Syndrome de Brugada

Torsades de pointes à couplage court

Pr Antoine Leenhardt

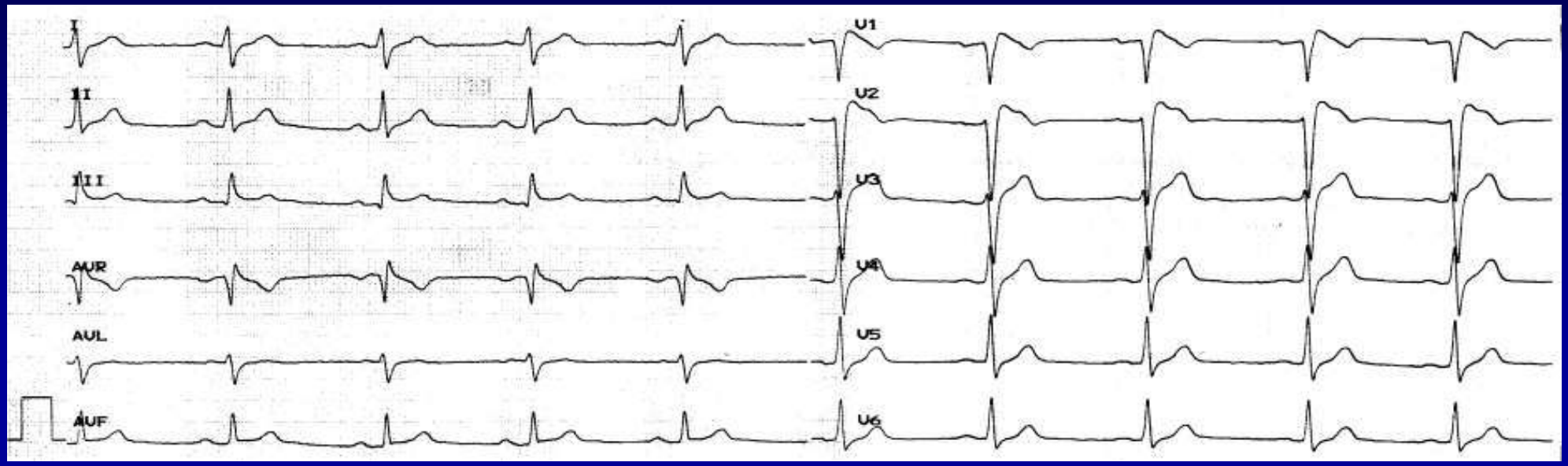
Département de Cardiologie

Hôpital Lariboisière

Université Paris 7

Paris, France

Syndrome de Brugada



- Retard de conduction intra-ventriculaire droite avec sus-décalage segment ST V1-V2-V3 (surélévation J ≥ 0.2 mV)
- Tachycardie ventriculaire polymorphe/FV => syncopes ou mort subite
- Cœur structurellement normal
- Incidence 1 / 1000 naissances ? Formes familiales

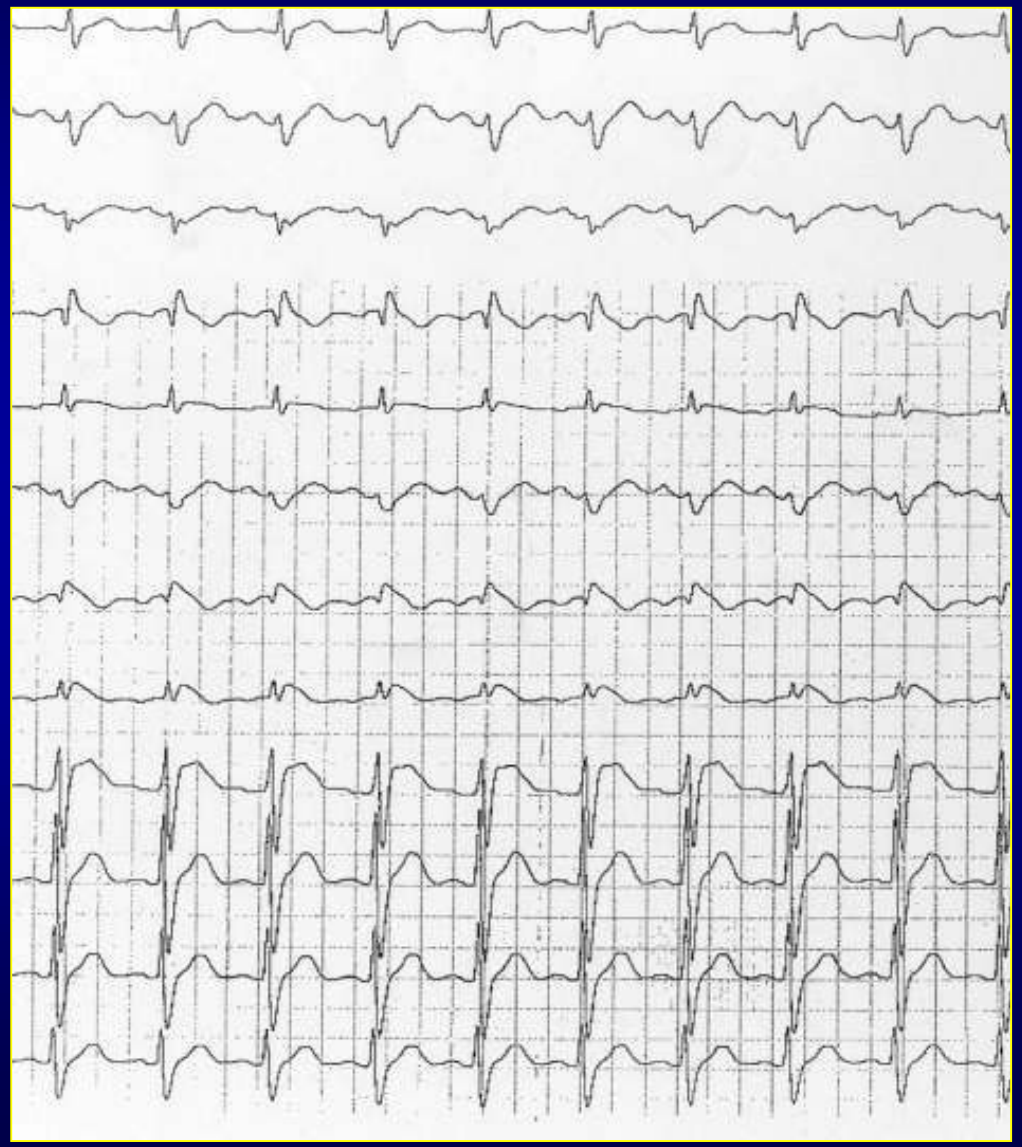
Syndrome de Brugada

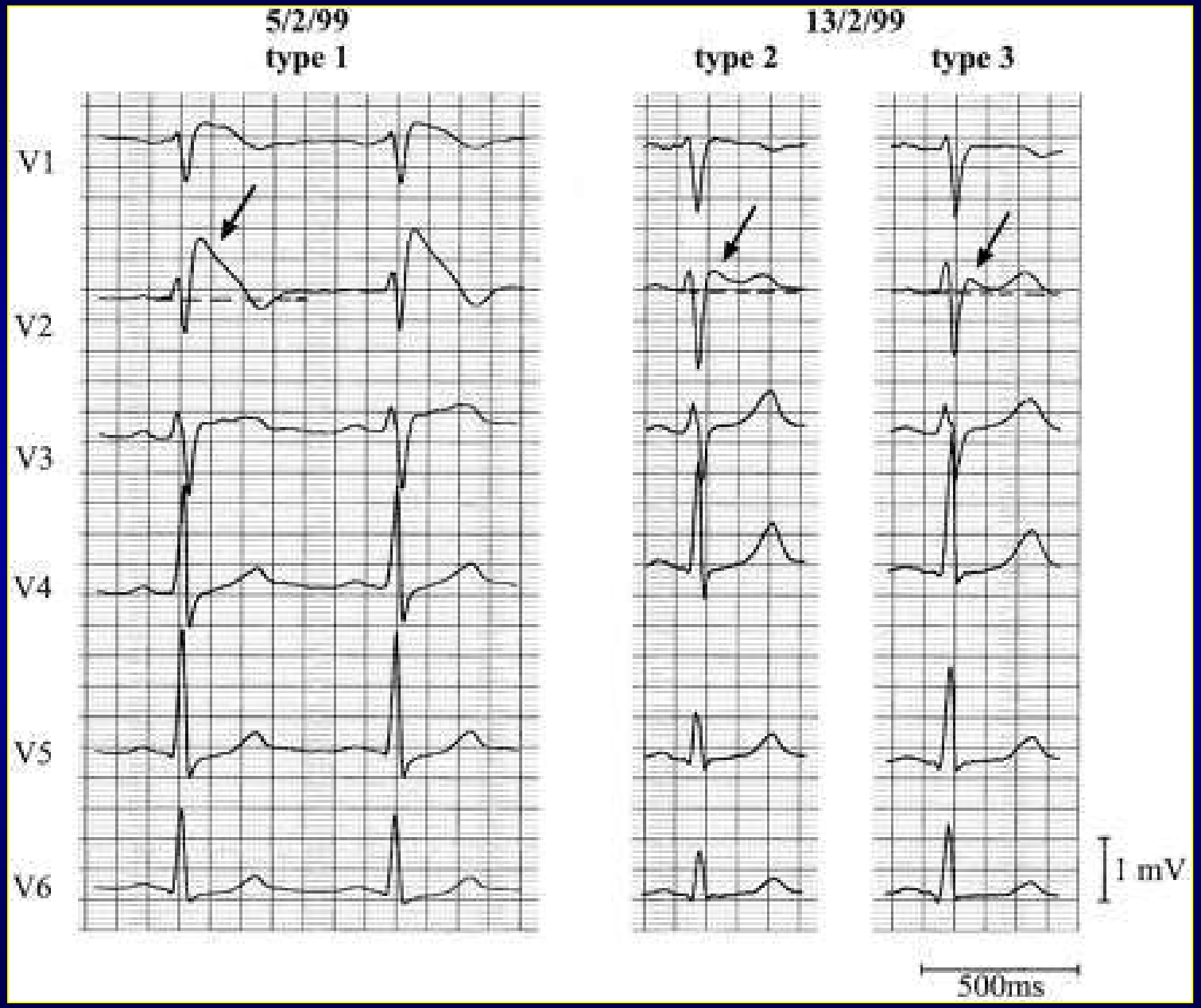
Autres caractéristiques électrocardiographiques

- Allongement intervalle PR dû à allongement HV
- Onde T négative ou plate en V1 et V2
- Grande variabilité de l'ECG dans le temps (SNA, AAR, autres drogues, température…)
- FA paroxystique : 10 % des cas

Diagnostic du syndrome de Brugada

- Homme de 40-50ans
- Anomalie ECG à rechercher en cas de syncope et de bilan de mort subite « idiopathique ».
- Test Ajmaline/Flécaine injectable
- Bilan familial
- Mutation génétique : SCN5A 25 % des cas.





