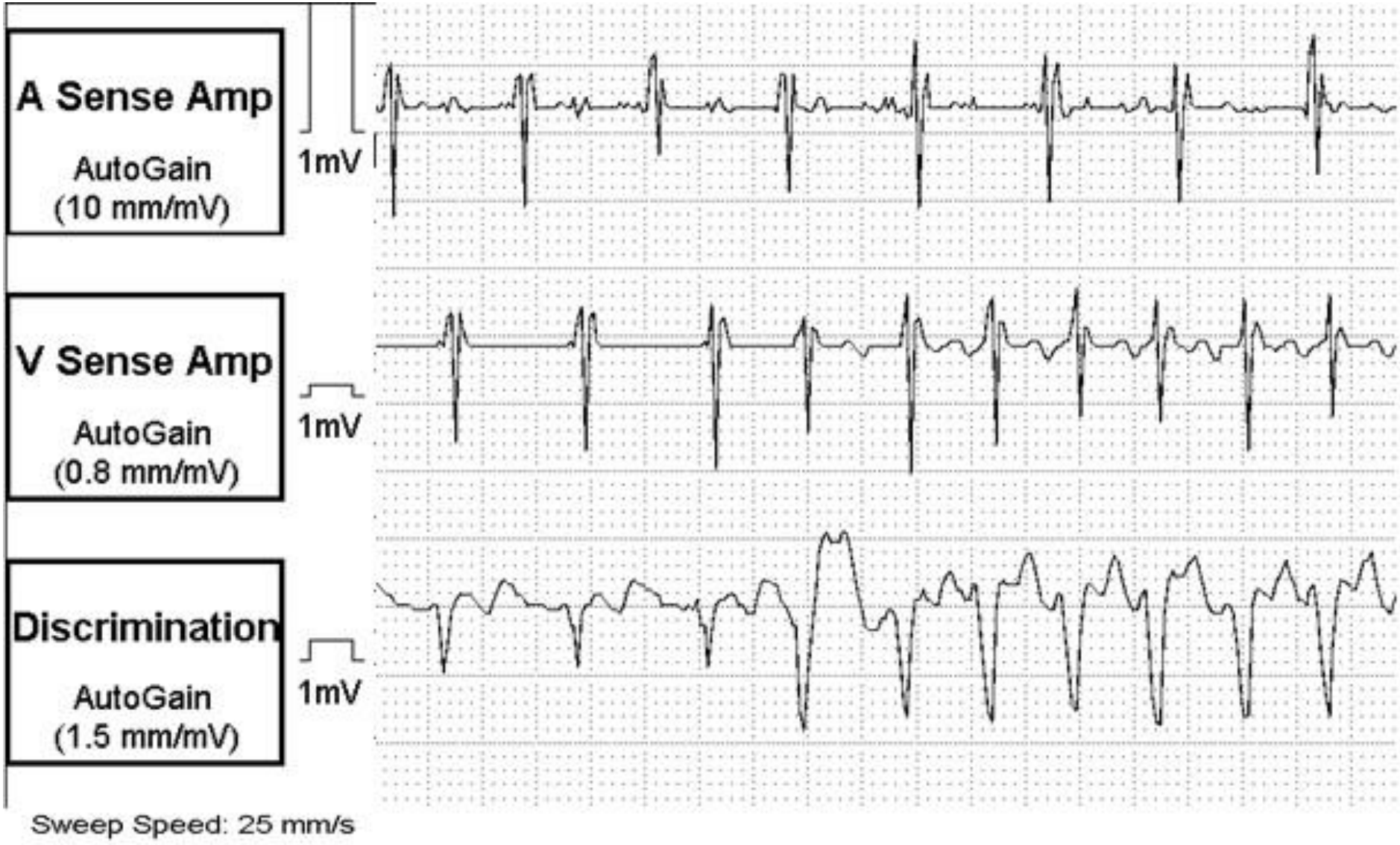
Am J Cardiol 2007;99:53



Cardiovasc Res 2005;67:367

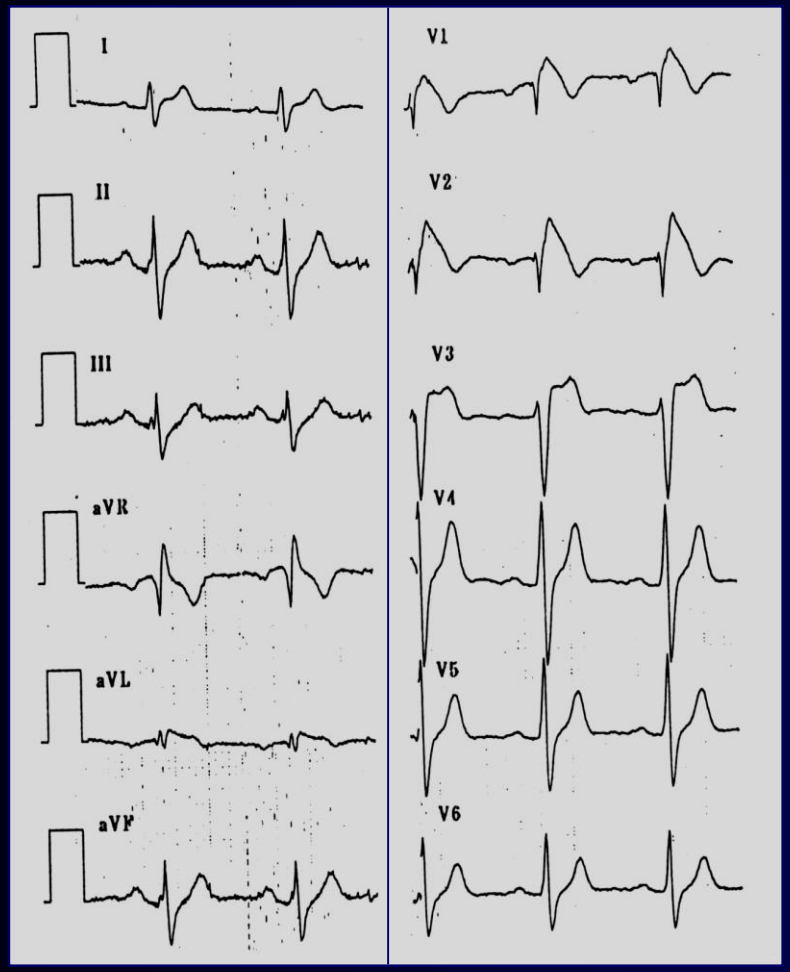
Exercise test

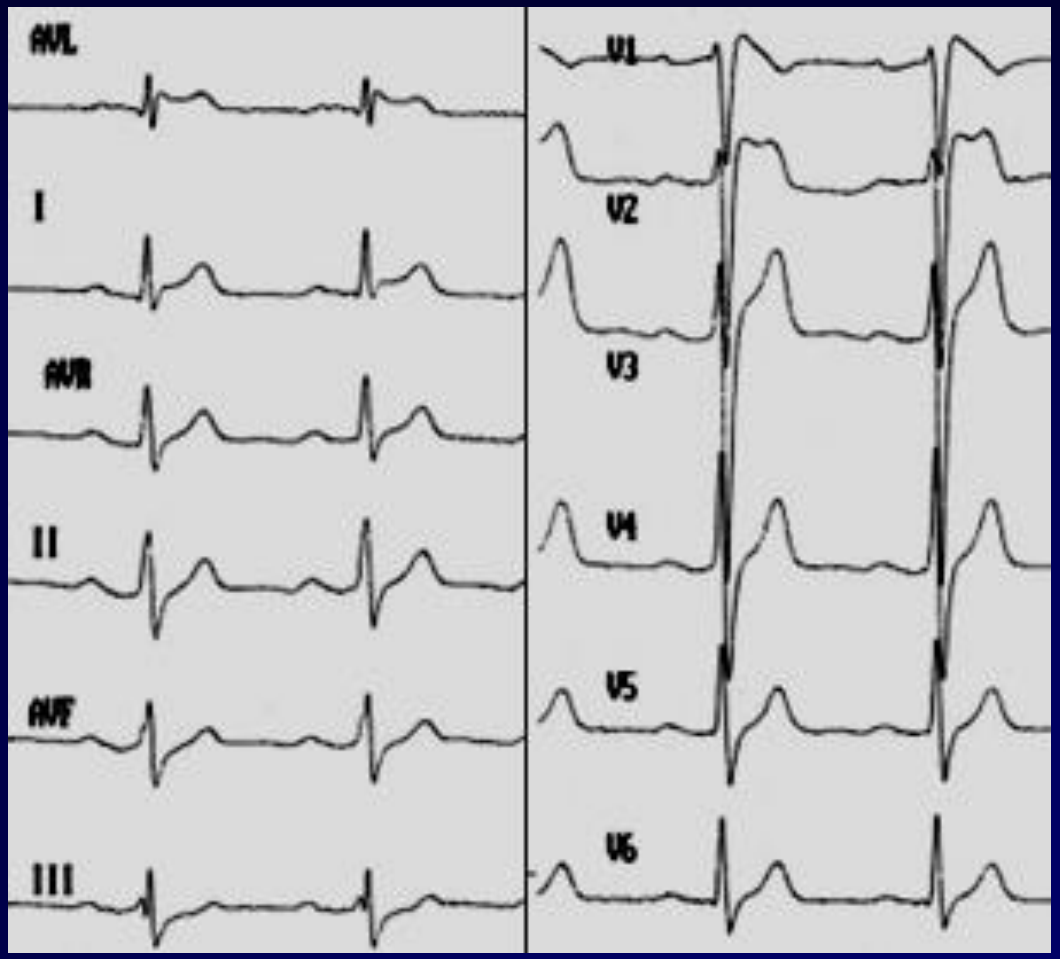



A Sense Amp
AutoGain
(10 mm/mV)
1mV
V Sense Amp
AutoGain
(0.8 mm/mV)
1mV
Discrimination
AutoGain
(1.5 mm/mV)
1mV
Sweep Speed: 25 mm/s

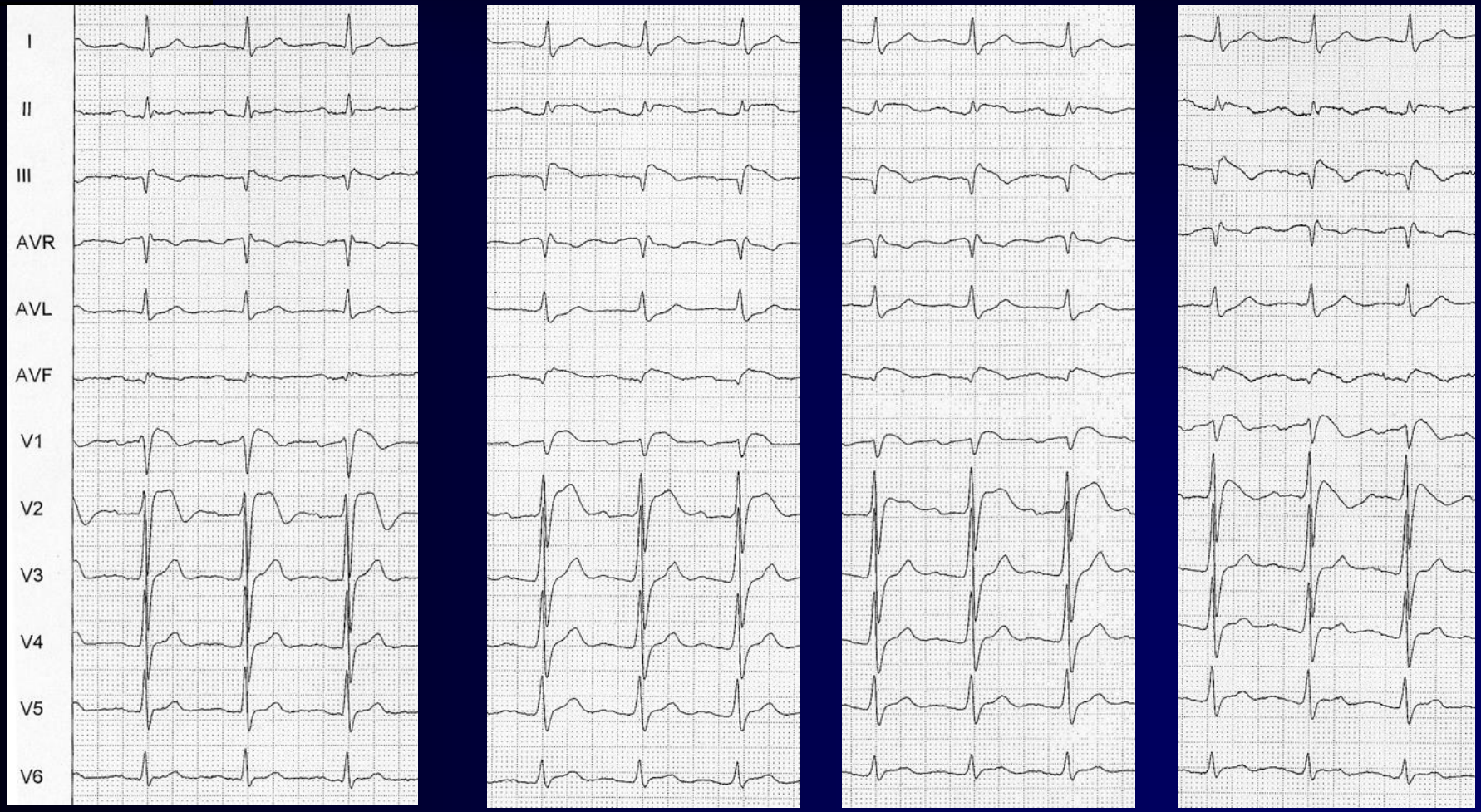
→ ST elevation not only in right precordial leads