Precordial leads of a resuscitated pt with Brugada syndrome.

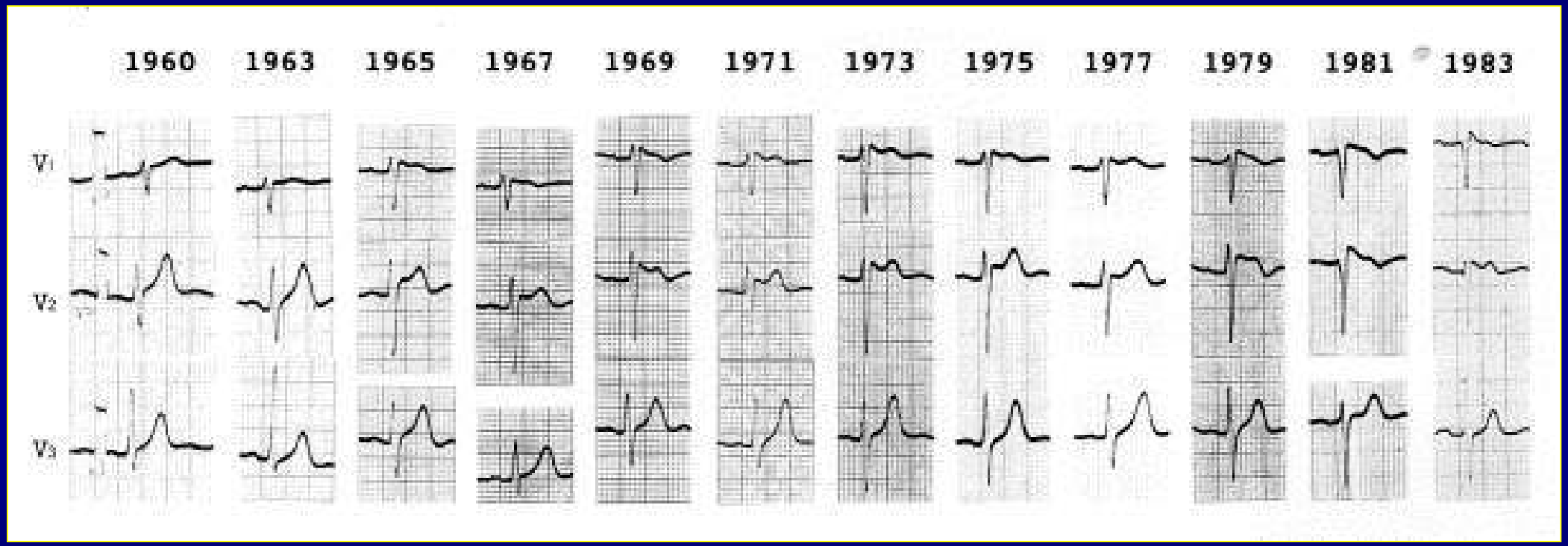
A. Wilde et al. Circulation 2002;106:2514

Proposed Diagnostic Criteria for the Brugada Syndrome

Consensus Report : ST-T segment abnormalities in leads V_1 to V_3

	Type 1	Type 2	Type 3
J wave amplitude	≥ 2 mm	≥ 2 mm	≥ 2 mm
T wave	negative	positive or biphasic	positive
ST-T configur.	coved type	saddleback	saddleback
ST segment (terminal portion)	gradually descending	elevated ≥ 1 mm	elevated < 1 mm

Circulation 2002;106:2514-9.

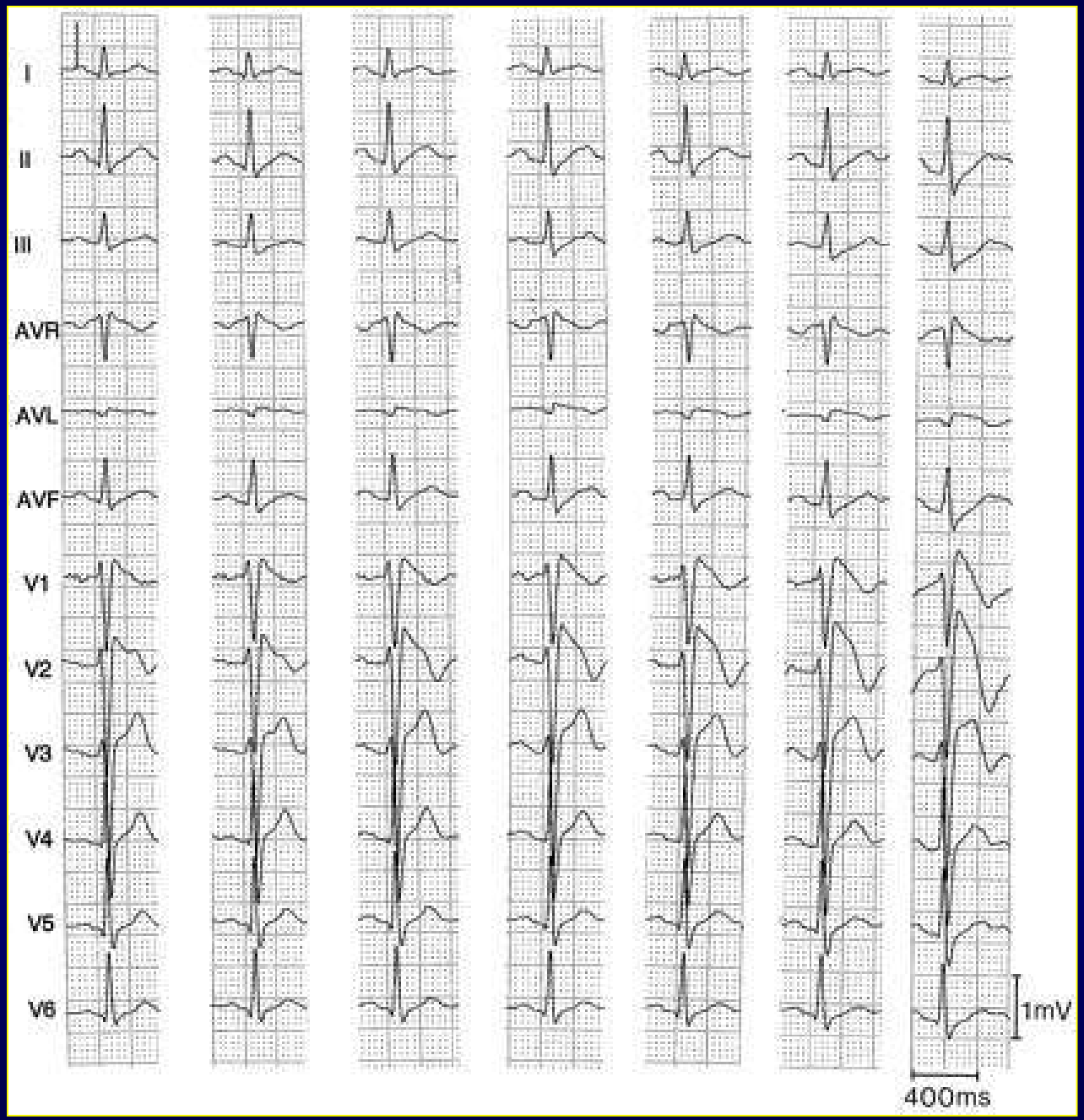

1960
1963
1965
1967
1969
1971
1973
1975
1977
1979
1981
1983
V1
V2
V3

Syndrome de Brugada

Tests pharmacologiques provocatifs

- After written informed consent was obtained, a single intravenous dose of one sodium channel blocker was administered.
- The patients were studied in the Electrophysiology Laboratory, where continuous ECG recordings were obtained.
- Drugs tested :
  - 1 mg/kg ajmaline was administered over a 5-minute period
  - 2 mg/kg flecainide was administered over a 5-minute period,
  - 10 mg/kg procainamide was infused at a rate of 100 mg/min.
- Results : the ECG changes during the infusion were considered positive when a terminal R wave and ST-segment elevation (>1 mm) occurred in leads V1 to V3.

from R Brugada Circulation 2000;101:510.