ST-segment elevation in lead aVL

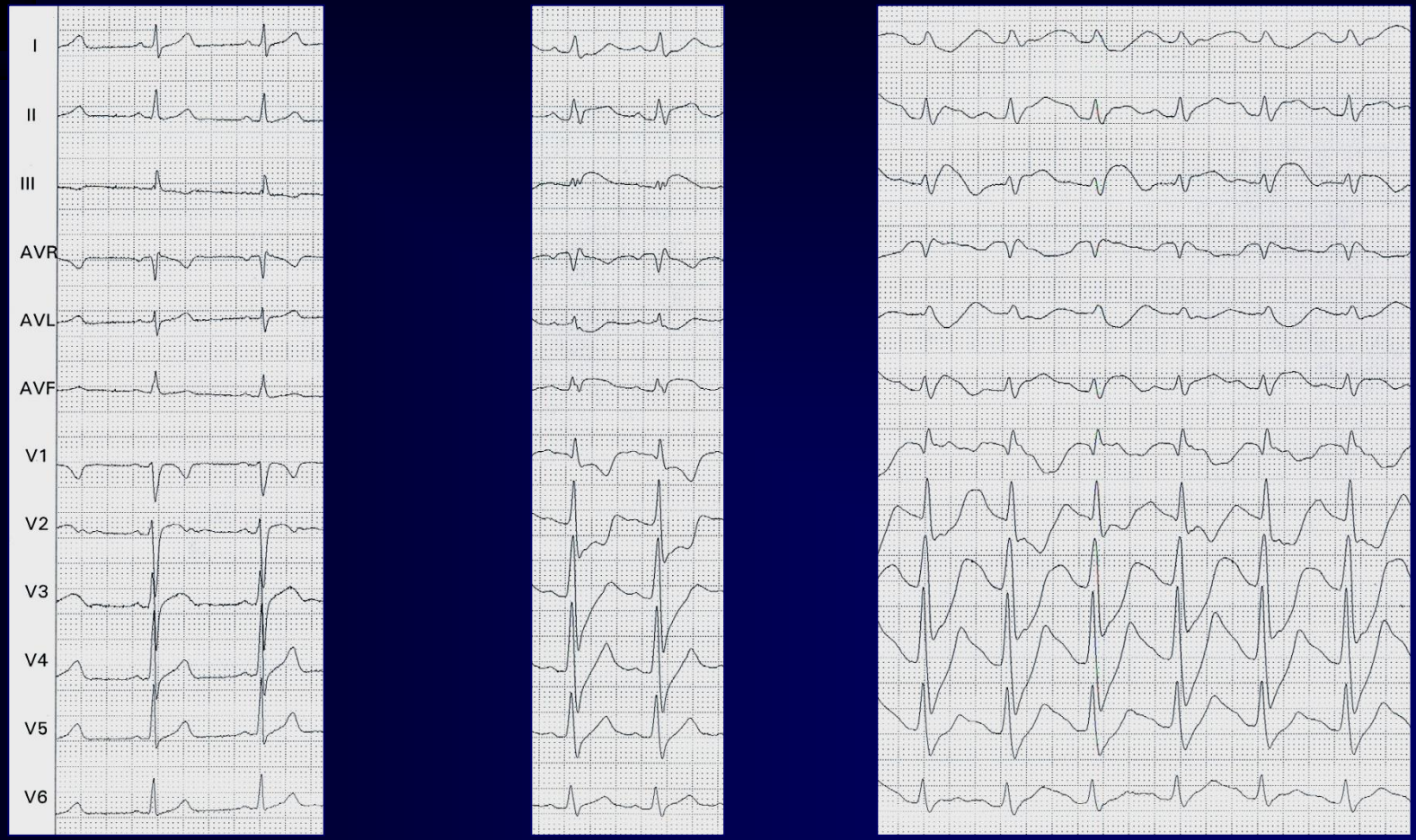




ST elevation in the inferior leads: Ajmaline IV

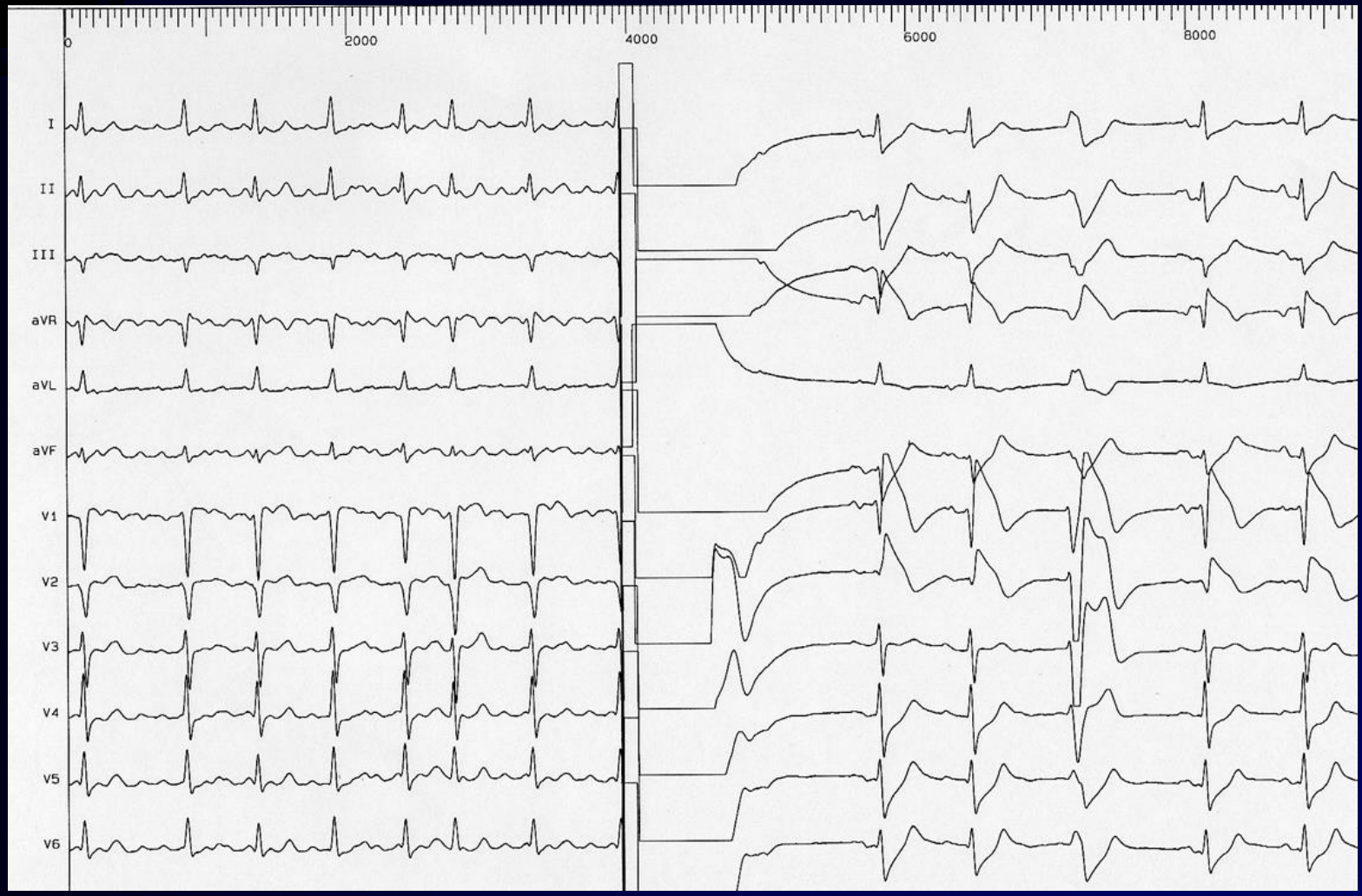


ST depression in the precordial leads and elevation in the inferior leads



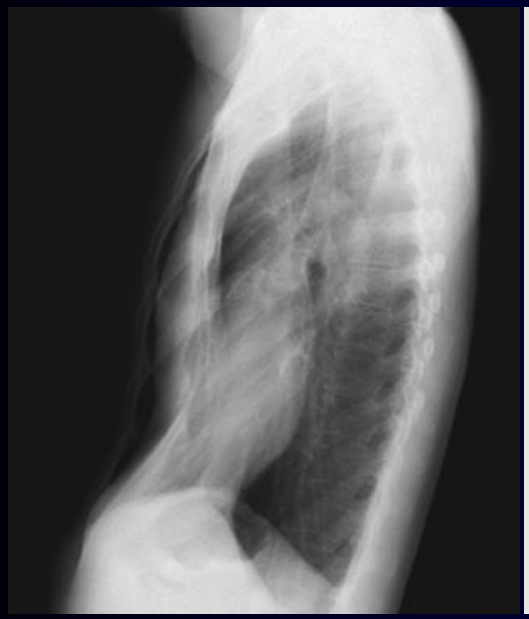
after ajmaline IV

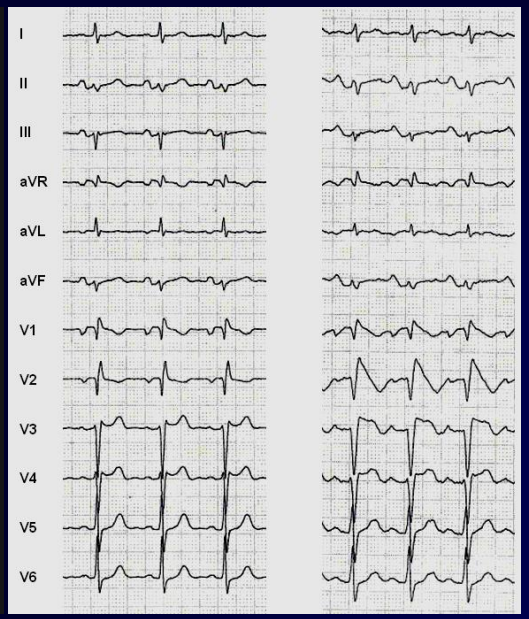
Unmasking Brugada syndrome with electrical cardioversion?



Phenocopies

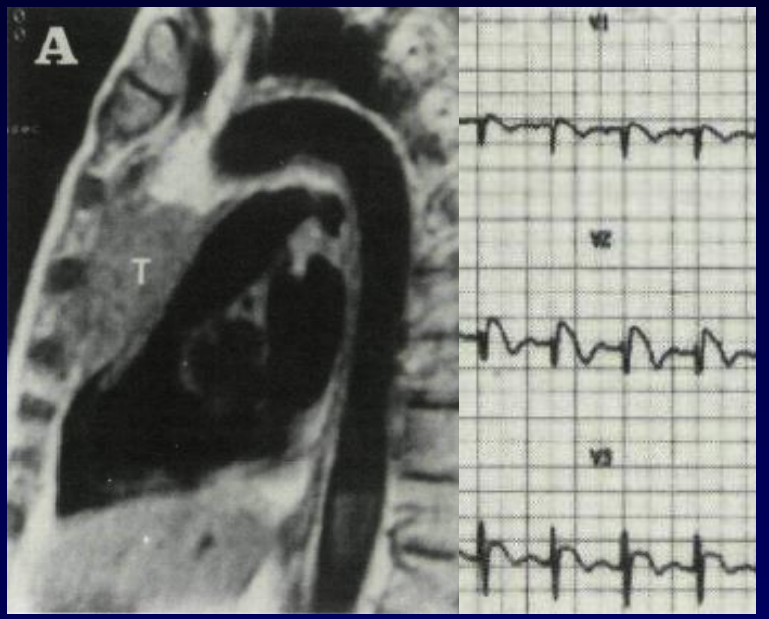
Pectus excavatum



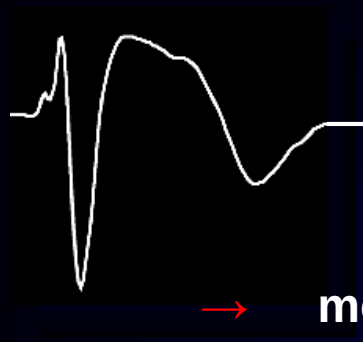


baseline ajmaline

Mediastinal tumor



PACE 1999;22:1264

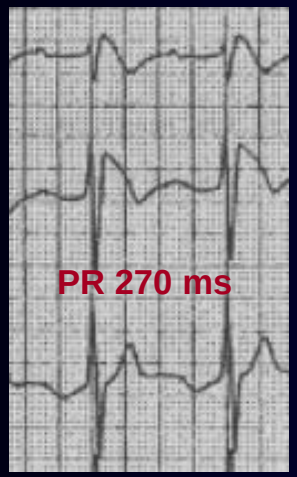


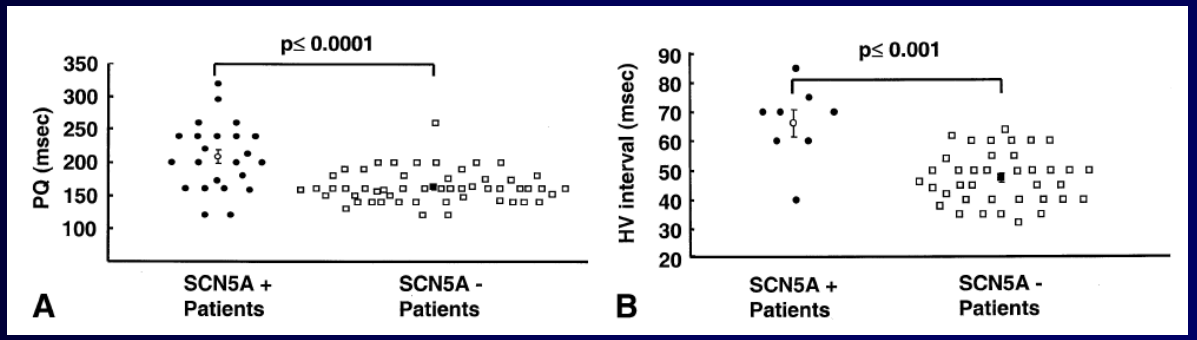
Conduction abnormalities

Asystole as cause of sudden death in BrS

→ most frequently observed in patients linked to SCN5A mutations

✓ atrial standstill	→	SA block III°
✓ sinoatrial conduction time ↑	→	SA block II°, cSNRT ↑
✓ slowed atrial conduction	→	P-wave duration ↑, PR ↑
✓ infrahisian conduction delay	→	PR ↑, QRS duration ↑, RBBB, LFHB





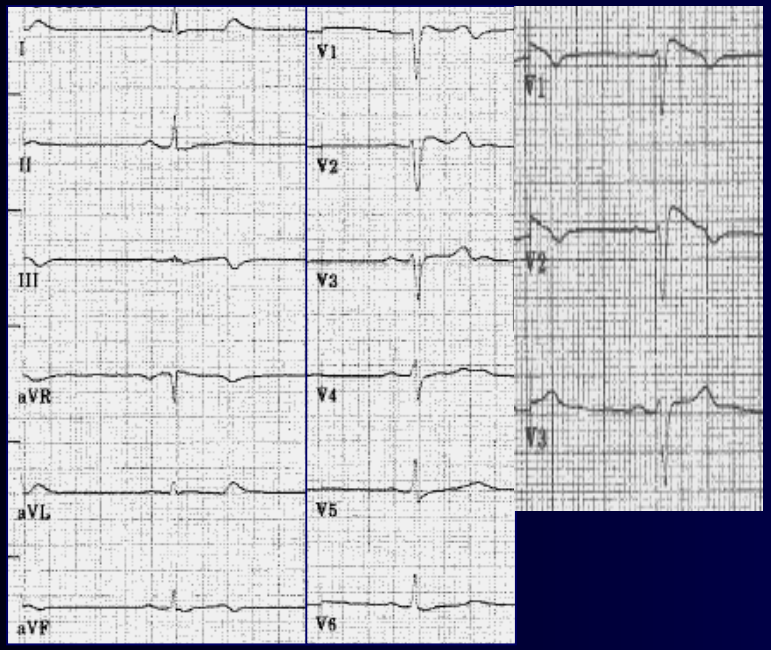
PQ 209±51 PQ 163±24 HV 66±13 HV 48±9

J Am Coll Cardiol 2002;40:350

Overlap syndromes

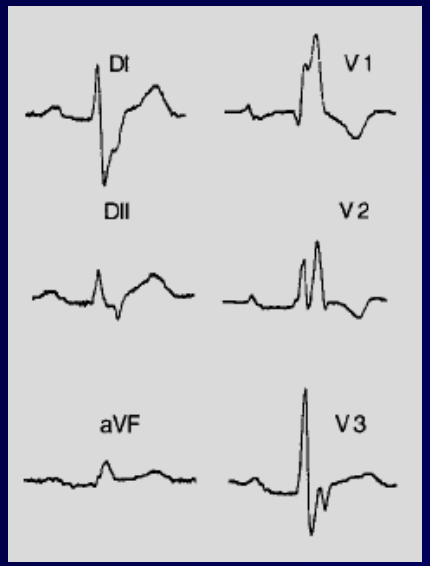
Brugada syndrome and

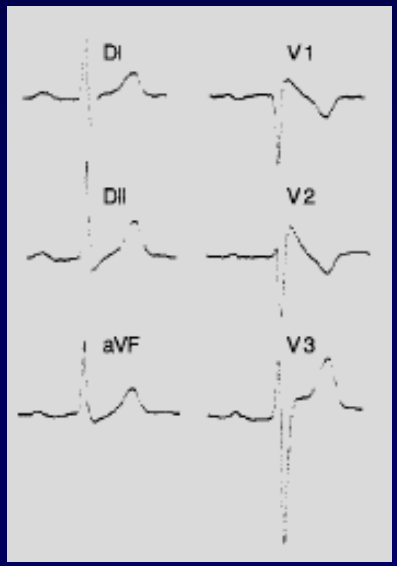
Long-QT 3



Circ Res 1999;85:1206

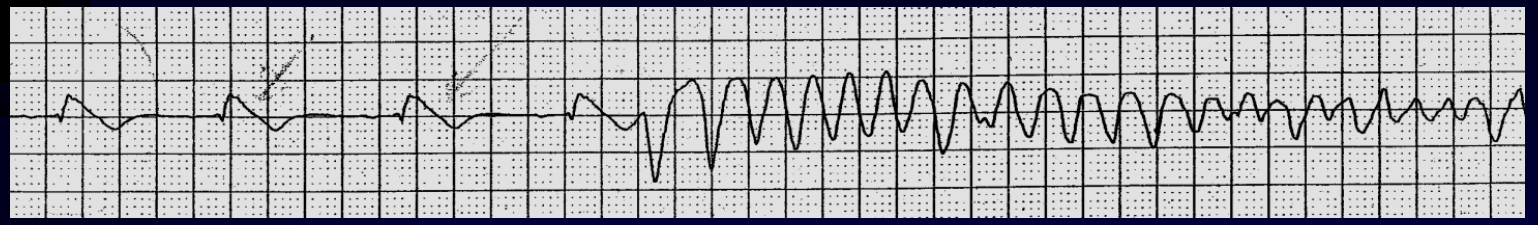
Familial conduction disease (Lev-Lenègre disease)

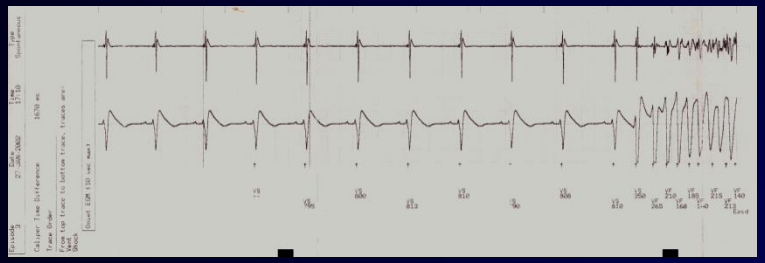


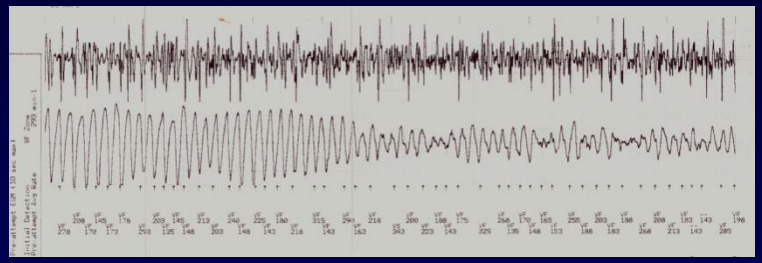


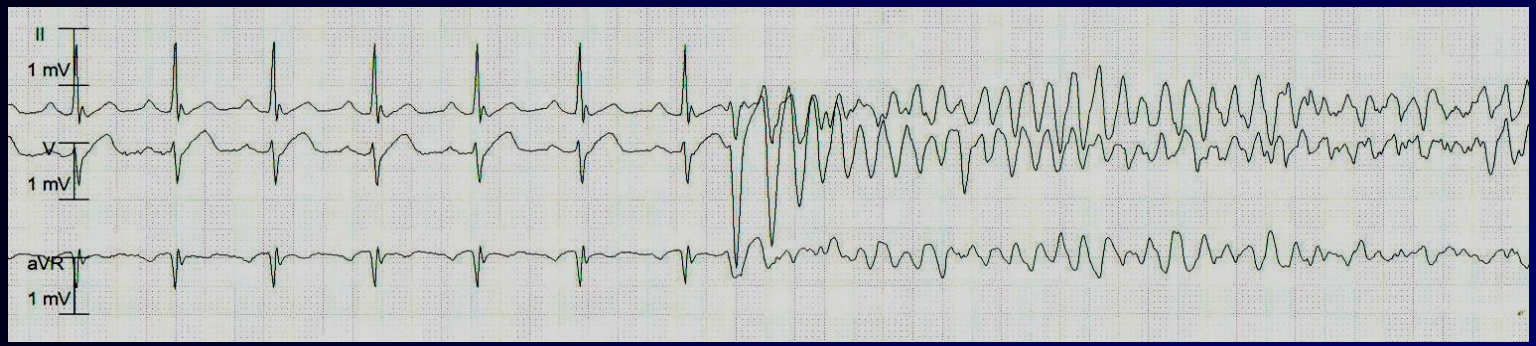
Circulation 2001;104:3081

Polymorphic ventricular tachycardia and VF

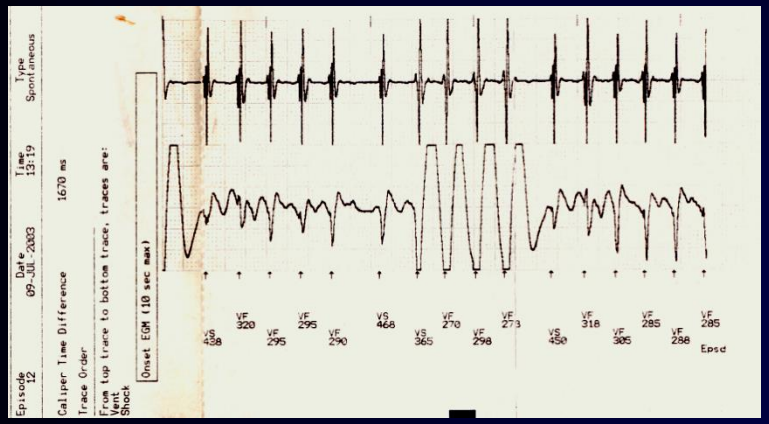


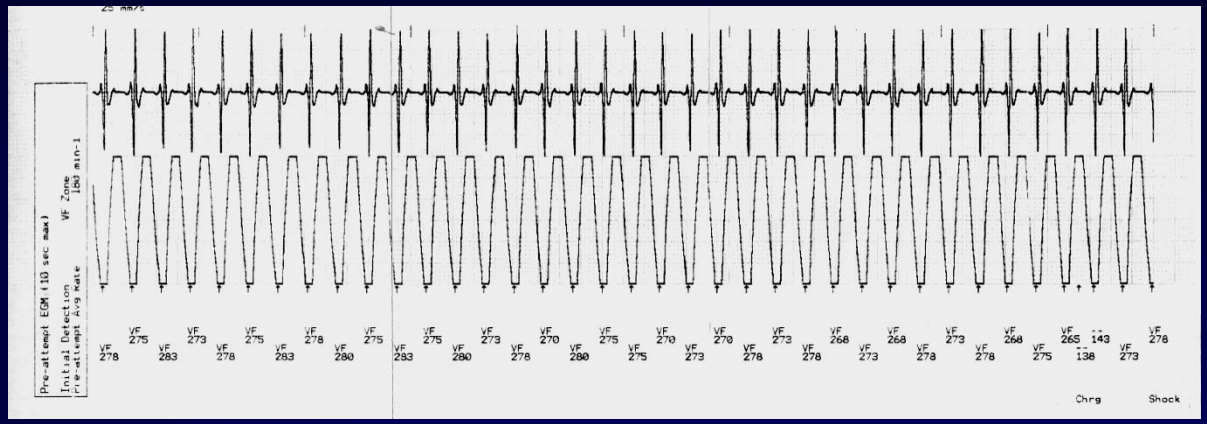


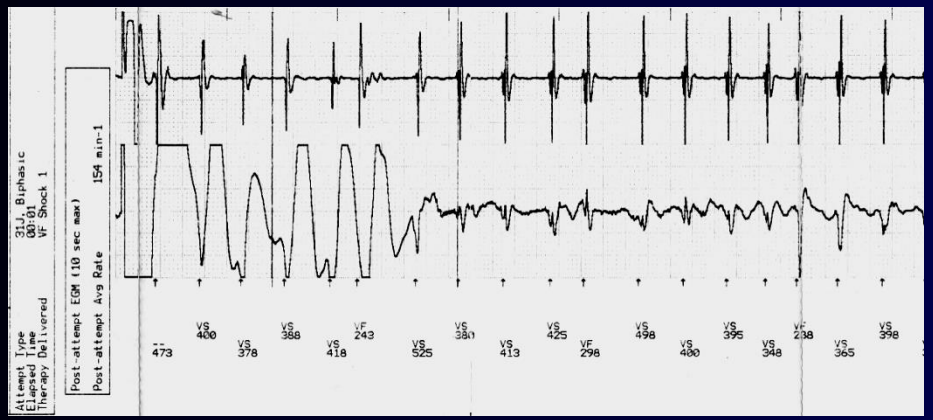




Monomorphic ventricular tachycardia

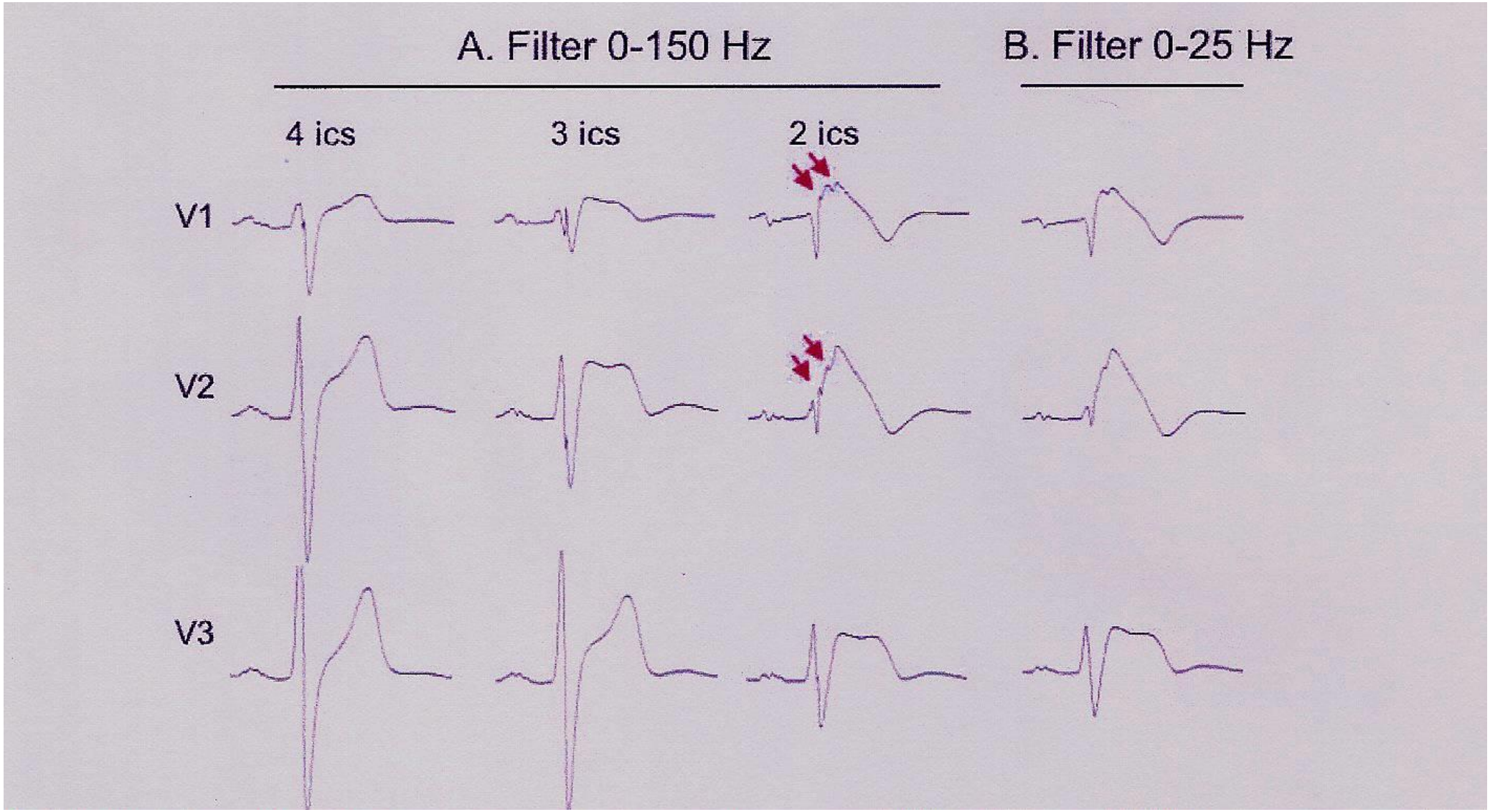


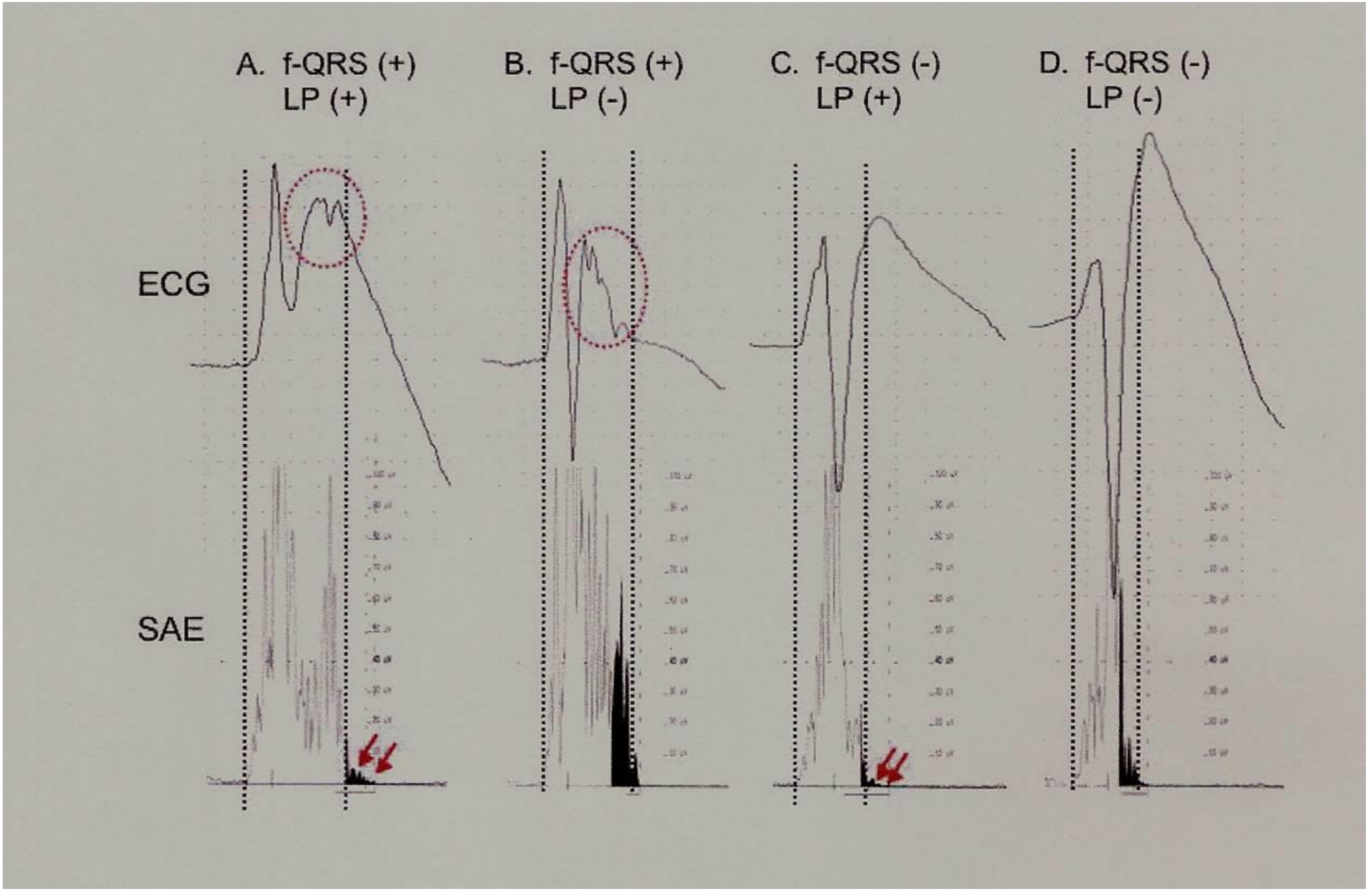


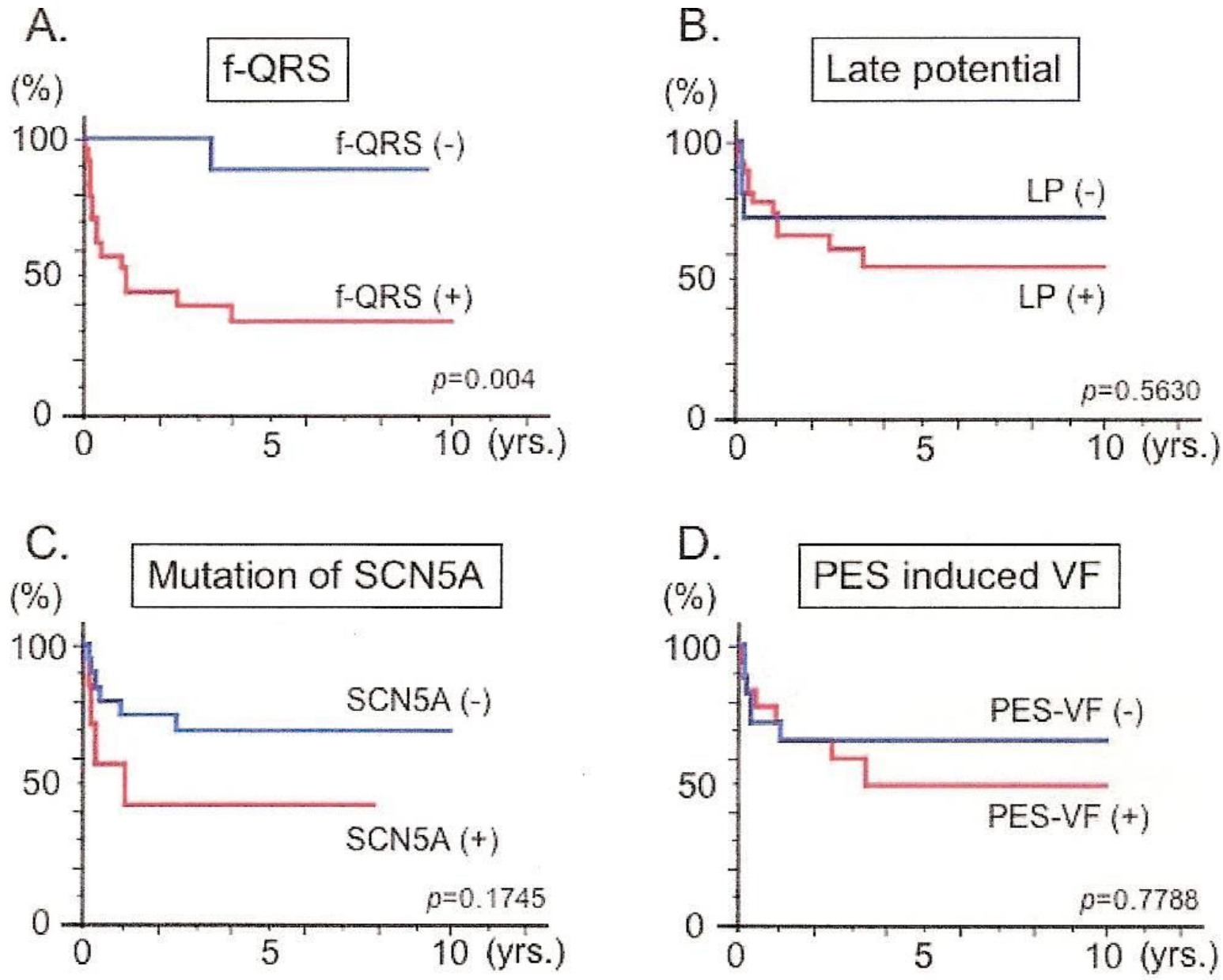


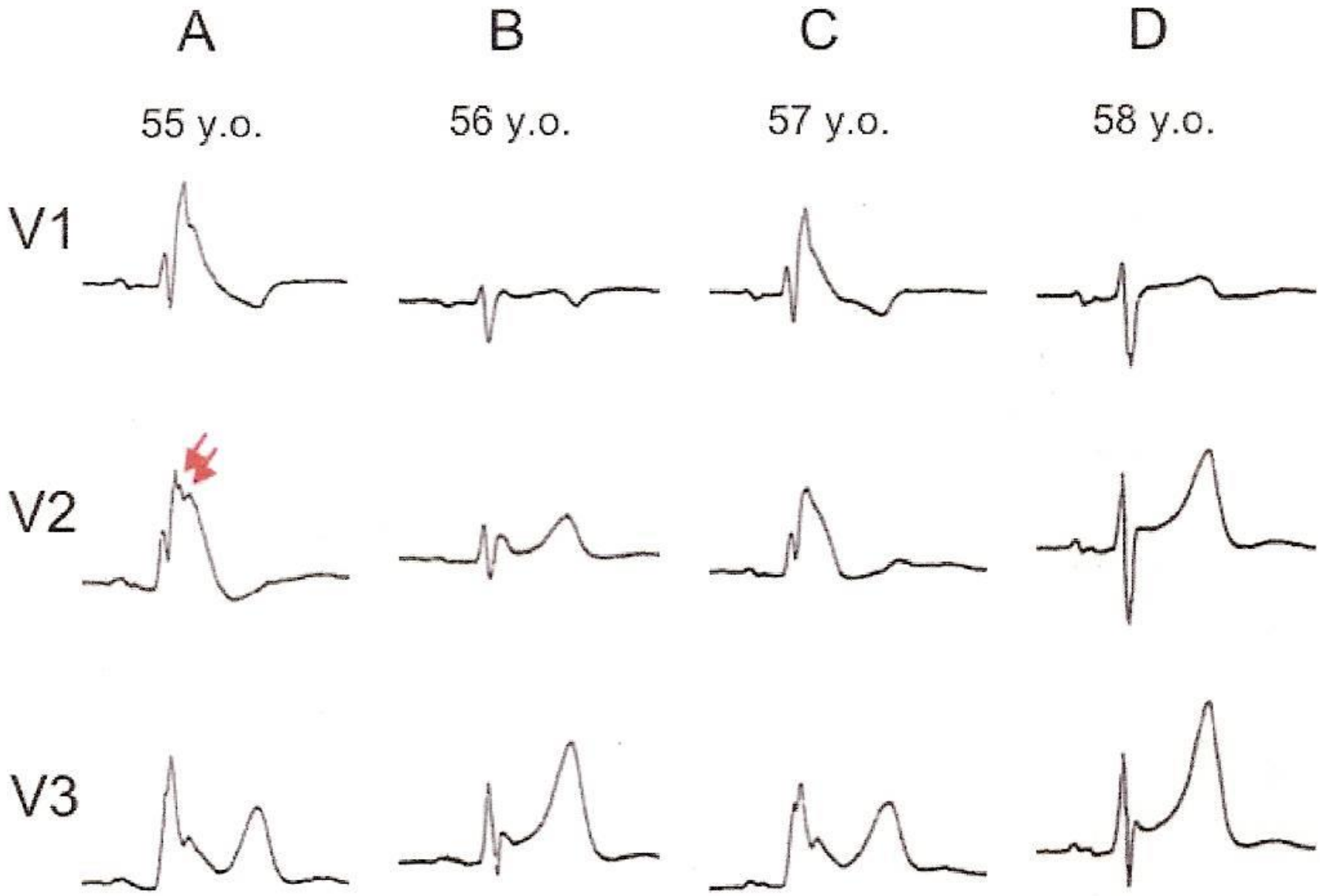
→ **Also in Brugada syndrome:**

4% of all ventricular arrhythmias.


A. Filter 0-150 Hz
B. Filter 0-25 Hz
4 ics
3 ics
2 ics
V1
V2
V3


A. f-QRS (+)
LP (+)
B. f-QRS (+)
LP (-)
C. f-QRS (-)
LP (+)
D. f-QRS (-)
LP (-)
ECG
SAE


A.
f-QRS
(%)
100
50
0
f-QRS (-)
f-QRS (+)
p=0.004
0
5
10 (yrs.)
B.
Late potential
(%)
100
50
0
LP (-)
LP (+)
p=0.5630
0
5
10 (yrs.)
C.
Mutation of SCN5A
(%)
100
50
0
SCN5A (-)
SCN5A (+)
p=0.1745
0
5
10 (yrs.)
D.
PES induced VF
(%)
100
50
0
PES-VF (-)
PES-VF (+)
p=0.7788
0
5
10 (yrs.)


A
B
C
D
55 y.o.
56 y.o.
57 y.o.
58 y.o.
V1
V2
V3

Management of patients with Brugada syndrome

Coved-type I ECG
spontaneously or after class I AAD

aborted SCD or syncope

ICD

asymptomatic

spontaneous coved-type ECG

+

EP study

+

ICD

-

Follow-up

-

Follow-up

Programmed ventricular stimulation in BS without previous cardiac arrest.

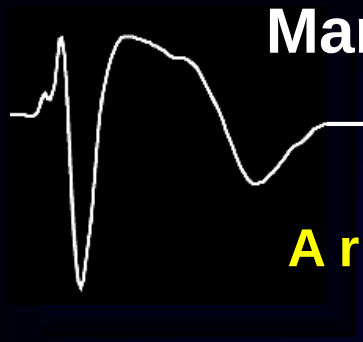
	Brugada (Circ 2003) 547	**Pooled (Circ 2016) 1247**
SYNCOPE	124 (23%)	429 (34%)
ASYMPTOMATIC	423 (77%)	883 (66%)
SPONTANEOUS TYPE I	391 (71%)	696 (56%)
DRUG-INDUCED TYPE I	156 (29%)	616 (44%)