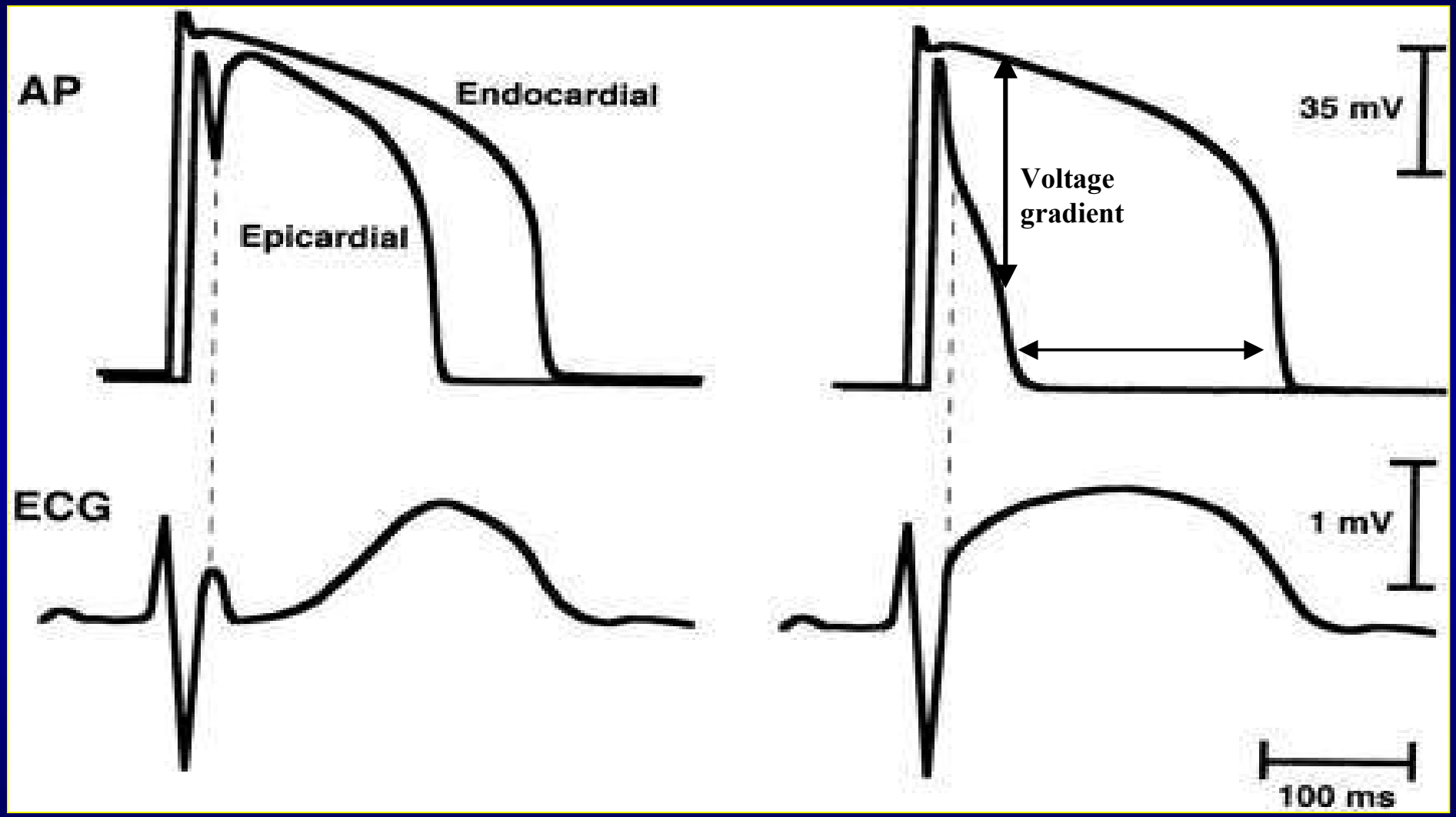
ECGs from a 35-year-old male who has been successfully resuscitated. From left to right: 2 control ECGs and 1, 2, 3, 4, and 5 minutes during IV infusion of 50 mg ajmaline.

The ECG is "saddle back" type (type 2) in the left panels and becomes coved in the right panels (type 1). Calibrations are standard.

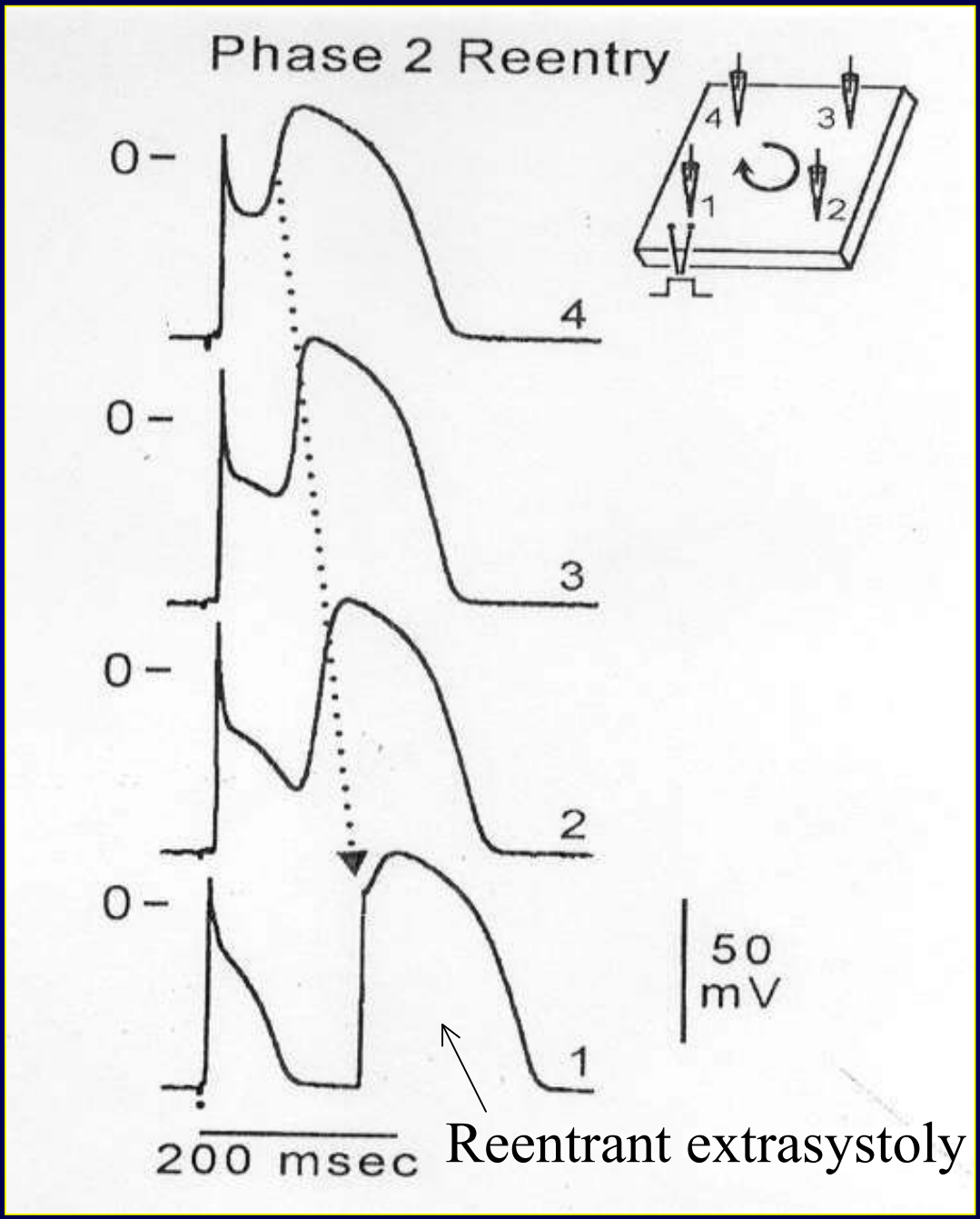
A. Wilde et al. Circulation 2002;106:2514

Syndrome de Brugada
Physiopathologie

- Pathologie « électrique » : « channelopathie »
- Les canaux mutés (mutations SCN5A 25 %) s'inactivent rapidement ou sont non fonctionnels.
- Création d'un gradient électrique épicardique et transmural par augmentation relative d'I_{to} aboutissant à la création de réentrées de phase 2.
- Majoration des dysfonctions en cas d'élévation de la température dans certaines formes.

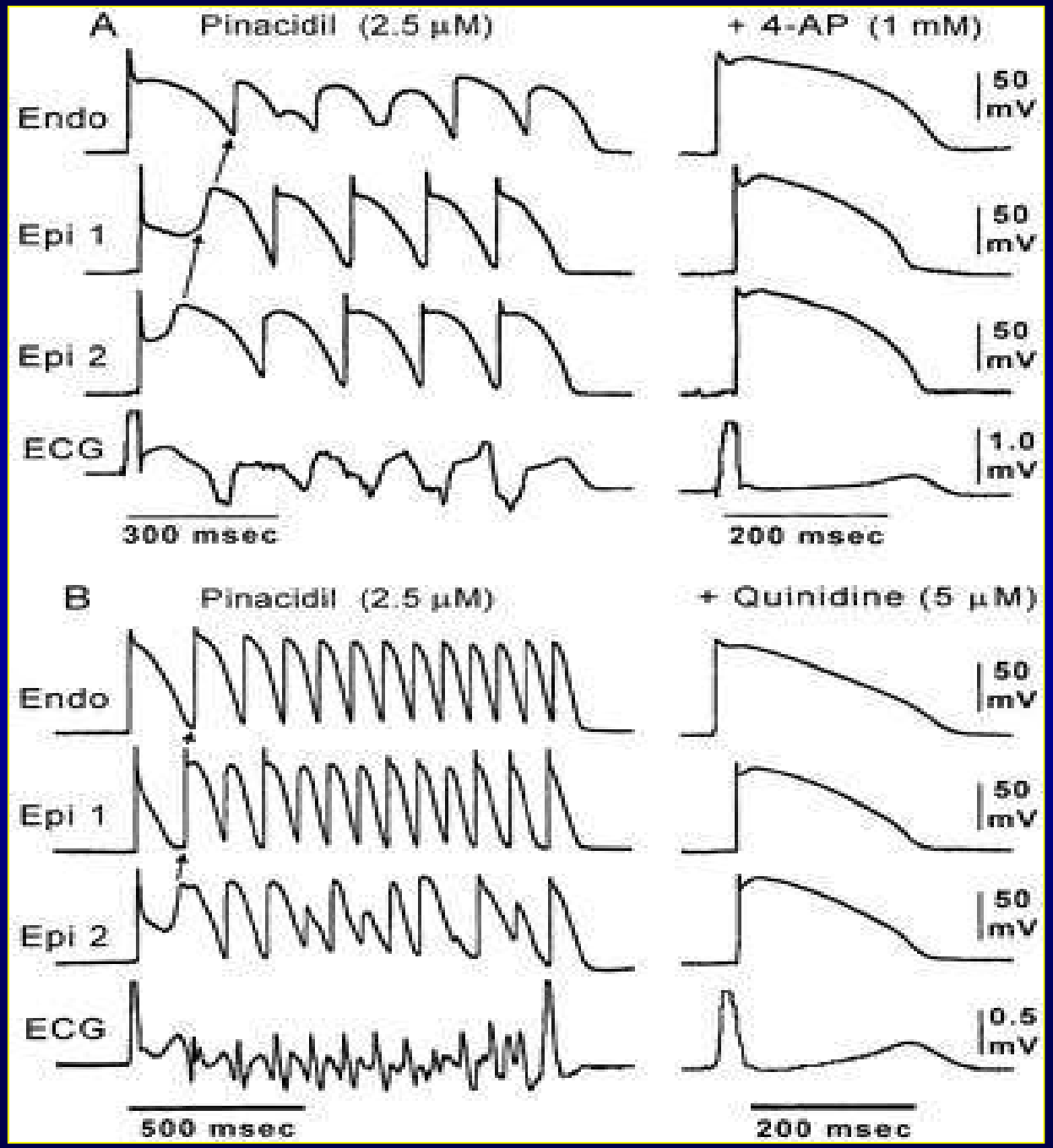


From M Alings Circulation 1999



Réentrée de phase 2 dans une préparation d'épicarde ventriculaire droit de chien exposée à une ischémie.

Lukas & Antzélévitch 1993

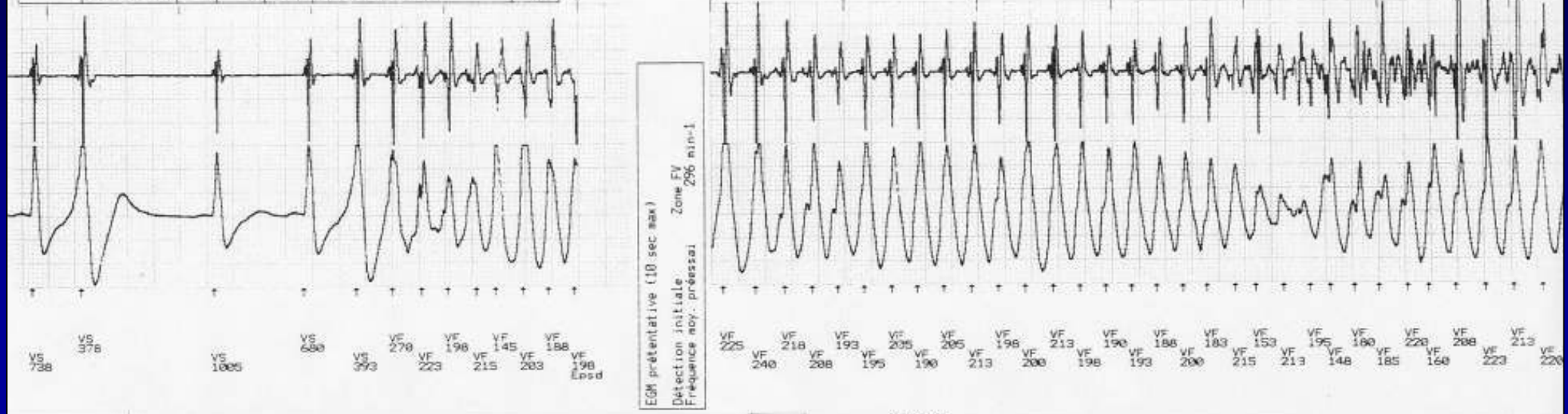


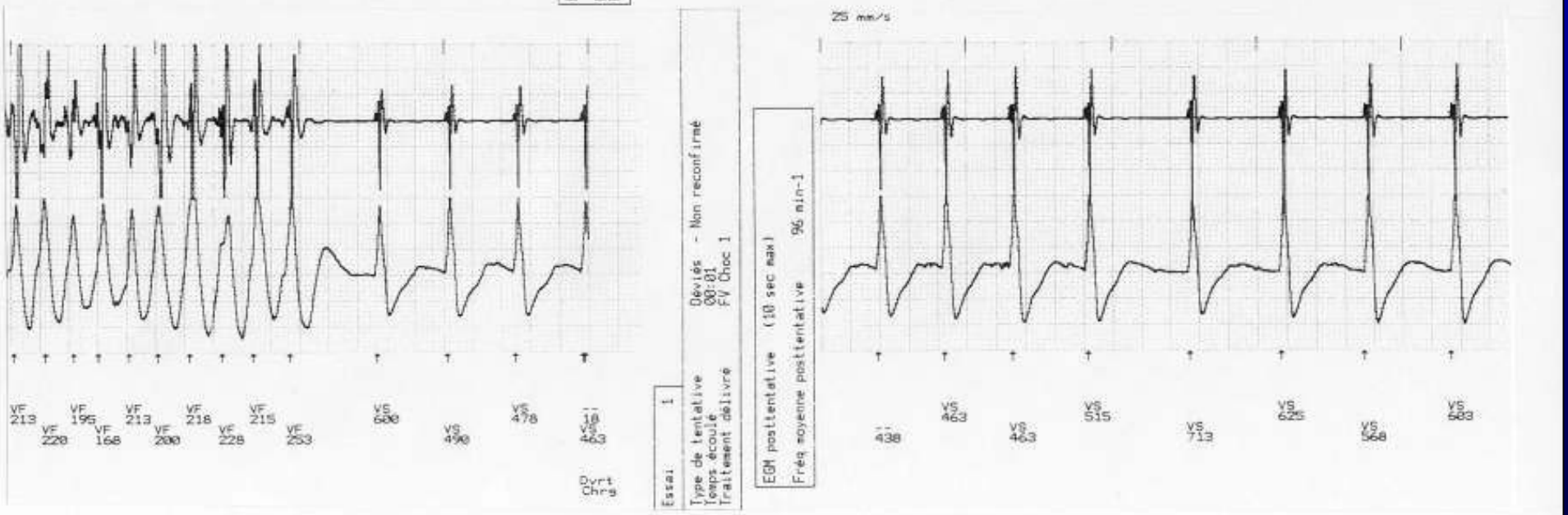
Effects of I_{to} blockers 4-AP and quinidine on pinacidil-induced phase 2 reentry and VT in arterially perfused RV wedge preparation.

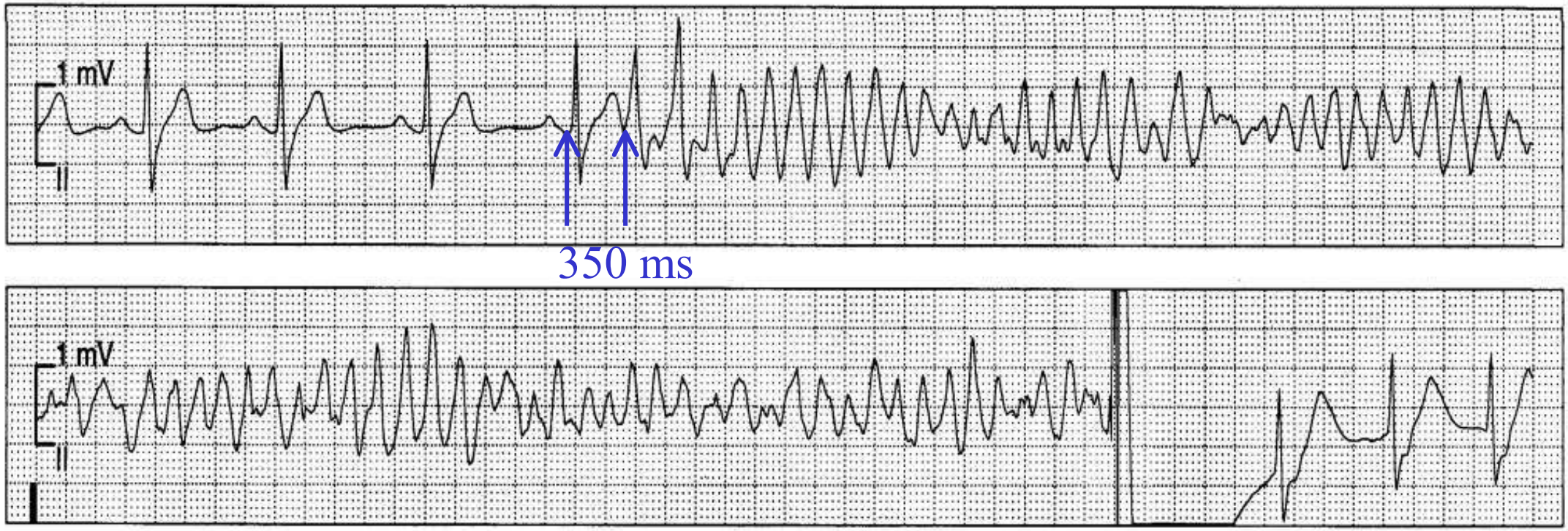
In both examples, 2.5 μmol/L pinacidil produced heterogeneous loss of AP dome in epic, resulting in ST-segment elevation, phase 2 reentry, and VT (left); 4-AP (A) and quinidine (B) restored epic AP dome, reduced both transmural and epicardial disp. of repolarisation, normalized ST segment, and prevented phase 2 reentry and VT in continued presence of pinacidil.

G.X Yan, C Antzelevitch Circulation. 1999;100:1660

Episode et Tentat. Nb.	Date/ heure et temps écoulé m:s	Stab ms	Début	Pré min-1	Traitement	Post min-1
7 1	03-JAN-2001 00:51 00:01	25	44%	296	FV Dévier-Reconf.	96






1 mV
II
350 ms
1 mV
II

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern.

Antagonist

Antoine Leenhardt, MD

Cardiology Department

Lariboisière Hospital

Paris 7 University

Paris, France

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

Position of the problem

- High incidence of events in symptomatic patients : No EPS needed. ICD only life-saving option in these patients.
- Lower risk of sudden death in asymptomatic patients. Questionable value of ICD in these patients : Importance of detection of patients *at risk :* prognostic value of EP in such patients is controversial.

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- This question refers only to ASYMPTOMATIC Brugada patients…
- In whom an EPS is justified (class IIb) :
  - Spontaneous type I Brugada patients
  - Sodium channel blocker-induced type I Brugada with a family history of SCD suspected to be due to BS.

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- Questions :
  - Prevalence of SD in asymptomatic Brugada patients ?
  - Prognostic value of EPS in asymptomatic Brugada patients ?
  - Prevalence of appropriate shocks in asymptomatic Brugada patients with ICD ?
  - Other alternatives ?

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- Questions :
  - Prevalence of SD in asymptomatic Brugada patients ?
  - Prognostic value of EPS in asymptomatic Brugada patients ?
  - Prevalence of appropriate shocks in asymptomatic Brugada patients with ICD ?
  - Other alternatives ?

Brugada Syndrome
Clinical data

	Abnormal basal ECG	Inducible VT/VF	Syncope Arrhythmias
Ressucitated SD	84 %	44 / 54 *83 %*	62 % *(54 ± 54 months)*
Syncope	85 %	41 / 62 *68 %*	19 % *(24 ± 36 months)*
Asymptomatic	58 %	45 / 136 *33 %*	8 % *(27 ± 29 months)*

334 pts, 255 M, 79 W, 42 ± 16 y.

J Brugada et al Circulation 2002; 105: 73-8.

Asymptomatic Brugada Syndrome

Probability of SD or VF during F-up

	Non inducible % (CI)	Inducible % (CI)
Spontaneously abnormal ECG	1.8 (0.6-5.1)	14.0 (8.1-23.0)
ECG abnormal only after AA drug challenge	0.5 (0.1-2.7)	4.5 (1.0-17.1)

J Brugada et al Circulation 2003; 108: 3092-6.