INDUCIBLE	163 (30%)	527 (42%)
NON-INDUCIBLE	245 (70%)	720 (58%)

All differences $p < 0,001$

Programmed ventricular stimulation in BS without previous cardiac arrest.

THREE YEAR % RISK OF EVENTS

	Non-inducible		**Inducible**	
SPONTANEOUS TYPE I	BRUGADA	POOLED	BRUGADA	POOLED
SYNCOPE	4	8	27	13
ASYMPTOMATIC	2	3	14	3
DRUG-INDUCED TYPE I	BRUGADA	POOLED	BRUGADA	POOLED
SYNCOPE	1	1	10	2
ASYMPTOMATIC	0,5	0,3	4	2



Management of patients with Brugada syndrome

A risk score to predict events during long-term followup.

→ 400 patients with mean fup of 80 months (12- 324).

41± 18 years, 58% male, spontaneous type I ECG 20%.

Syncope 28%, SCD 5%, asymptomatic 67%.

Family Hx SCD 46%, with 8% family Hx of SCD <35 years.

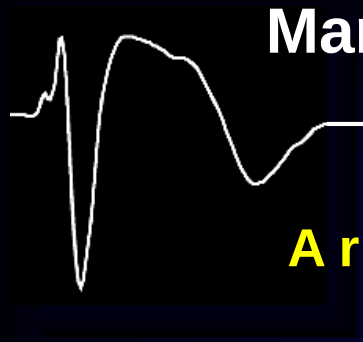
Atrial fibrillation 8,5%, SND 2%.

Inducible during EPS 20%

ICD implantation 44%.

Global event rate 1,7% year.

Sieira J, Brugada P. et al. In press



Management of patients with Brugada syndrome

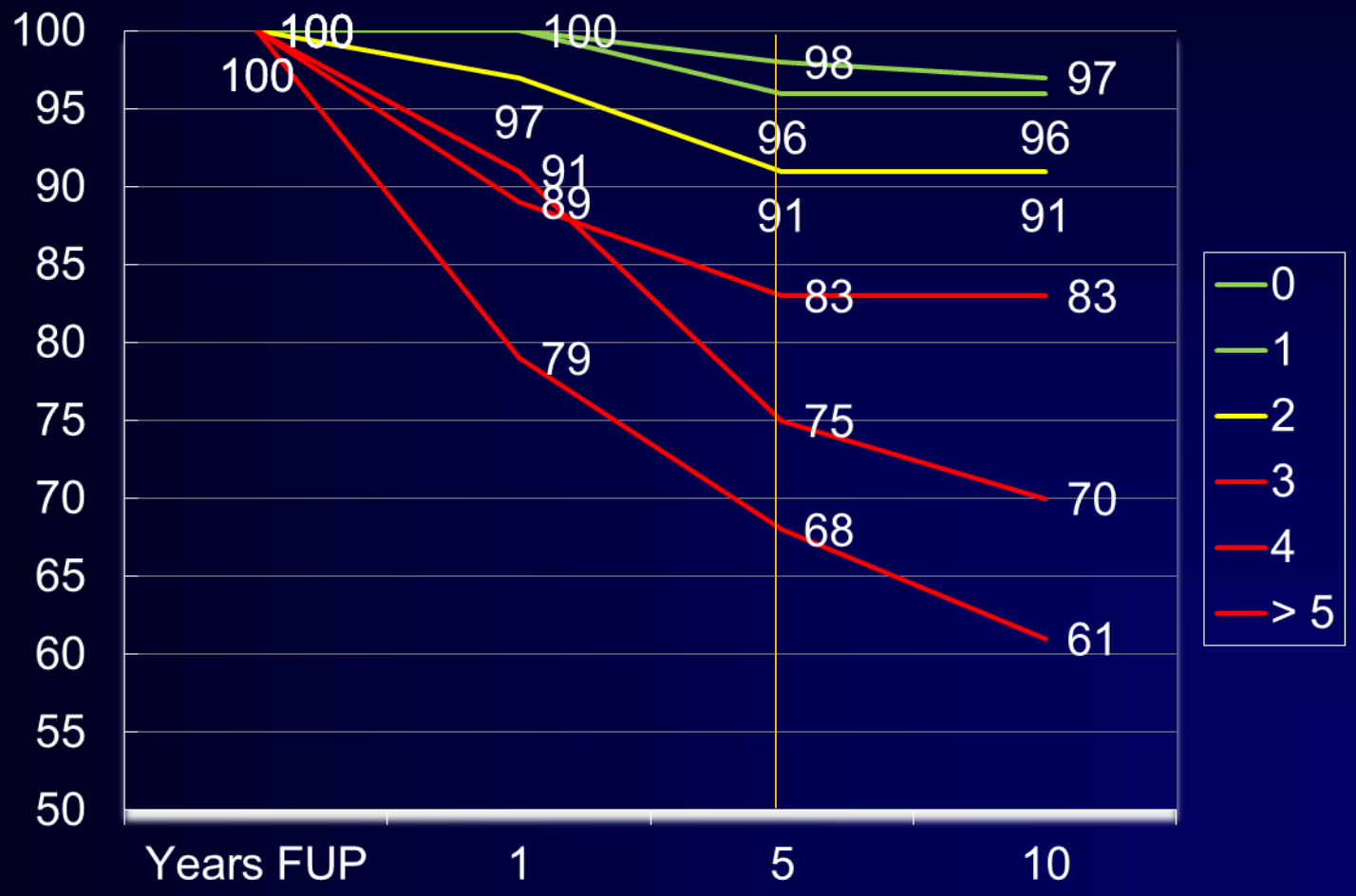
A risk score to predict events during long-term followup.

RISK FACTOR	POINTS
Spontaneous type I ECG	1
Early family Hx SCD	1
Inducible at EPS	2
Syncope	2
Sinus node dysfunction	3
Resuscitated SCD	4

Global model C-statistic 0,89. Reduced model C-statistic 0,83

Management of patients with Brugada syndrome

A risk score to predict events during long-term followup.



Brugada syndrome a curiosity?

Papadakis et al. JACC 2018.

303 SADS FAMILIES WITH NEGATIVE AUTOPSY

911 Relatives tested:

ECG, normal and high precordial leads

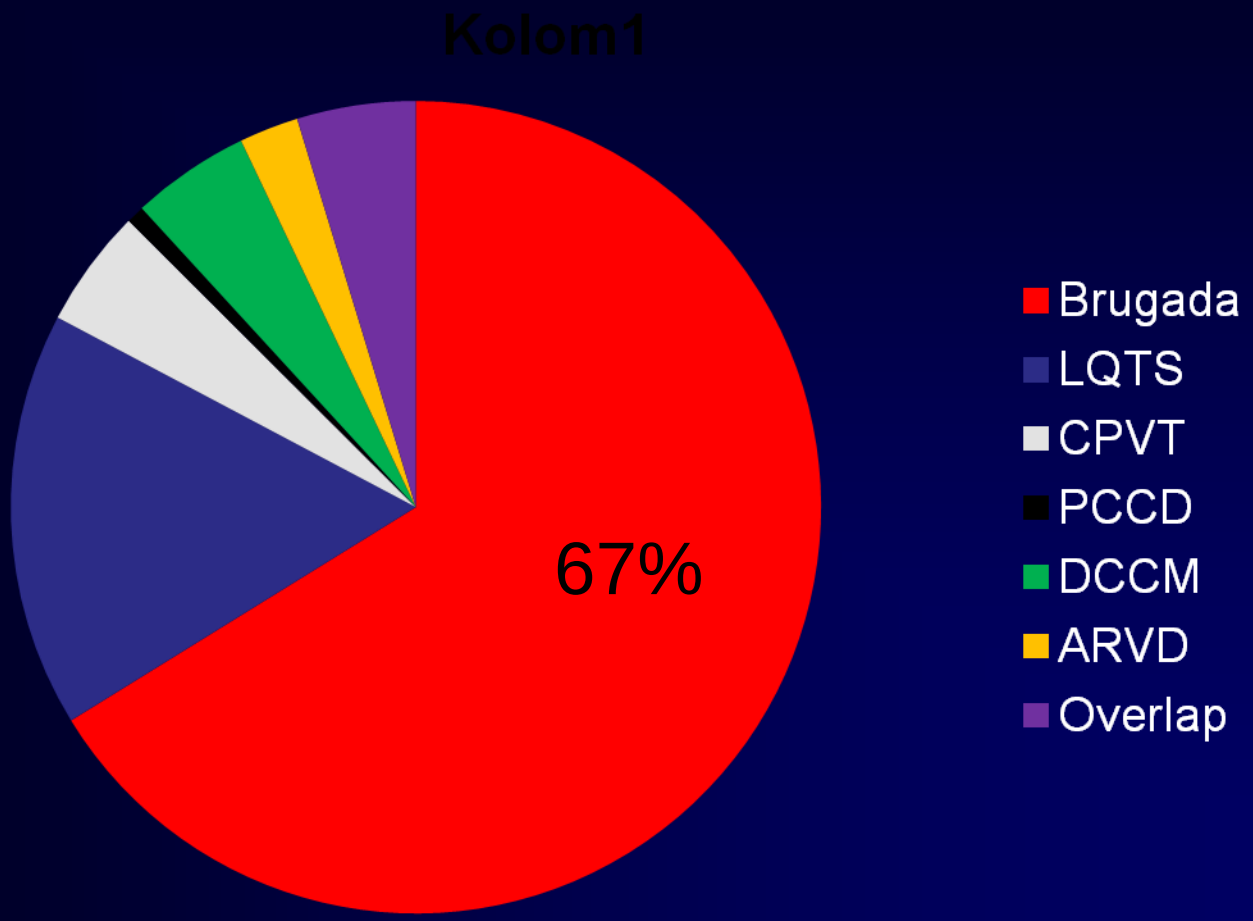
Exercise test, 24 hours Holter, echocardiography, adrenaline test