Long-term prognosis of individuals with Brugada Syndrome

Clinical Presentation	Aborted Sudden Death	Syncope	Asymptomatic	*P*
No.	24 (24)	65 (56)	123 (85)	
Male/female	22/2(22/2)	46/19(43/13)	84/39(67/18)	NS
Age, y	45.7±10.8 (45.7±10.9)	45.6±15.6 (46.1±15.0)	43.8±14.4 (46.8±13.0)	NS
Basal coved-type ECG, n	15 (15)	40 (38)	70 (62)	NS
Family history of SCD, n	3 (3)	16 (10)	41 (21)	NS
Family history of BS, n	6 (6)	36 (28)	62 (24)	NS
Inducible VT/VF, n	15 (15)	40 (37)	38 (34)	0.003
Screened for *SCN5A*, n	24 (24)	56 (47)	103 (65)	NS
SCN5A mutations, n	3 (3)	16 (12)	38 (17)	NS
Follow-up, mo	83.2±66.4 (83.2±66.4)	38.9±37.3 (40.3±39.7)	33.7±52.2 (32.4±60.0)	0.0001
Events during F-up	**4 (17 %)**	**4 (6 %)**	**1 (0,8 %)**	

212 individuals (mean age, 45 ± 6 years) with a type 1 Brugada ECG pattern

From L Eckardt et al. Circulation. 2005;111:257-263.

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- Questions :
  - Prevalence of SD in asymptomatic Brugada patients ?
  - Prognostic value of EPS in asymptomatic Brugada patients ?
  - Prevalence of appropriate shocks in asymptomatic Brugada patients with ICD ?
  - Other alternatives ?

EPS value in the asymptomatic Brugada syndrome

- The stimulation protocol (site, nb of extra stimuli, coupling interval) greatly influences the degree of inducibility.
- Short coupling interval of less than 200 ms are necessary to induce more patients (39 % of symptomatic patients and 45 % of asymptomatic patients would not have been inducible).

From L Eckardt et al Eur Heart J. 2002; 23:1394-1401.

Brugada Syndrome

Probability of SD or VF : clinical and EP data

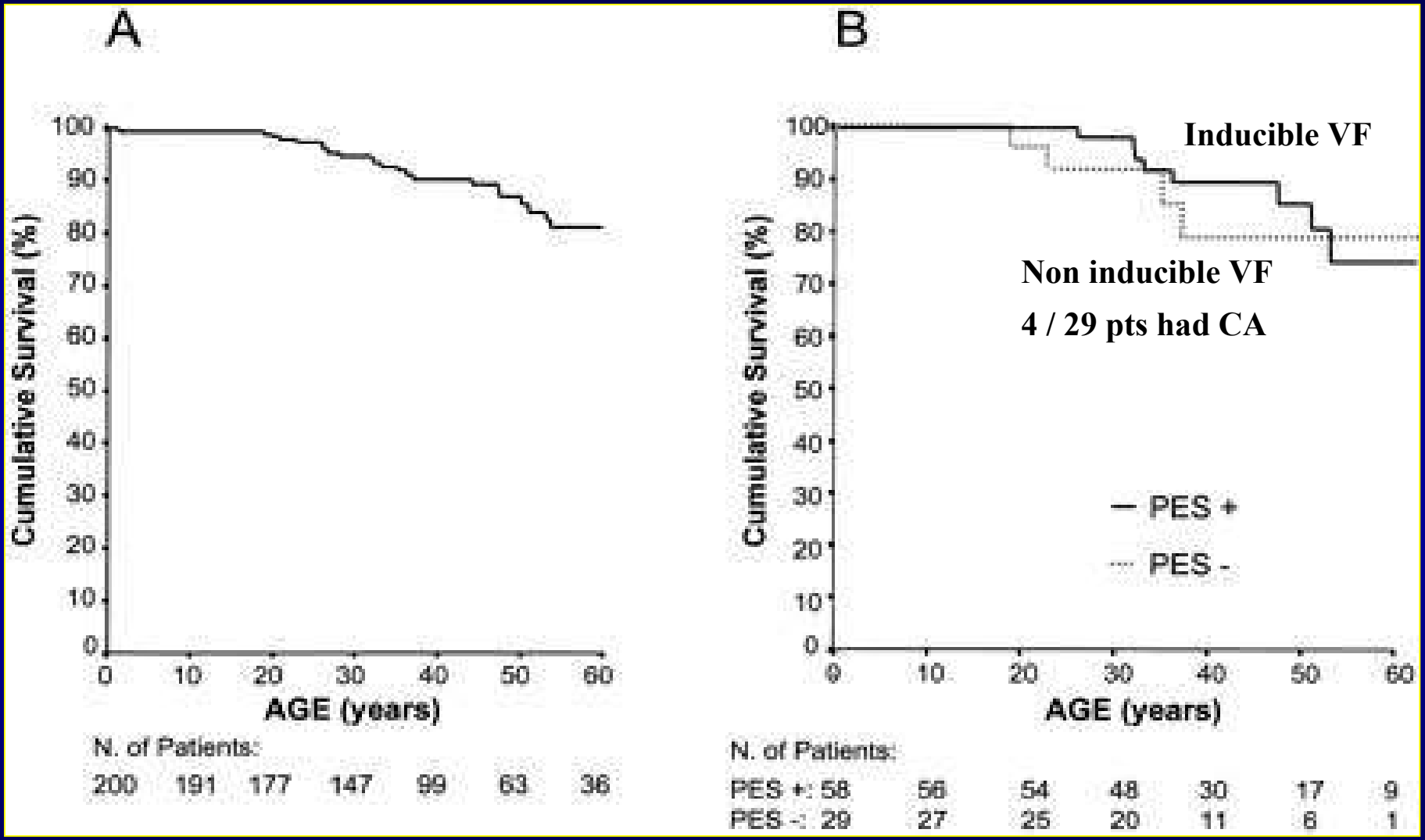
Multivariate analysis

	Hazard ratio	95 % CI	*P*
Inducible	5.88	2.0-16.7	0.0001
Syncope	2.50	1.2-5.3	0.017
Abnormal basal ECG	2.86	0.7-12.3	0.103

547 patients with no previous cardiac arrest. F-up : 24±33 months

J Brugada et al Circulation 2003; 108: 3092-6.

Risk stratification in Brugada syndrome



A, Kaplan-Meier analysis of cumulative survival from CA in 200 patients affected with Brugada syndrome (130 probands and 70 affected family members).

B, Kaplan-Meier analysis of cumulative survival from cardiac arrest, based on the outcome of PES. Log-rank test, *P*>0.05, NS.

From S Priori et al. Circulation. 2002;105:1342

Long-term prognosis of individuals with Brugada Syndrome

Clinical Presentation	Aborted Sudden Death	Syncope	Asymptomatic	*P*
No.	24 (24)	65 (56)	123 (85)	
Male/female	22/2(22/2)	46/19(43/13)	84/39(67/18)	NS
Age, y	45.7±10.8 (45.7±10.9)	45.6±15.6 (46.1±15.0)	43.8±14.4 (46.8±13.0)	NS
Basal coved-type ECG, n	15 (15)	40 (38)	70 (62)	NS
Family history of SCD, n	3 (3)	16 (10)	41 (21)	NS
Family history of BS, n	6 (6)	36 (28)	62 (24)	NS
Inducible VT/VF, n	15 (15)	40 (37)	38 (34)	0.003
Screened for *SCN5A*, n	24 (24)	56 (47)	103 (65)	NS
SCN5A mutations, n	3 (3)	16 (12)	38 (17)	NS
Follow-up, mo	83.2±66.4 (83.2±66.4)	38.9±37.3 (40.3±39.7)	33.7±52.2 (32.4±60.0)	0.0001
Events during F-up	**4 (17 %)**	**4 (6 %)**	**1 (0,8 %)**	

212 individuals (mean age, 45 ± 6 years) with a type 1 Brugada ECG pattern

4 of 9 patients with arrhythmic events during follow-up were not inducible during PES.

From L Eckardt et al. Circulation. 2005;111:257-263.

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- Questions :
  - Prevalence of SD in asymptomatic Brugada patients ?
  - Prognostic value of EPS in asymptomatic Brugada patients ?
  - Prevalence and predictive factors of appropriate shocks in asymptomatic Brugada patients with ICD ?
  - Other alternatives ?

Outcome of patients with Brugada syndrome according to ICD indication

	Syncope (n=88)	Asymptomatic (n=114)	Resuscitated SCD (n=18)
Median follow-up, months	39.5 (19-59)	31 (17-52)	25.5 (10.5-49.5)
Patients with appropriate shocks	9 (10)	5 (4)	4 (22)
Median delay to first shock, mo	24 (6.5-48)	18 (1.5-43)	2.5 (2-7.5)
Median shock	4 (2-17)	4 (2.5-11)	5.5 (1-10.75)
Patients with complications	22 (25)	35 (31)	5 (28)
Patients with inappropriate shocks	23 (20)	23 (20)	3 (17)
ICD implantation data available	78 (88)	101 (89)	17 (94)
High DFT	12 (15)	10 (10)	2 (12)
High pacing threshold	19 (24)	29 (29)	5 (29)
Low R-wave amplitude	9 (12)	19 (19)	1 (6)

Summary

18 (8%)

62 (28%)

45 (20%)

Mean follow-up of 38 ± 27 months

From F. Sacher et al. Circulation. 2006;114:2317-24.