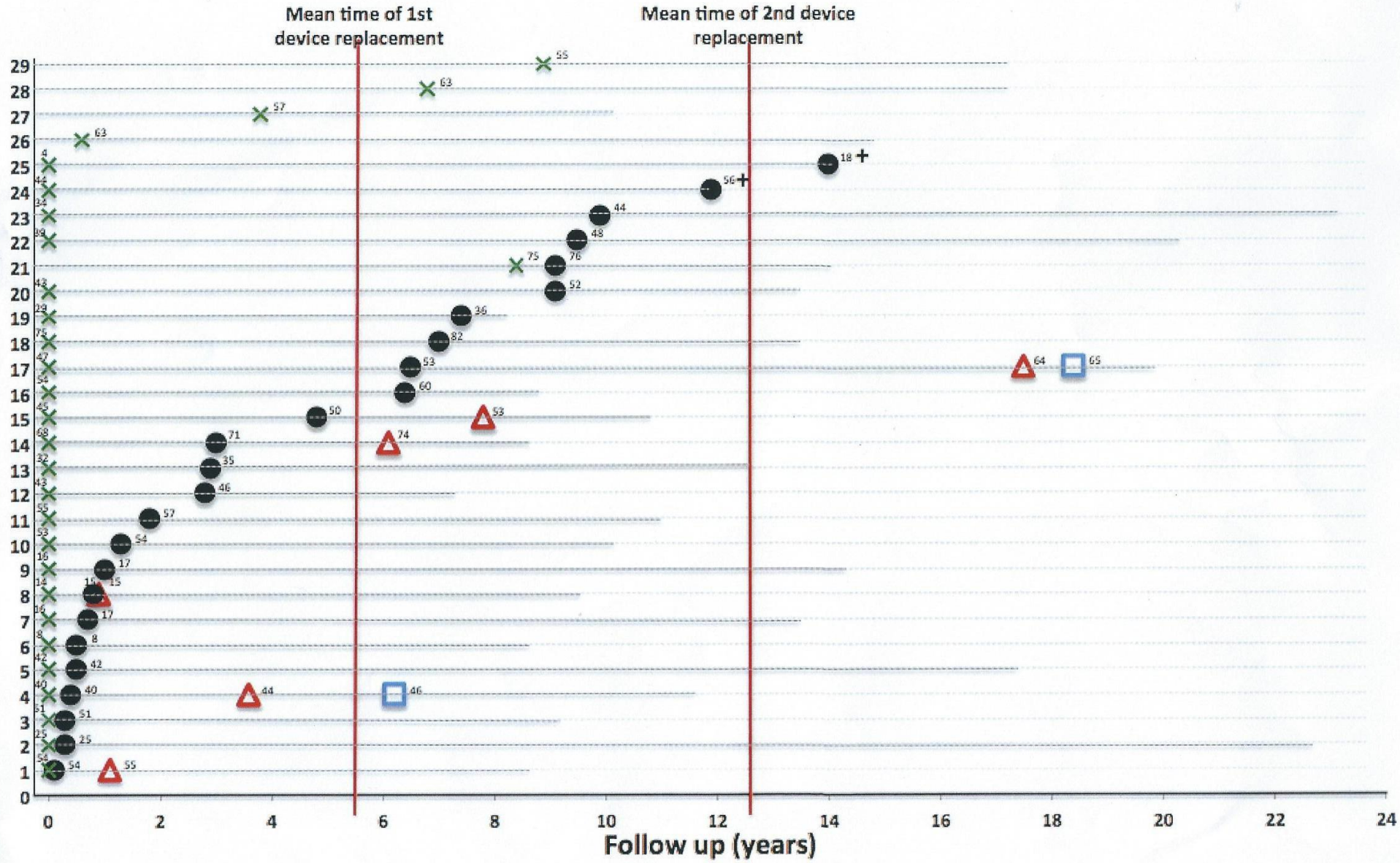
Ajmaline test in 74%

Brugada syndrome a curiosity?

DIAGNOSTIC YIELD	
Inherited cardiac disease	128 (42%) families
No diagnosis	175 (58%)
Brugada syndrome	28% - 85 (67% of fam. diagnosis)
LQT syndrome	7%- 22
CPVT	2%- 5
PCCD	0.3%- 1
DCM	2%- 7
ARVD	1%- 3
Overlap syndromes	2%- 5

Brugada syndrome a curiosity?




Mean time of 1st device replacement
Mean time of 2nd device replacement
Follow up (years)
0
2
4
6
8
10
12
14
16
18
20
22
24
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

Brugada Syndrome:

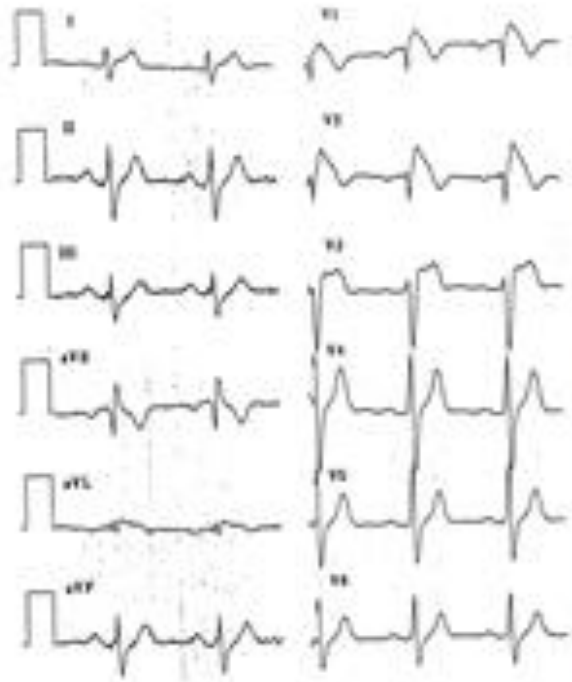
From Mutation to Ablation

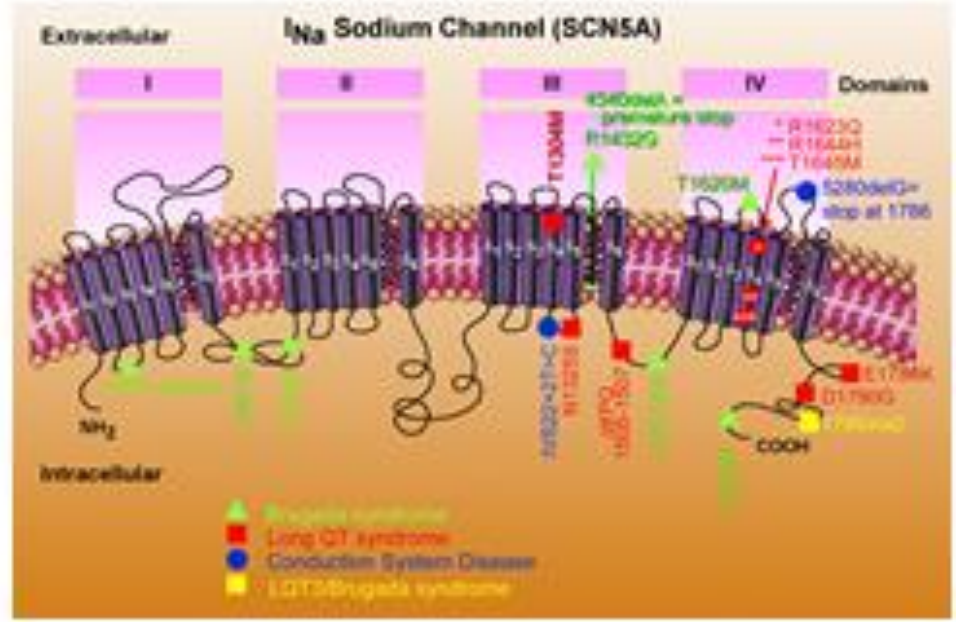
Prof. Dr. Pedro Brugada,
Scientific Director,
Cardiovascular Division, UZ Brussel-VUB
Brussels, Belgium.

The Start

1992 Phenotype: ECG/ Sudden death

1998 Genotype: Mutations in gene SCN5A





The initial doubts

- Right ventricular dysplasia
- Long QT syndrome
- Coronary spasm
- Normal variant of the ECG

The initial doubts turned around?

- Is Right Ventricular Dysplasia Brugada syndrome?

- ARVD1Ipl 107970 TGFB3 14q23-q24
- ARVD2 600996 RYR2 1q42-q43 Cathecolamine Induced Polymorphic Ventricular Tachycardia (CPVT)
- ARVD3 602086 ? 14q12-q22
- ARVD4 602087 ? 2q32.1-q32.3
- ARVD5 604400 TMEM43 3p23
- ARVD6 604401 ? 10p14-p12
- ARVD7 609160 DES 10q22.3
- ARVD8 607450 DSP 6p24
- ARVD9 609040 PKP2 12p11 Plakophillin 2
- ARVD10 610193 DSG2 18q12.1-q12
- ARVD11 610476 DSC2 18q12.1
- ARVD12 611528 JUP 17q21

2 decades later

- 2015 Genotype:

  18 known genes leading to the same phenotype!

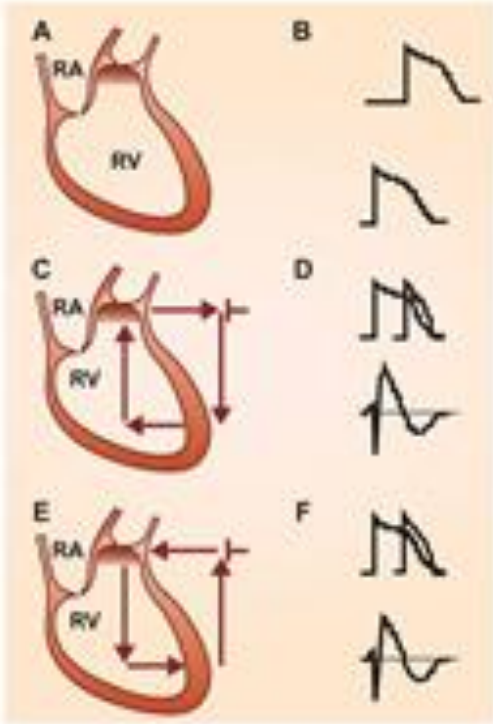
- SCN5A mutations most common (35%)

  > 300 variants

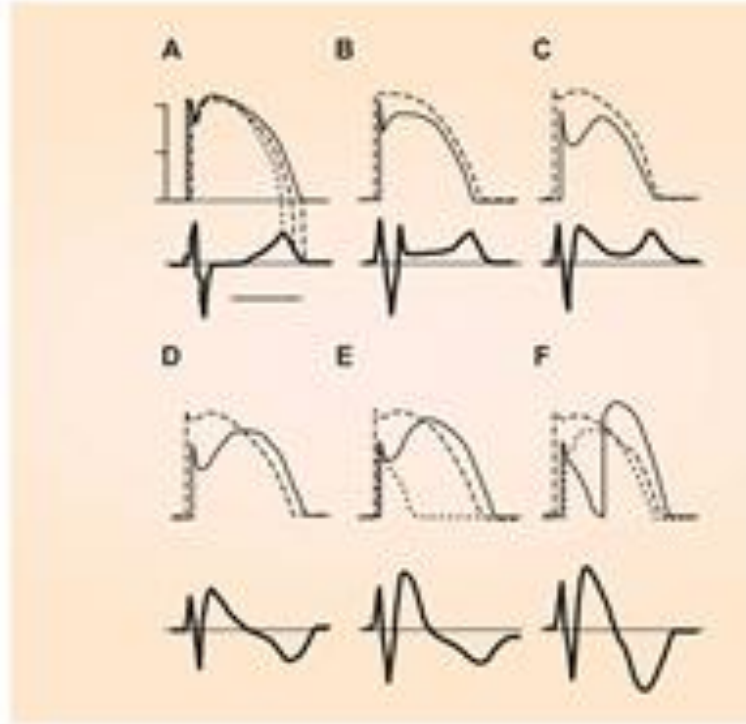
  For most, unknown pathophysiologic effects (T°C, drugs)

Suggested mechanisms.

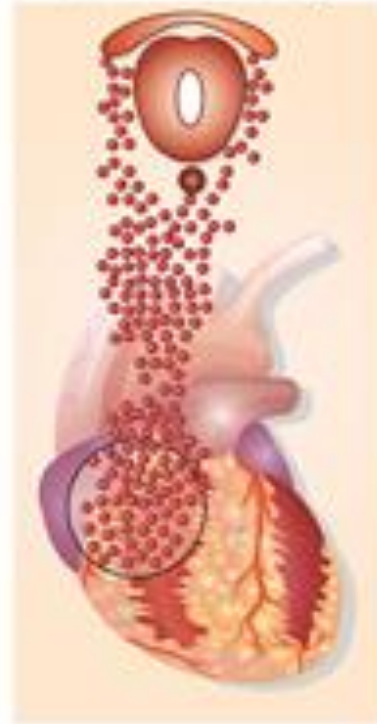
Slow conduction



Repolarization abnormality



Development abnormality



March 2015

- BrS1 SCN5A ↓
- BrS2 GPD1-L ↓
- BrS3 CACNA1C ↓
- BrS4 CACNB2 ↓
- BrS5 SCN1B ↓
- BrS6 KCNE3 ↑
- BrS7 SCN3B ↓
- BrS8 KCNH2 ↓
- BrS9 KCNJ8 ↑
- BrS10 CANA2D1 ?
- BrS11 RANGFR ↓
- BrS12 KCNE5 ↑
- BrS13 KCND3 ↑
- BrS14 HCN4 ?
- BrS15 SLMAP ↓
- BrS16 TRMP4 ↓↑
- BrS17 SCN2B ↓
- BrS18 PKP2 ↓

Next-generation sequencing in Brugada syndrome.

- 45 BrS patients SCN5A negative.
- Resequence of 28 genes.
- 30 rare genetic variants identified in 12 genes in 22 patients:

1.AKAP9 (LQTS)	3
2.ANK2 (LQTS)	5
3.KCNJ2 and CASQ2 (CPVT)	1
4.RYR2 (CPVT)	3

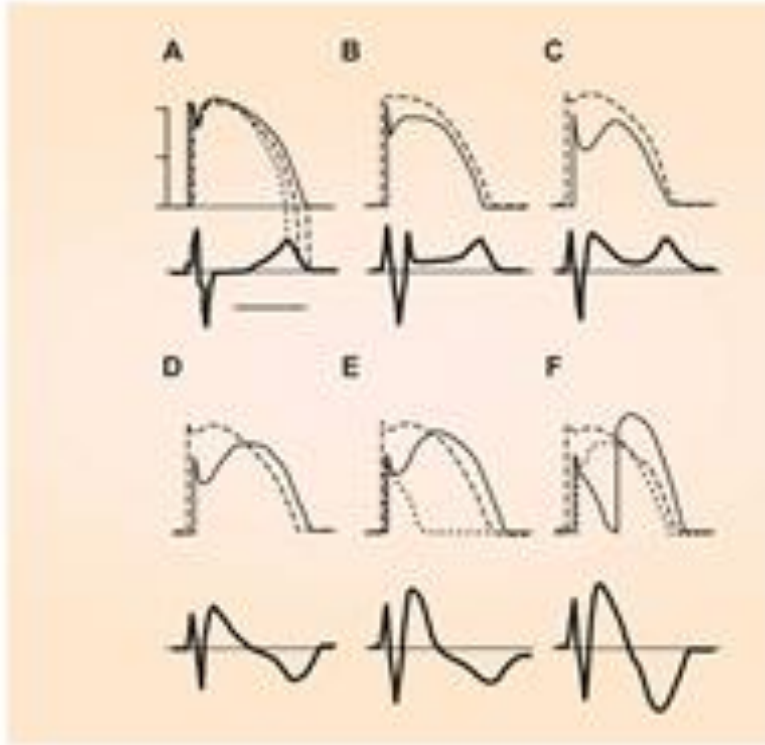
Allegue,..,Brugada R. Plos One, July 2015

Suggested mechanisms.

Slow conduction

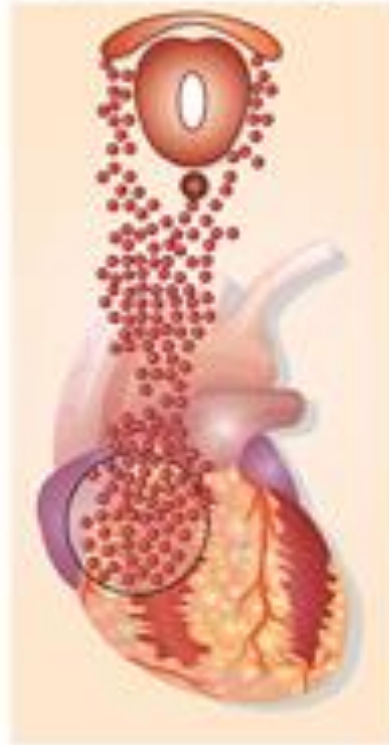
Na+ channel

Repolarization abnormality



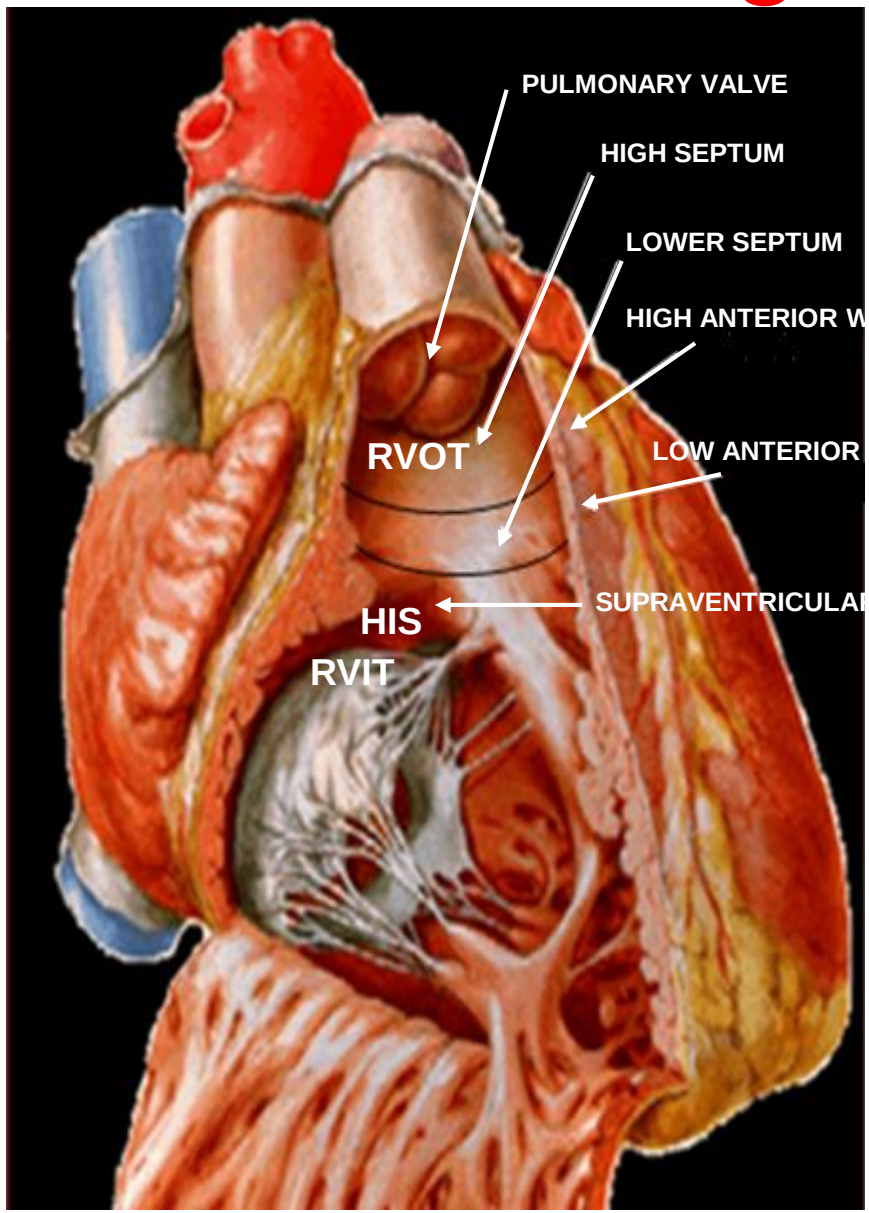
K+, Ca++, Cl- channels

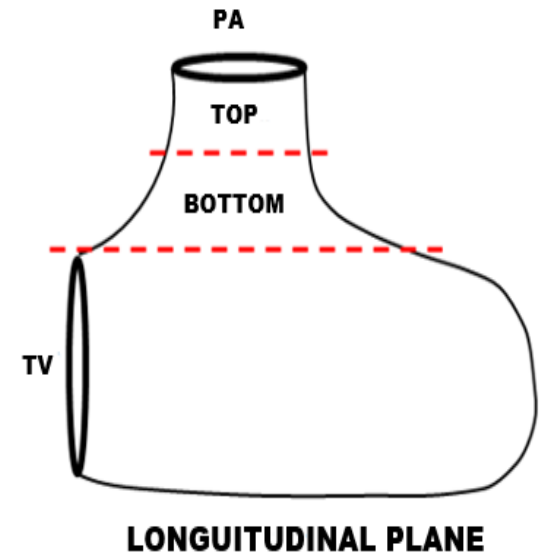
Development abnormality



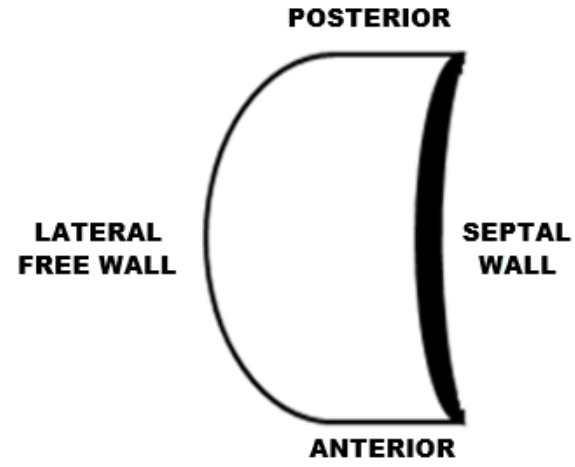
Somatic mutations

Anatomic target for ablation



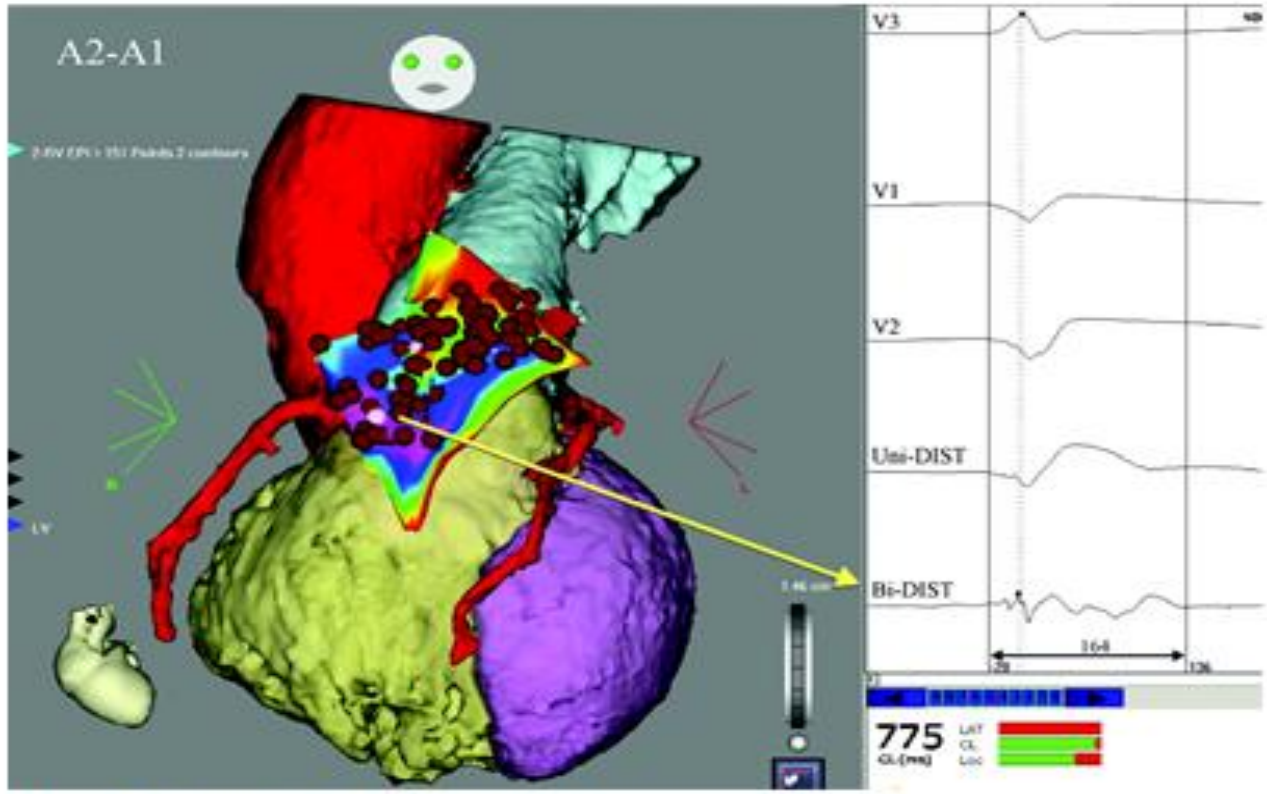


LONGUITUDINAL PLANE



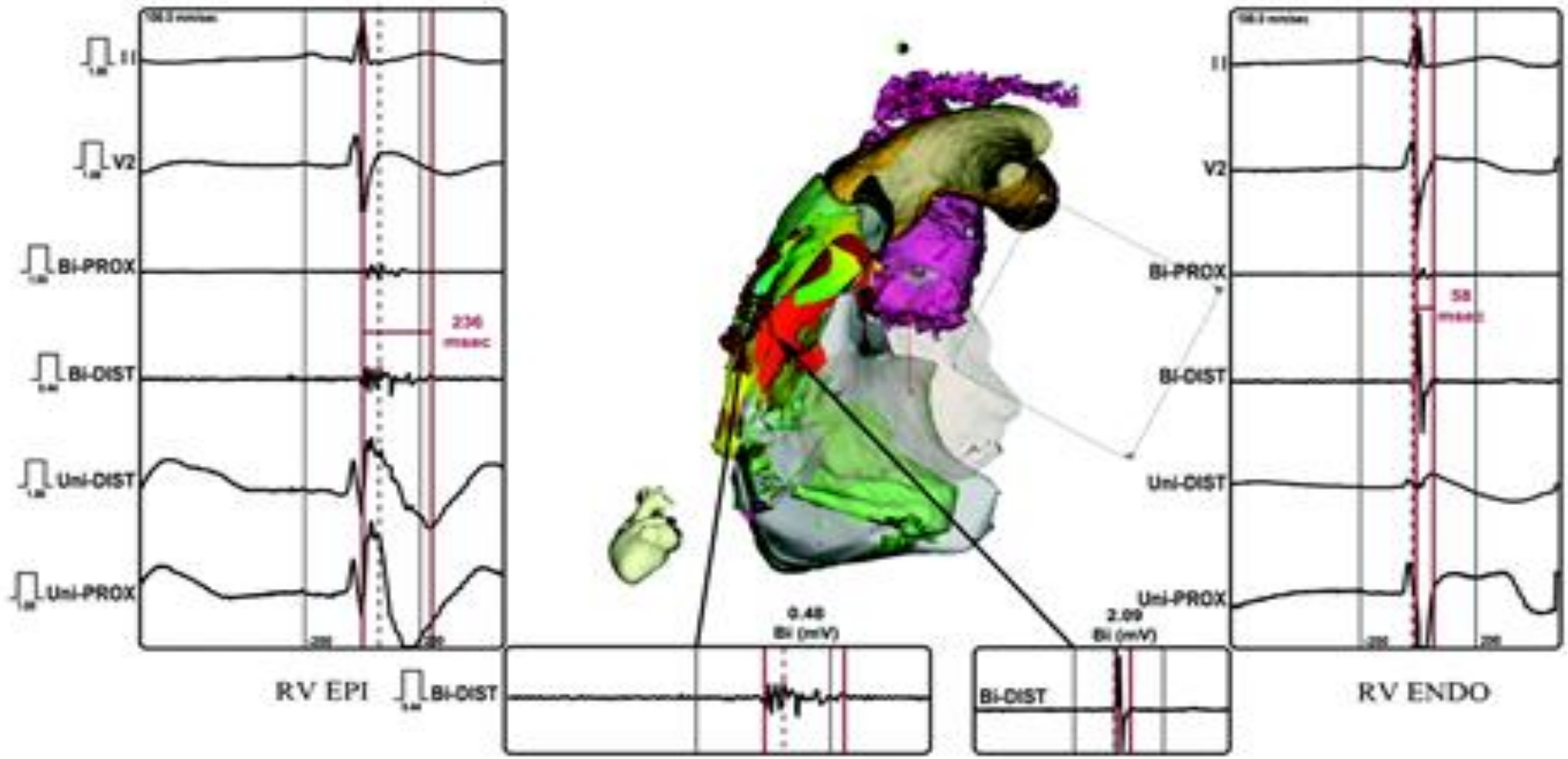
TRANSVERSE PLANE

Epicardial ablation in Brugada syndrome



Nademanee K et al. *Circulation*. 2011;123:1270-1279

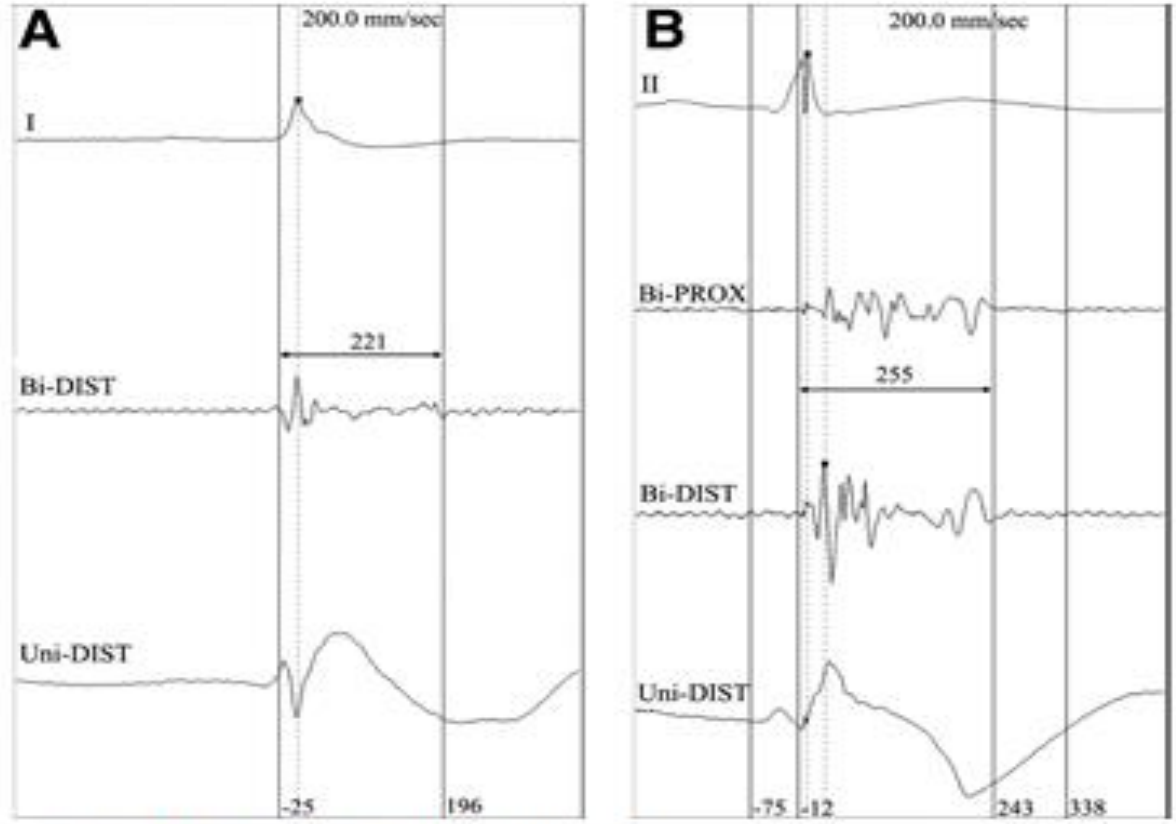
Slow conduction in epicardium



Nademanee K et al. *Circulation*. 2011;123:1270-1279

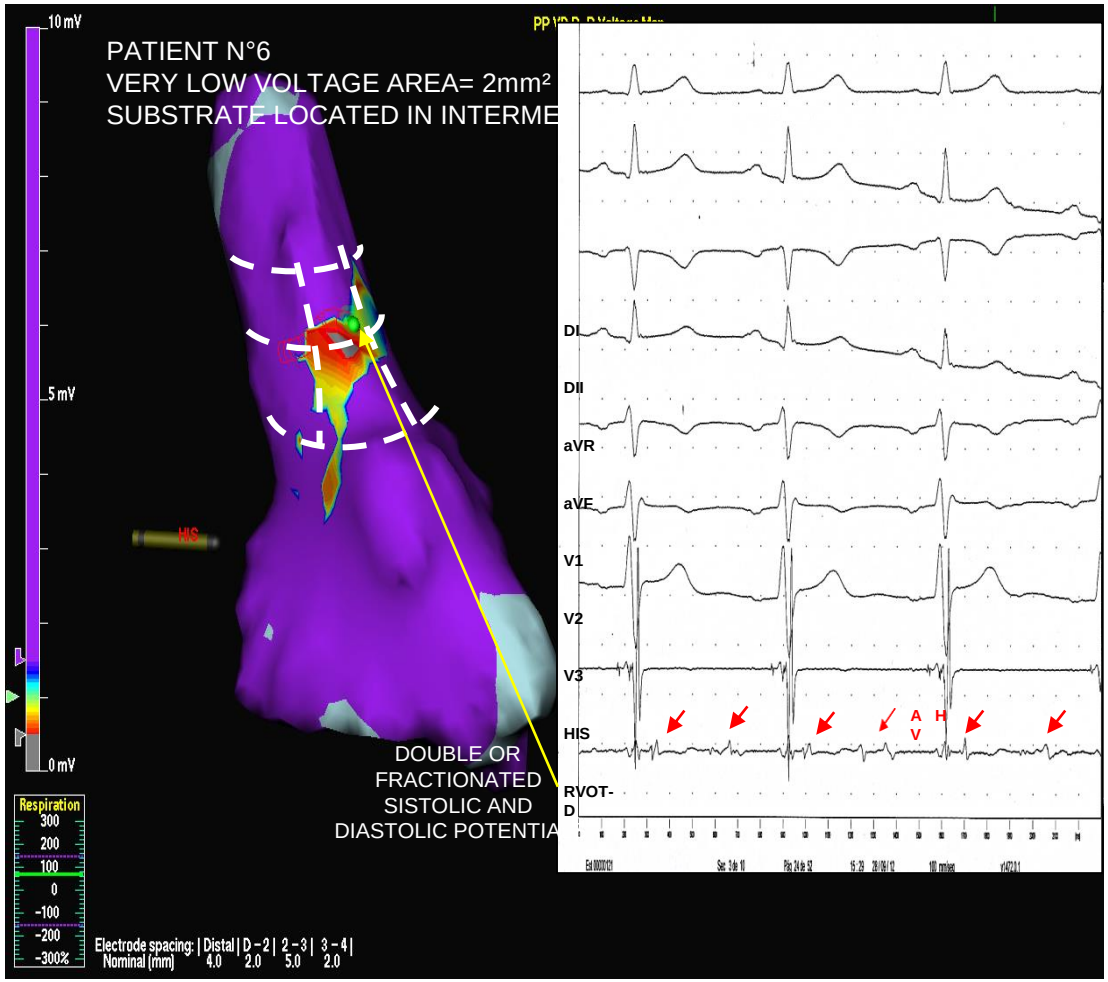
Slow conduction

Examples of electrograms with fractionated LPs that present as good target sites for catheter ablation.