Predictive factors of appropriate shocks

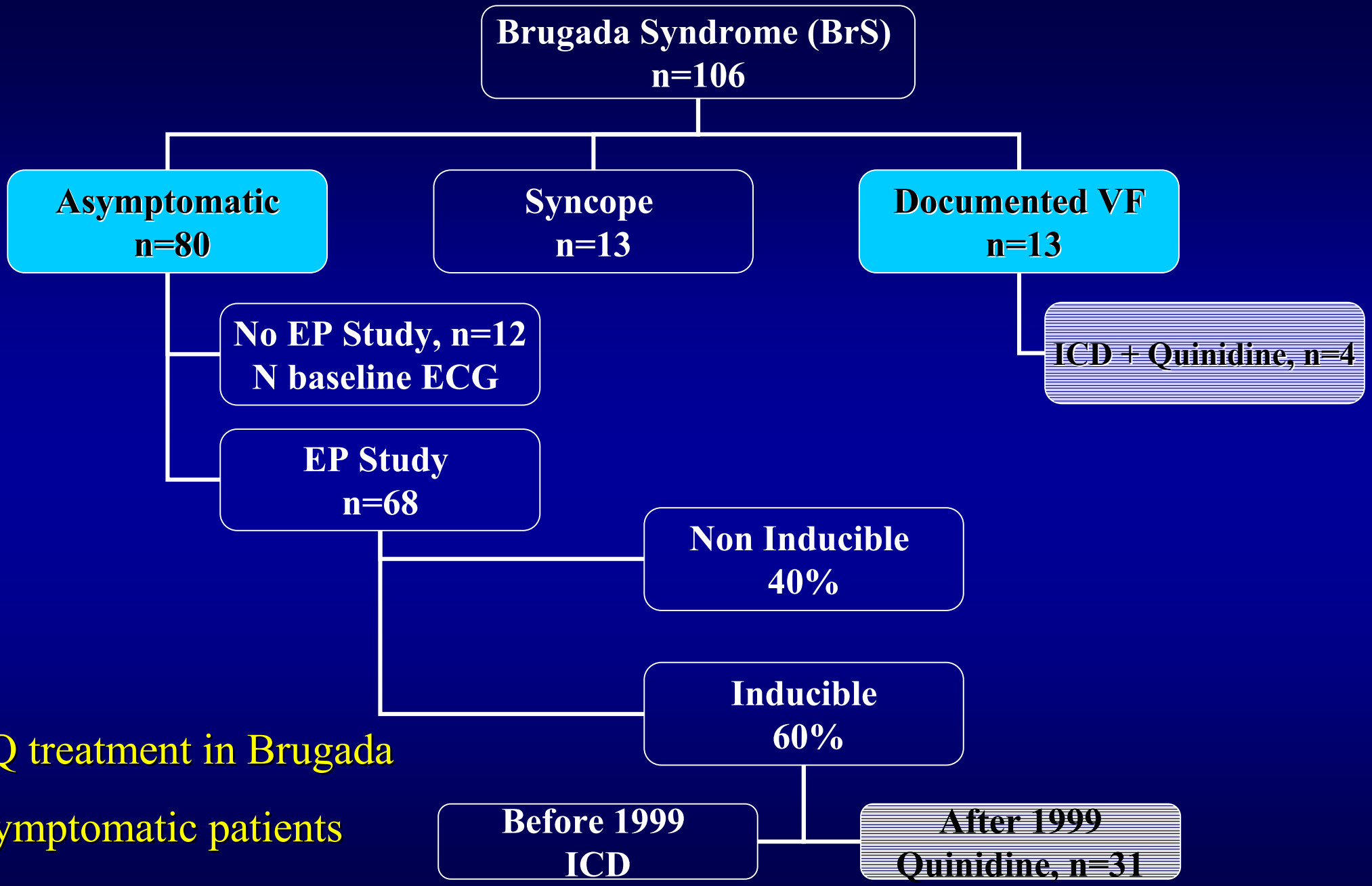
	Appropriate Shock, n (%) (n=18)	Unadjusted HR (95% CI)	*P*	Adjusted HR* (95% CI)	*P*
Sex, male	16 (89)	0.58 (0.13-2.53)	0.47	0.47 (0.10-2.22)	0.34
Family history of SCD	5 (28)	0.31 (0.10-0.96)	0.04	0.33 (0.10-1.07)	0.07
History of supraventricular tachycardia	2 (11)	1.03 (0.23-4.61)	0.97	1.52 (0.32-7.26)	0.60
Spontaneous type 1 ECG	15 (83)	1.40 (0.45-4.32)	0.56	0.95 (0.29-3.09)	0.93
No. of patients with EPS	15 (83)				
Inducible at EPS	13 (87)	1.30 (0.63-2.60)	0.50	0.86 (0.40-1.86)	0.70
Patients with genetic test	8 (44)				
SCN5A mutation	2 (25)	0.73 (0.34-1.60)	0.44	0.63 (0.27-1.45)	0.27
ICD implantation data available	16 (89)				
High DFT	2 (13)	0.45 (0.09-2.20)	0.32	0.38 (0.06-2.33)	0.30
High pacing threshold	6 (38)	1.69 (0.61-4.69)	0.31	2.00 (0.72-5.56)	0.19
Low R-wave amplitude	2 (13)	0.76 (0.17-3.45)	0.72	1.46 (0.30-7.19)	0.65

*Adjusted for age and indication of ICD.

F. Sacher et al. Circulation. 2006;114:2317-24.

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- Questions :
  - Prevalence of SD in asymptomatic Brugada patients ?
  - Prognostic value of EPS in asymptomatic Brugada patients ?
  - Prevalence of appropriate shocks in asymptomatic Brugada patients with ICD ?
  - Other alternatives ?



HQ treatment in Brugada asymptomatic patients

Hermida JS et al JACC 2004

Methods- Study Population

- 31 Asymptomatic BrS patients with inducible arrhythmia received hydroquinidine chlorhydrate (HQ) (Male=31, mean age 48±11years).
  - EP guided therapy
  - HQ doses were adjusted according to plasmatic level in case of persistent VT/VF inducibility under 600 mg/d
  - When VT/VF inducibility was not prevented or in case of HQ intolerance, an ICD was implanted

HQ treatment in Brugada asymptomatic patients : conclusions

1- In this preliminary study, HQ prevented VT/VF inducibility in 76% (22/29) of asymptomatic patients with BrS and inducible arrhythmia.

2-During long term therapy:

- 2/21 arrhythmic events under HQ. Outcome of Tx might have been improved by a careful monitoring of QT interval (10% QT interval prolongation)
- 19 patients without any event with a mean 3 y. F-up.

EP-Guided Quinidine Therapy ADVANTAGES

- Prevents arrhythmic events (NSVT/VF)
- Low cost
- Low incidence rate of hospitalizations
- Bridge to ICD (young patients +++)
- “Noninvasive” mode of treatment

ICD DISADVANTAGES

- Does not prevent NSVT and VF (adjuvant AA drugs frequently required)
- ICD complications (infections, leads problems, spurious shocks, psychological disorders, etc..) without available long-term data
- High cost (multiple replacements)

MANAGEMENT OF ASYMPTOMATIC BRUGADA SYNDROME

EP-guided quinidine therapy may be a reasonable therapy if:

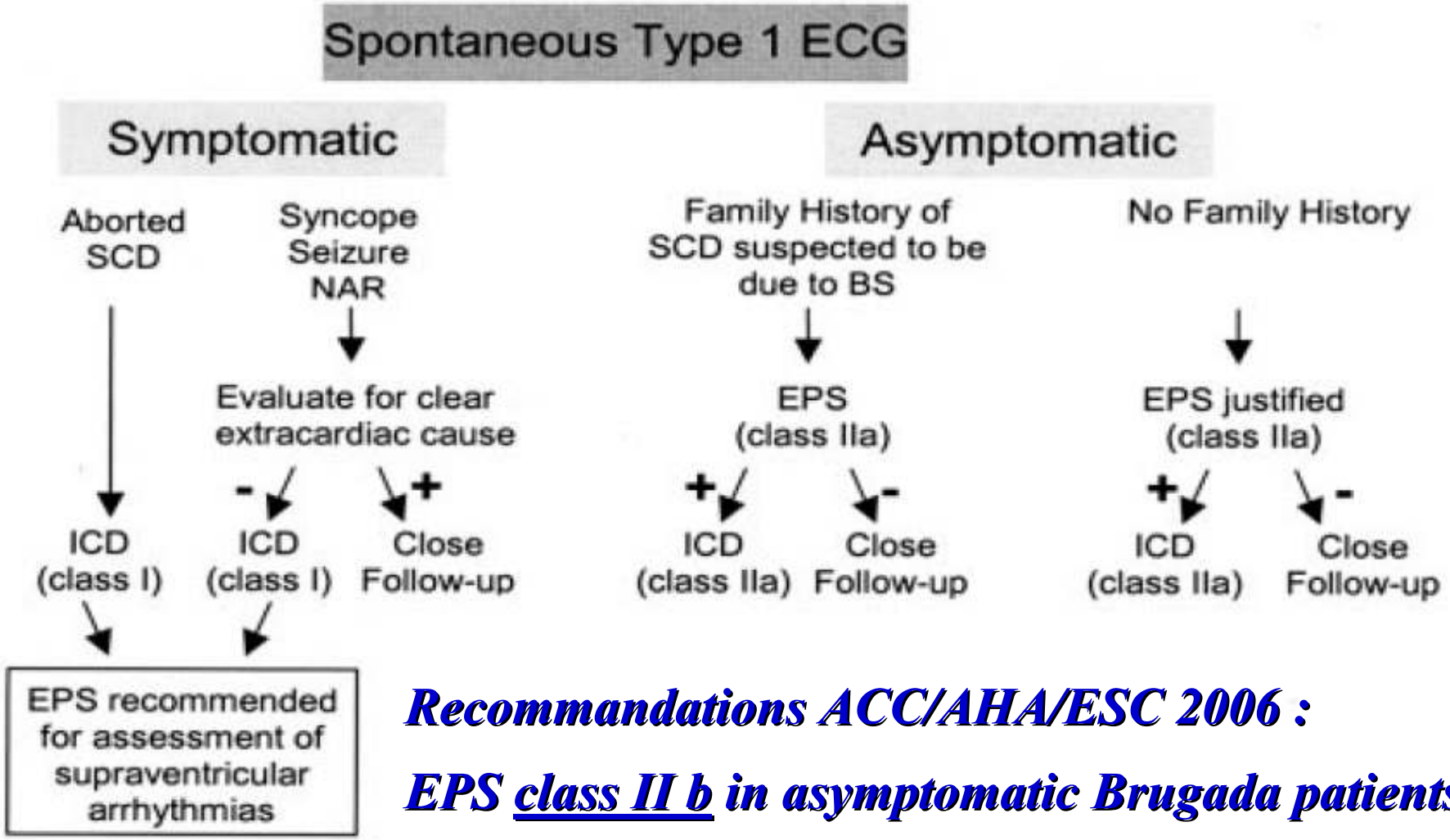
- Patients have inducible VF at EPS
- Quinidine prevents VF re-induction
- Patients exhibit a good tolerance to the medication
- Patients are willing to commit themselves to a long-life drug regimen.

Randomized clinical trials comparing ICD therapy and Quinidine therapy seem warranted.

An ICD should be implanted in all the inducible patients with a Brugada ECG pattern ?

- This question refers only to ASYMPTOMATIC Brugada patients
- The answer is NO, for the following reasons :
  - Low prevalence of SD in asymptomatic Brugada patients
  - Questionable prognostic value of EPS in Brugada patients
  - Low prevalence of appropriate shocks and high prevalence of inappropriate shocks in asymptomatic Brugada patients with ICD
  - Other alternatives : quinidine may be an alternative.

Indications for ICD implantation in Brugada syndrome



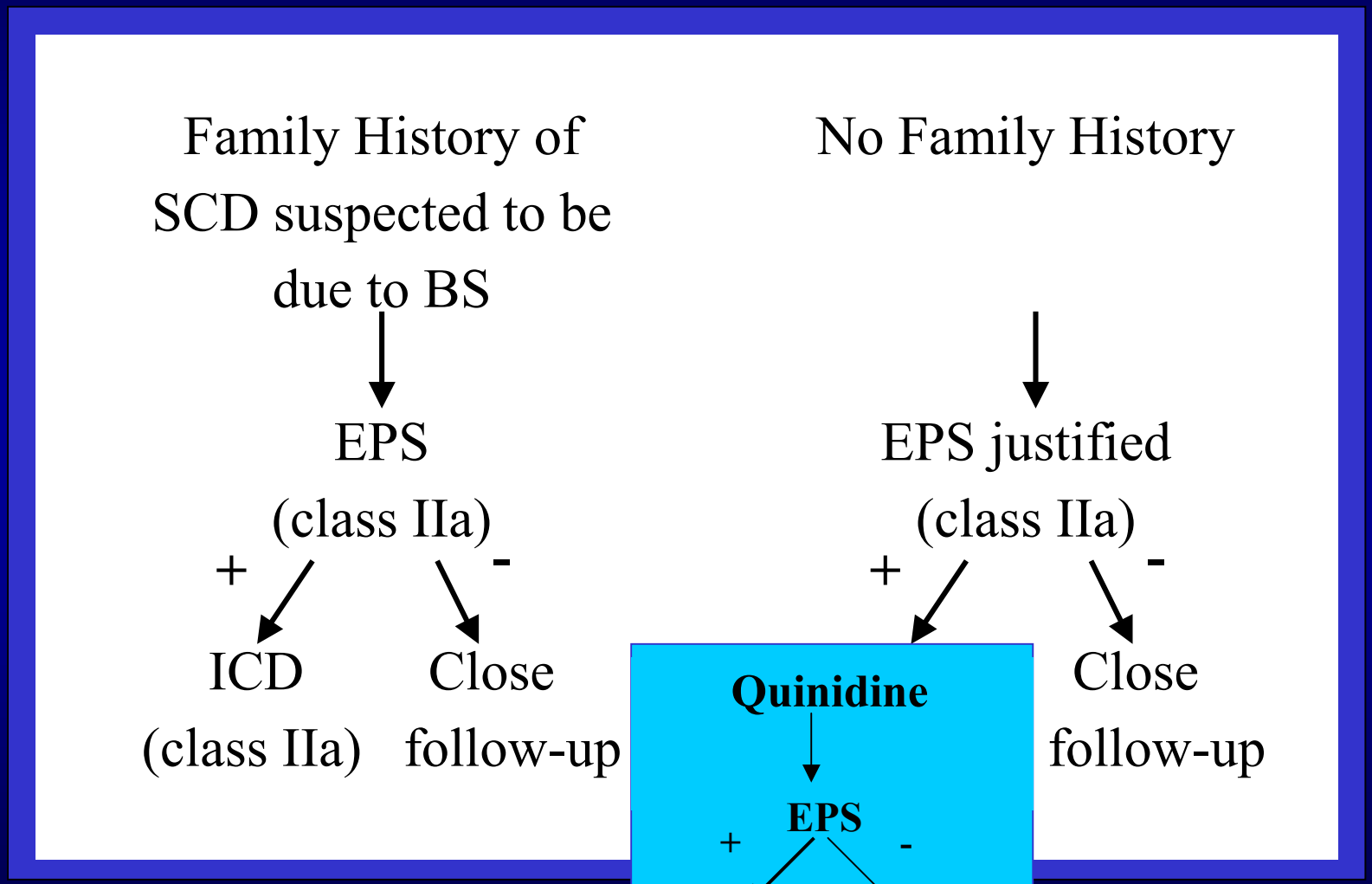
Recommandations ACC/AHA/ESC 2006 :

EPS class II b in asymptomatic Brugada patients.

Second consensus conference

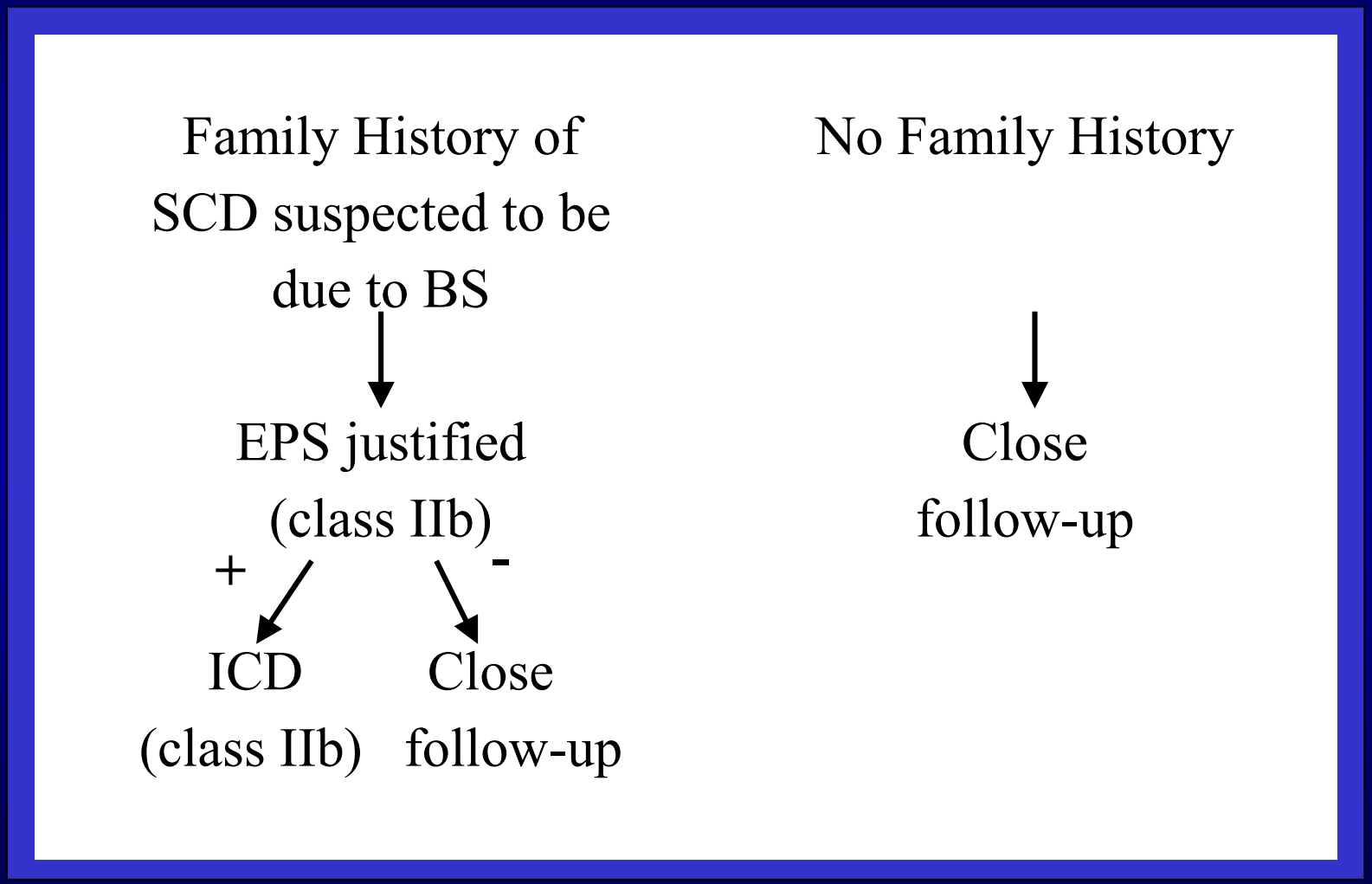
C. Antzelevitch et al Circulation. 2005;111:659-70