Nademanee K et al. *Circulation*. 2011;123:1270-1279

Endocardial ablation in Brugada syndrome.



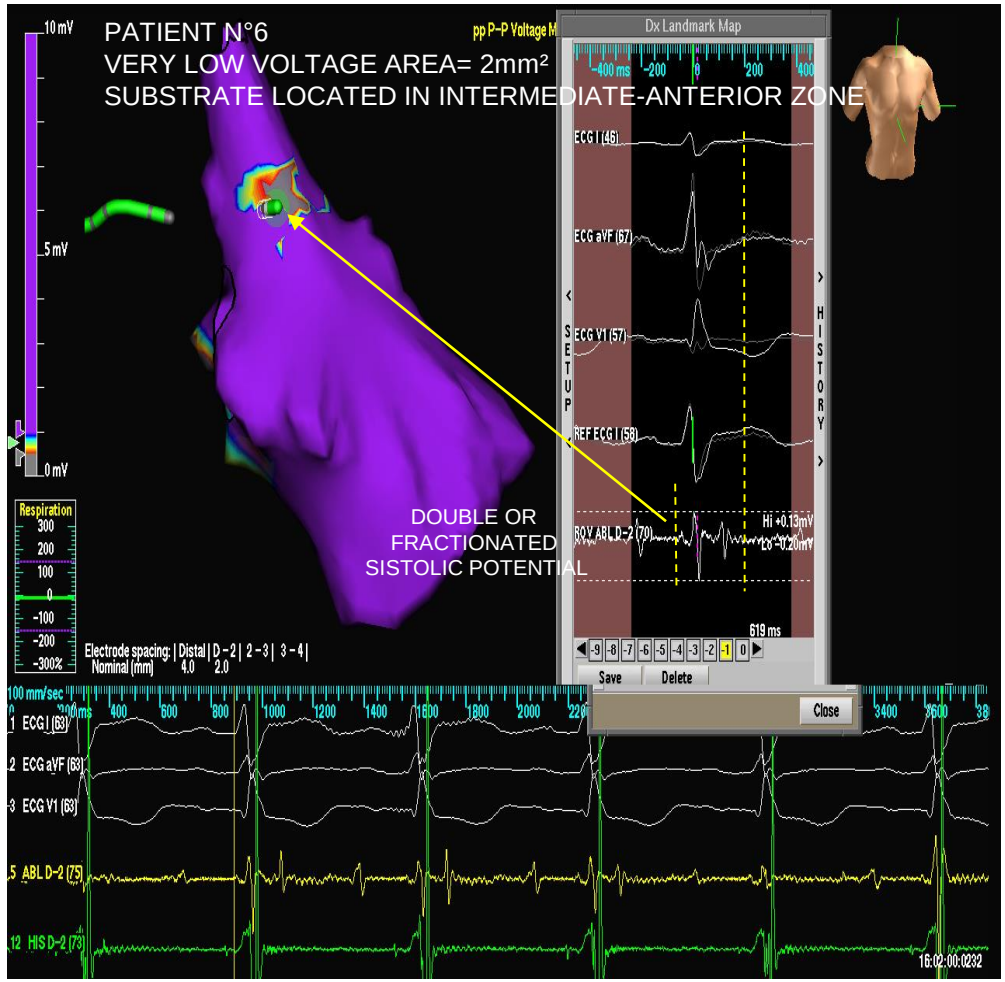
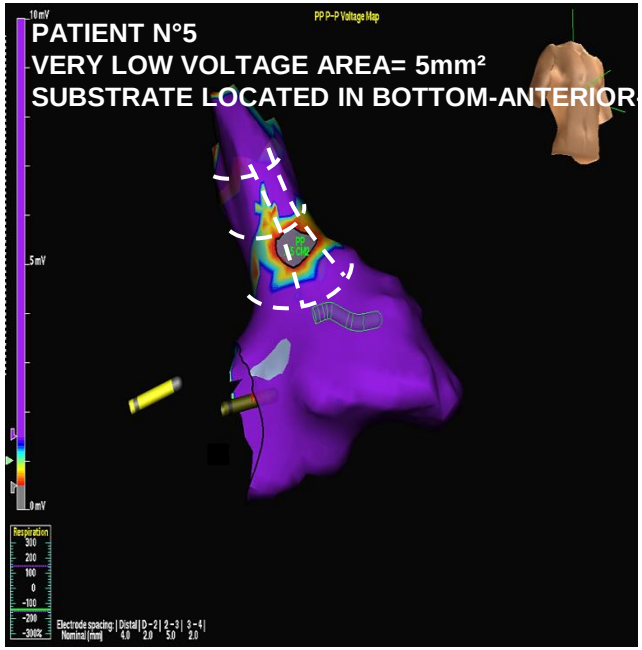
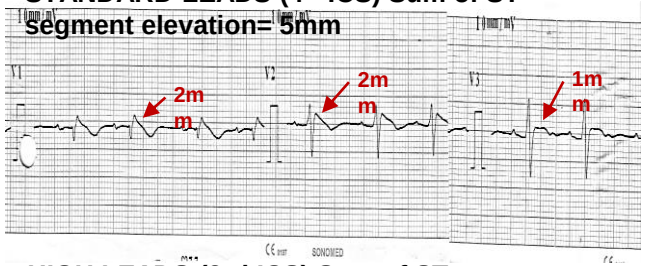


FIGURE 3

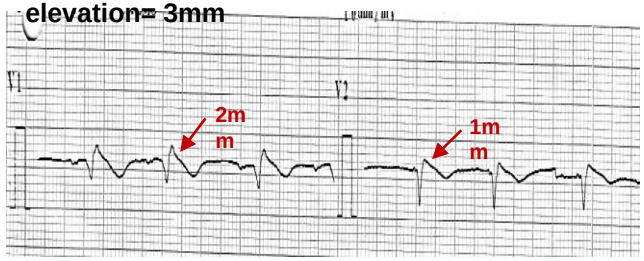
A



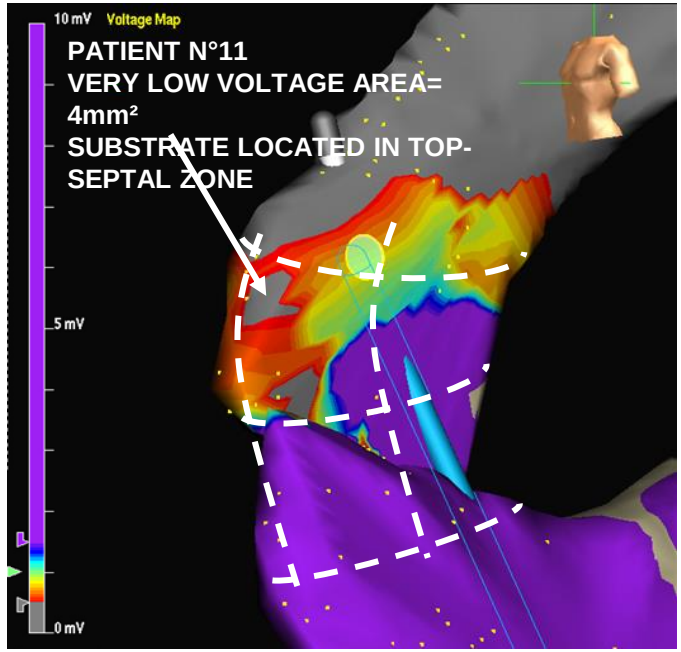
STANDARD LEADS (4th ICS) Sum of ST-Segment elevation= 5mm



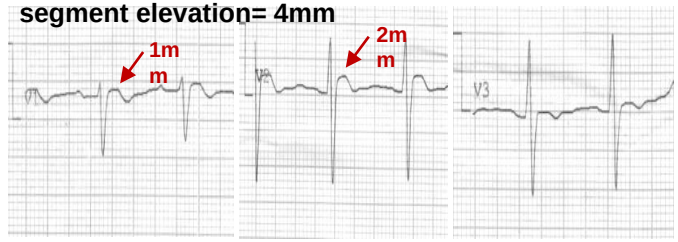
HIGH LEADS (3rd ICS) Sum of ST-segment elevation= 3mm



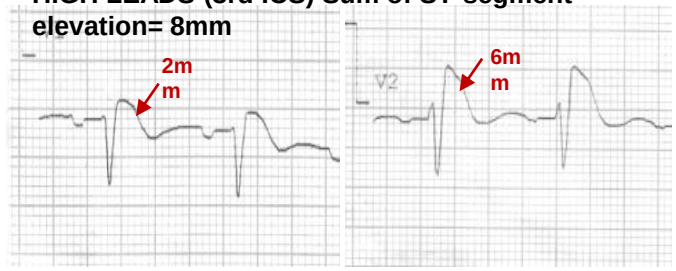
B



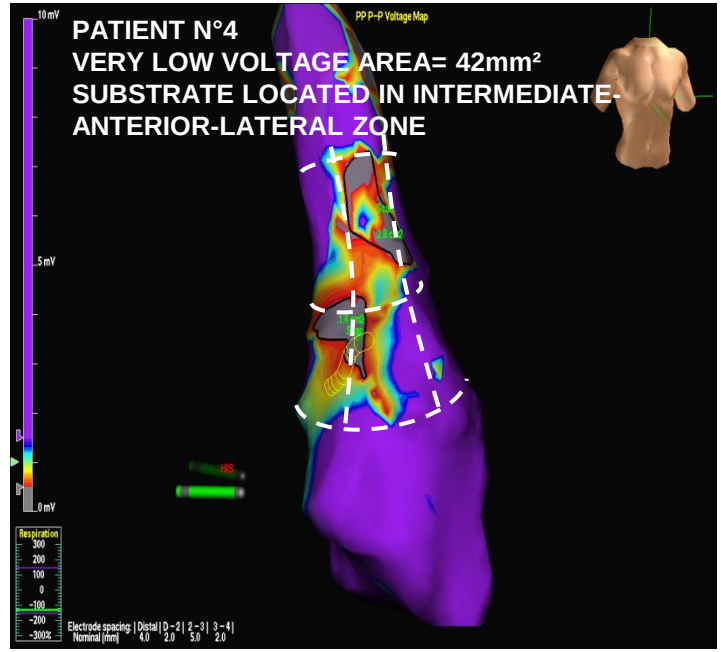
STANDARD LEADS (4th ICS) Sum of ST-segment elevation= 4mm



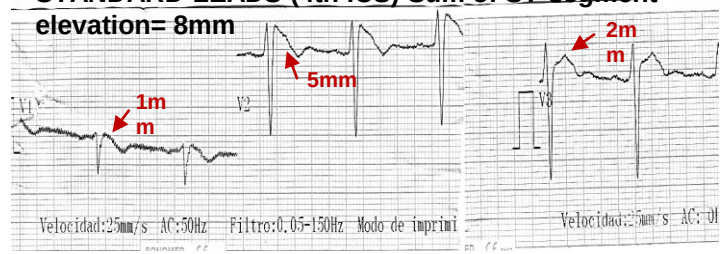
HIGH LEADS (3rd ICS) Sum of ST-segment elevation= 8mm



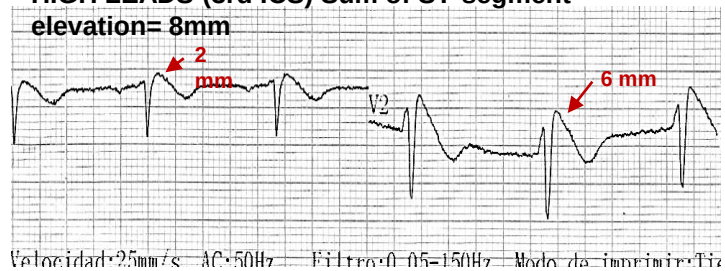
C



STANDARD LEADS (4th ICS) Sum of ST-segment elevation= 8mm

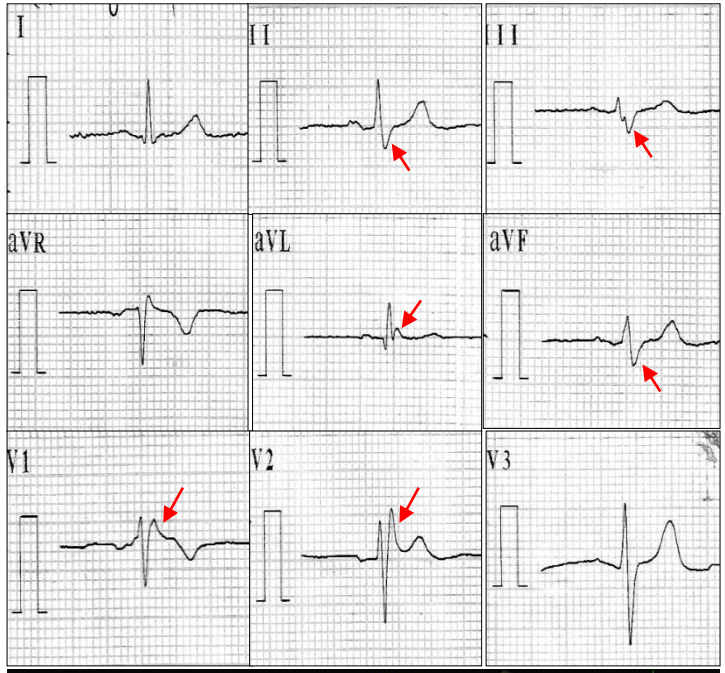


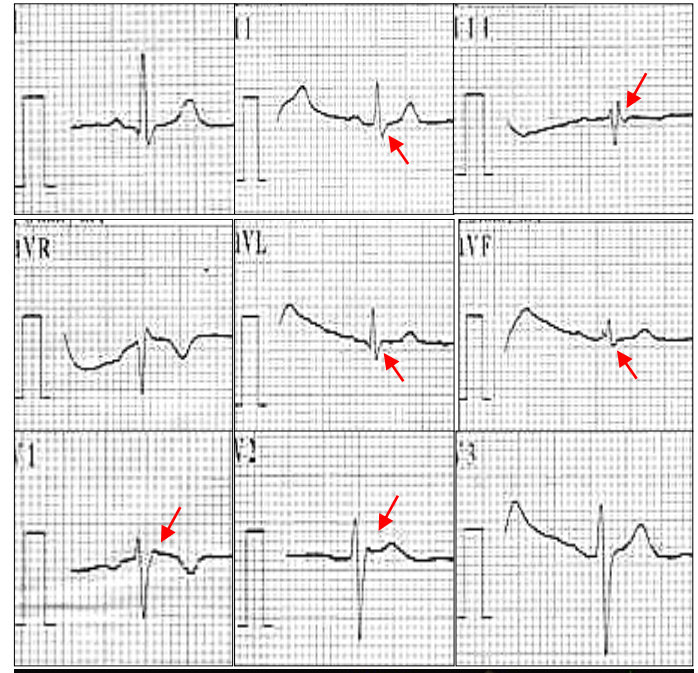
HIGH LEADS (3rd ICS) Sum of ST-segment elevation= 8mm