Asymptomatic spontaneous type 1 Brugada



Lariboisiere's Hospital rules since 2003

Asymptomatic sodium channel blocker-induced type 1 Brugada



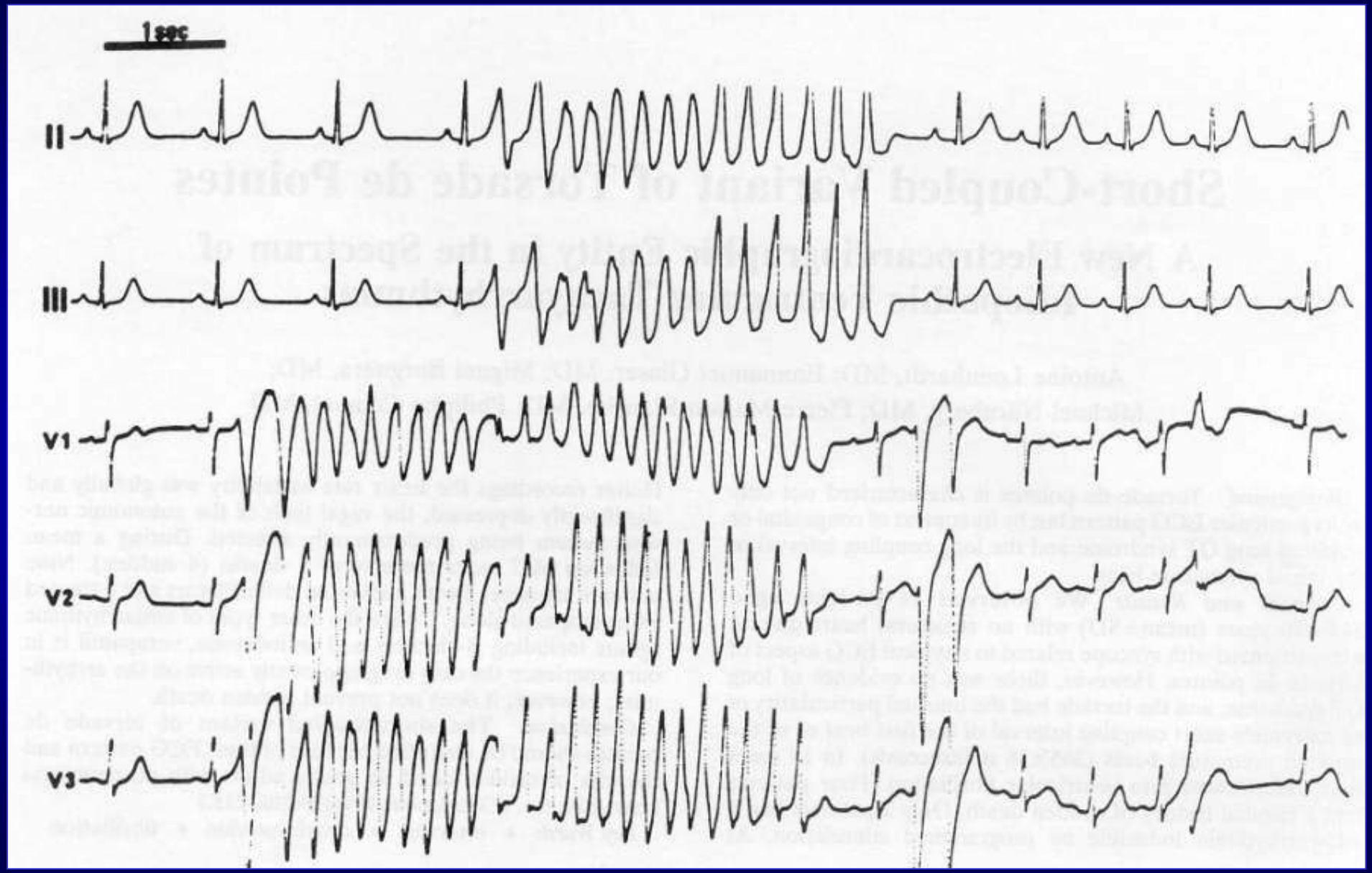
Second consensus conference

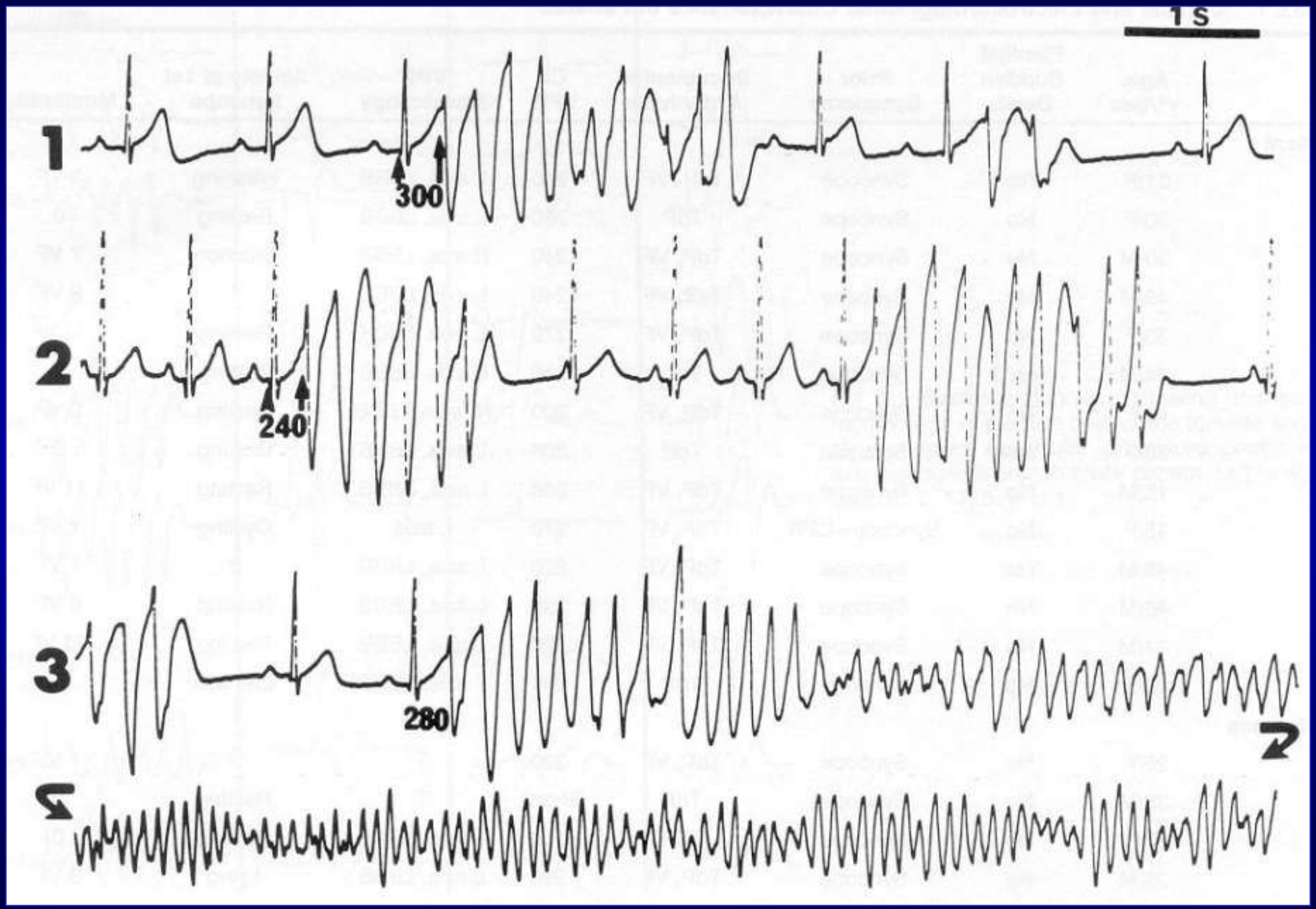
C. Antzelevitch et al Circulation. 2005;111:659-70

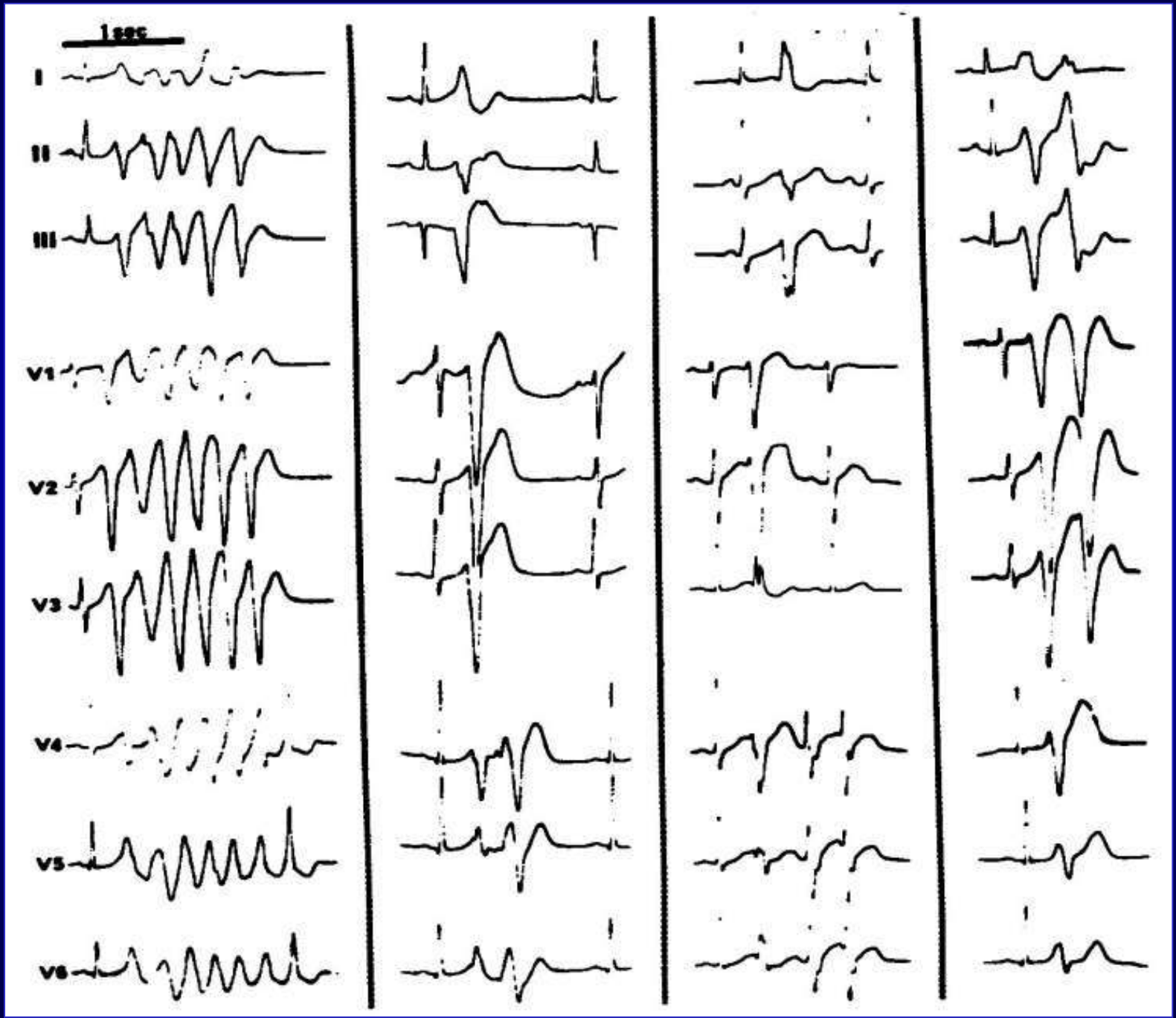
SHORT-COUPLED TORSADES DE POINTES

PATIENTS

- 20 patients (13 women), mean age 34.9 +/-12 years
- History of syncope : documented TdP : 20, VF : 14
- No structural heart disease
- No surface ECG abnormality (normal QT)
- Familial history of sudden death : 7 pts.
- F. up : 3 - 19 years (8 ± 5)


1sec
II
III
V1
V2
V3


1 s
1
300
2
240
3
280


1sec
I
II
III
V1
V2
V3
V4
V5
V6

SHORT-COUPLED TORSADES DE POINTES

TREATMENT

- No efficacy of class I antiarrhythmic agents, beta-blockers, and amiodarone in the first 14 patients.
- Verapamil :
  - ECG and clinical efficacy
  - No accurate sudden death prevention
- Systematic ICD implantation.
- Role of RF ablation ?