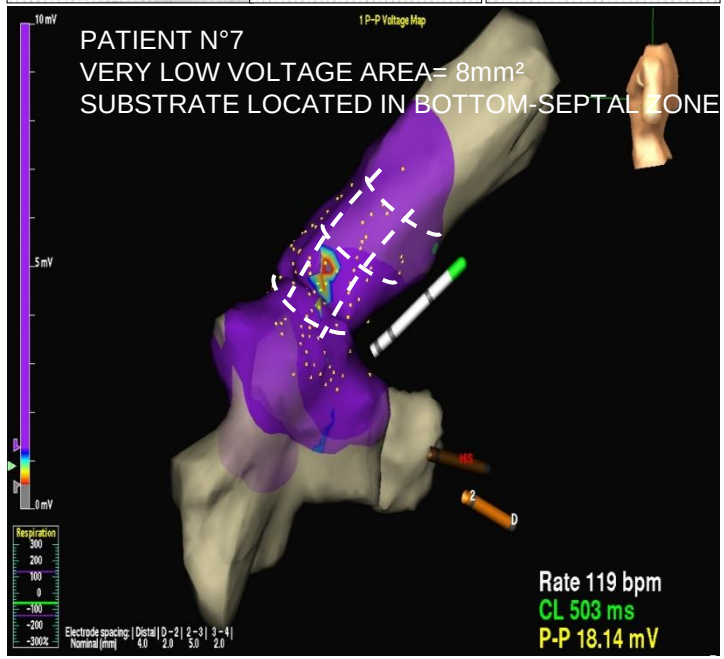


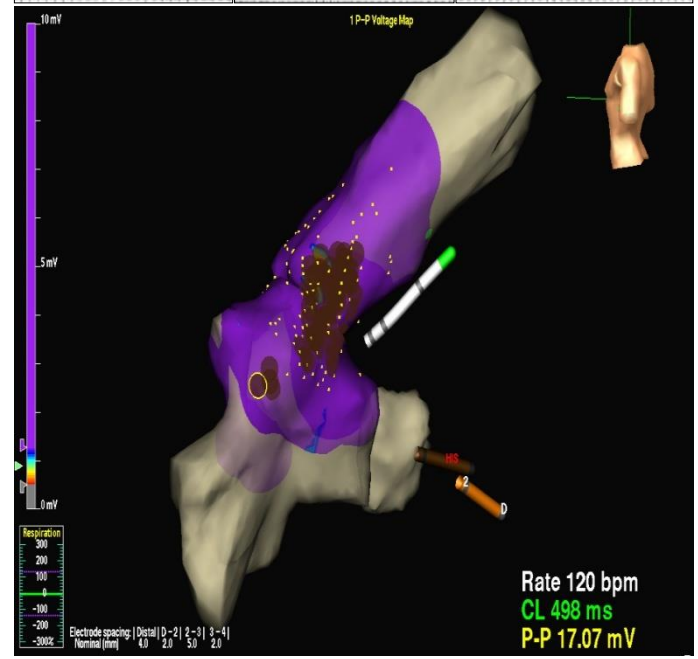
PRE ABLATION

POST ABLATION



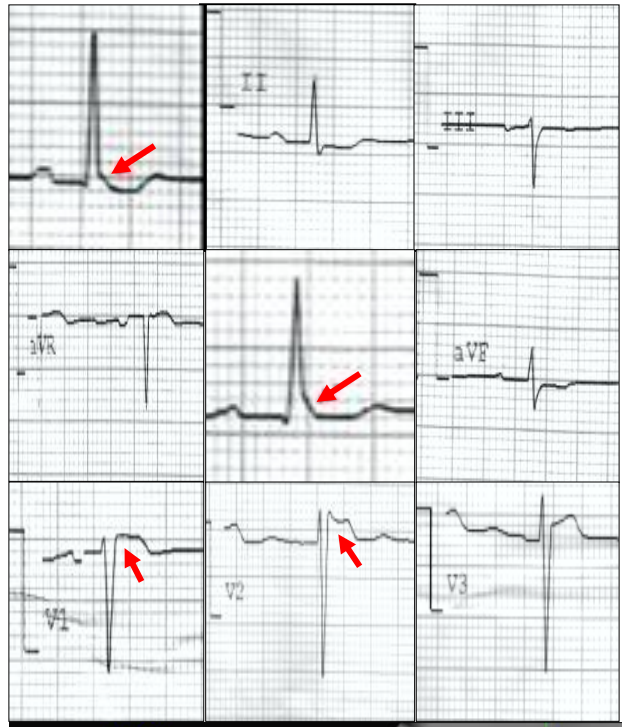


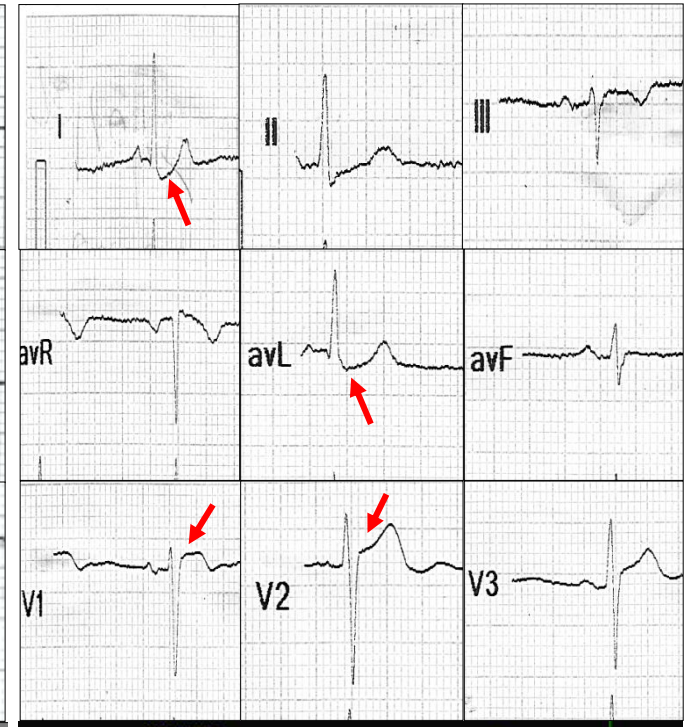


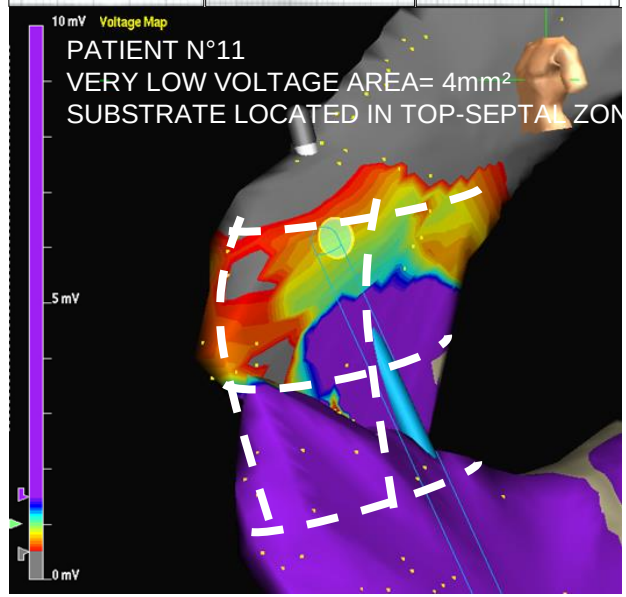


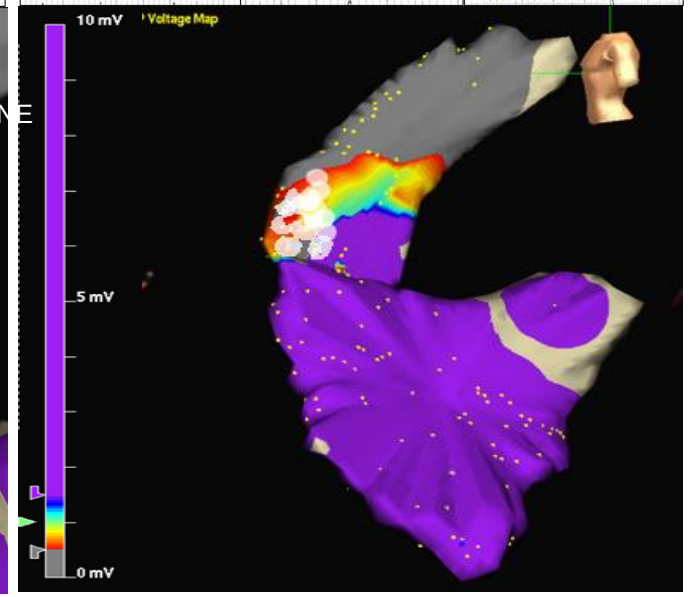
PRE ABLATION

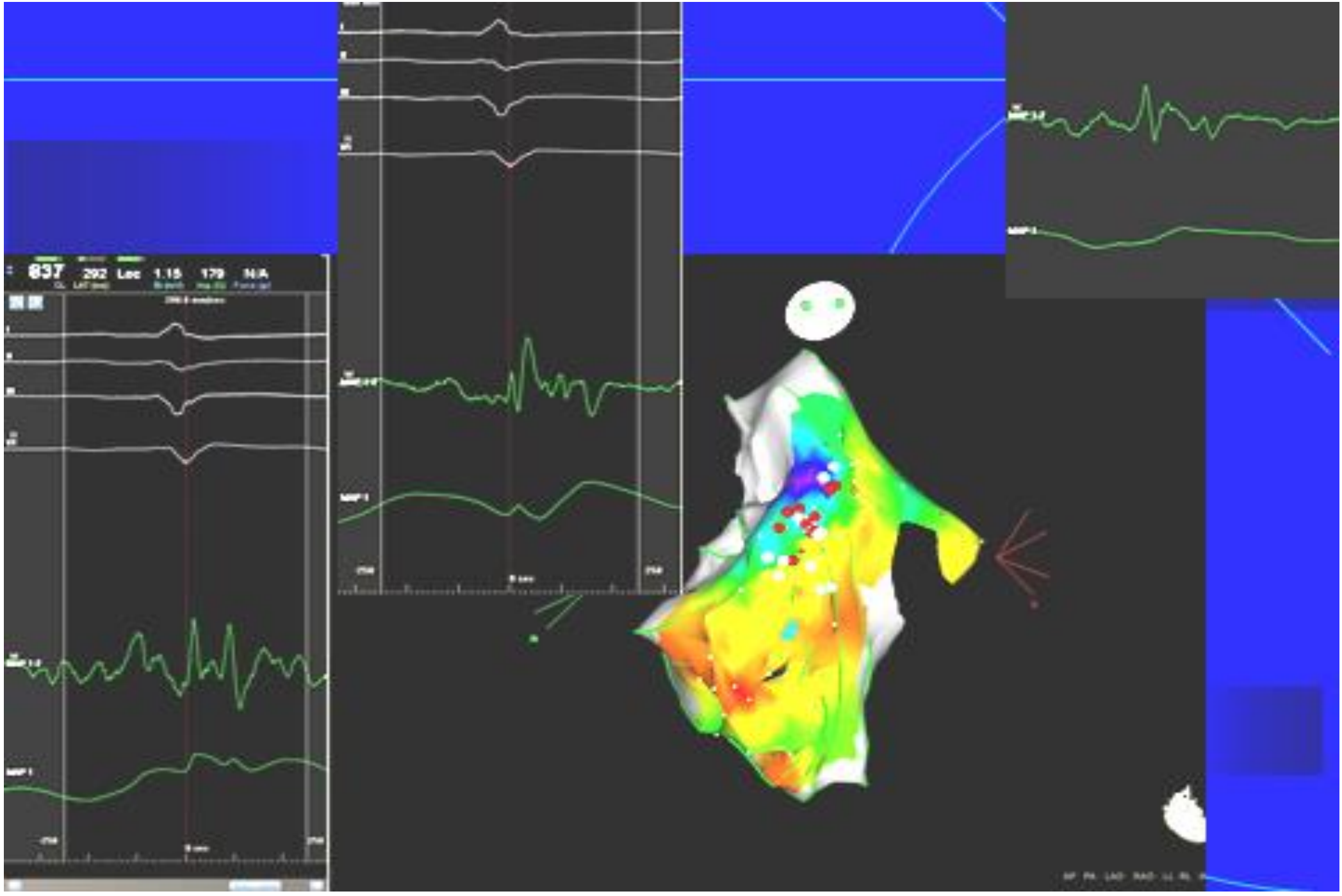
POST ABLATION

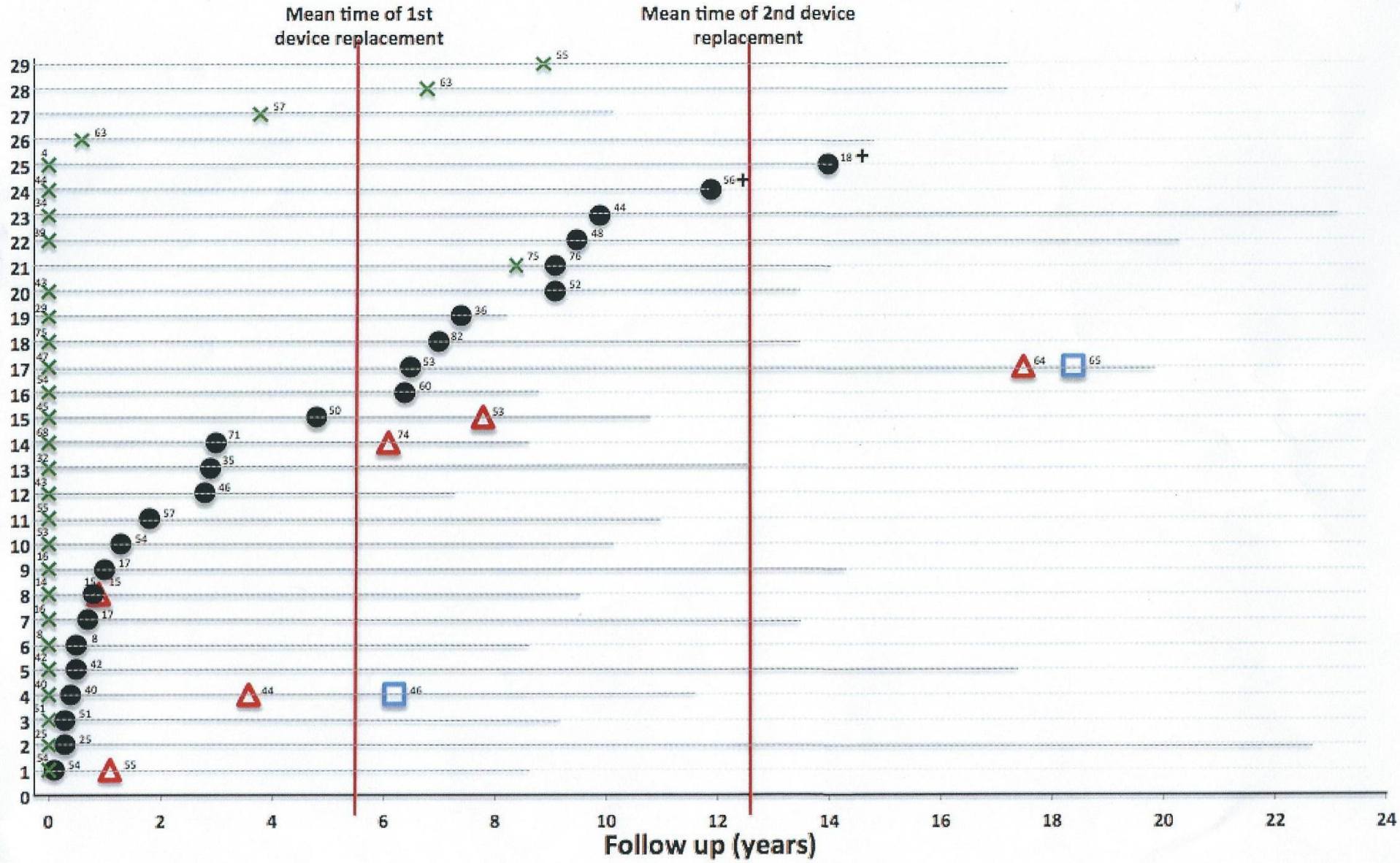









837
292 Loc 1.15 179 N/A


Mean time of 1st device replacement
Mean time of 2nd device replacement
Follow up (years)
0
2
4
6
8
10
12
14
16
18
20
22
24
1
2
3
4
5
6
7
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24
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26
27
28
29

50 years of Romano-Ward syndrome

With Conor Ward (91) and Frederic Sacher, Dublin 2014

PGD: No long QT

With permission

PGD

Fertilized	16
Biopsied	15
Affected	8
Unaffected	5
Inconclusive	2
Cryopreserved	3
Transferred	2

PGD: No Brugada syndrome

PGD

Fertilized	8
Biopsied	6
Affected	5
Unaffected	1
Inconclusive	0
Cryopreserved	0
Transferred	1