Brugada Syndrome and Sudden Cardiac Death

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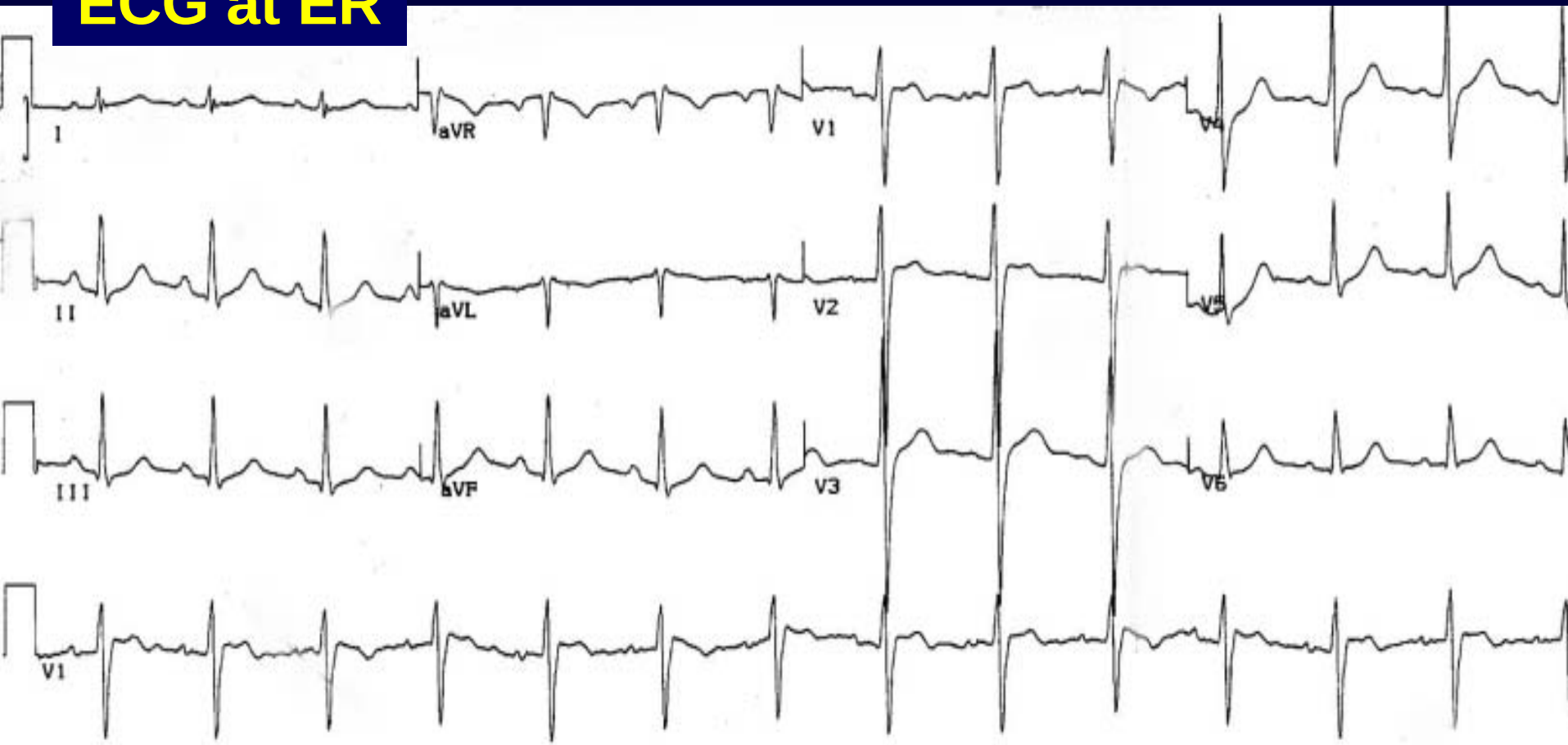
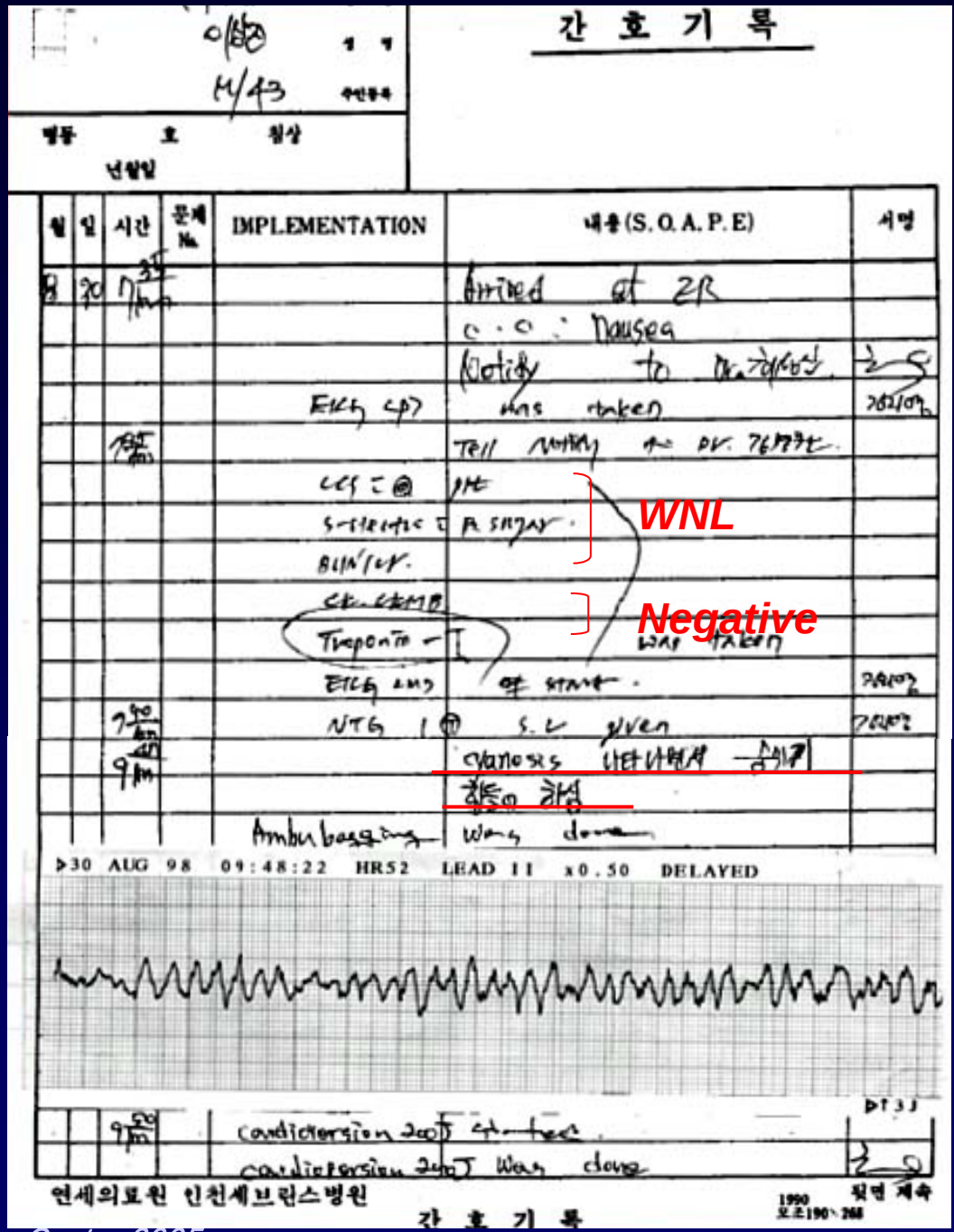
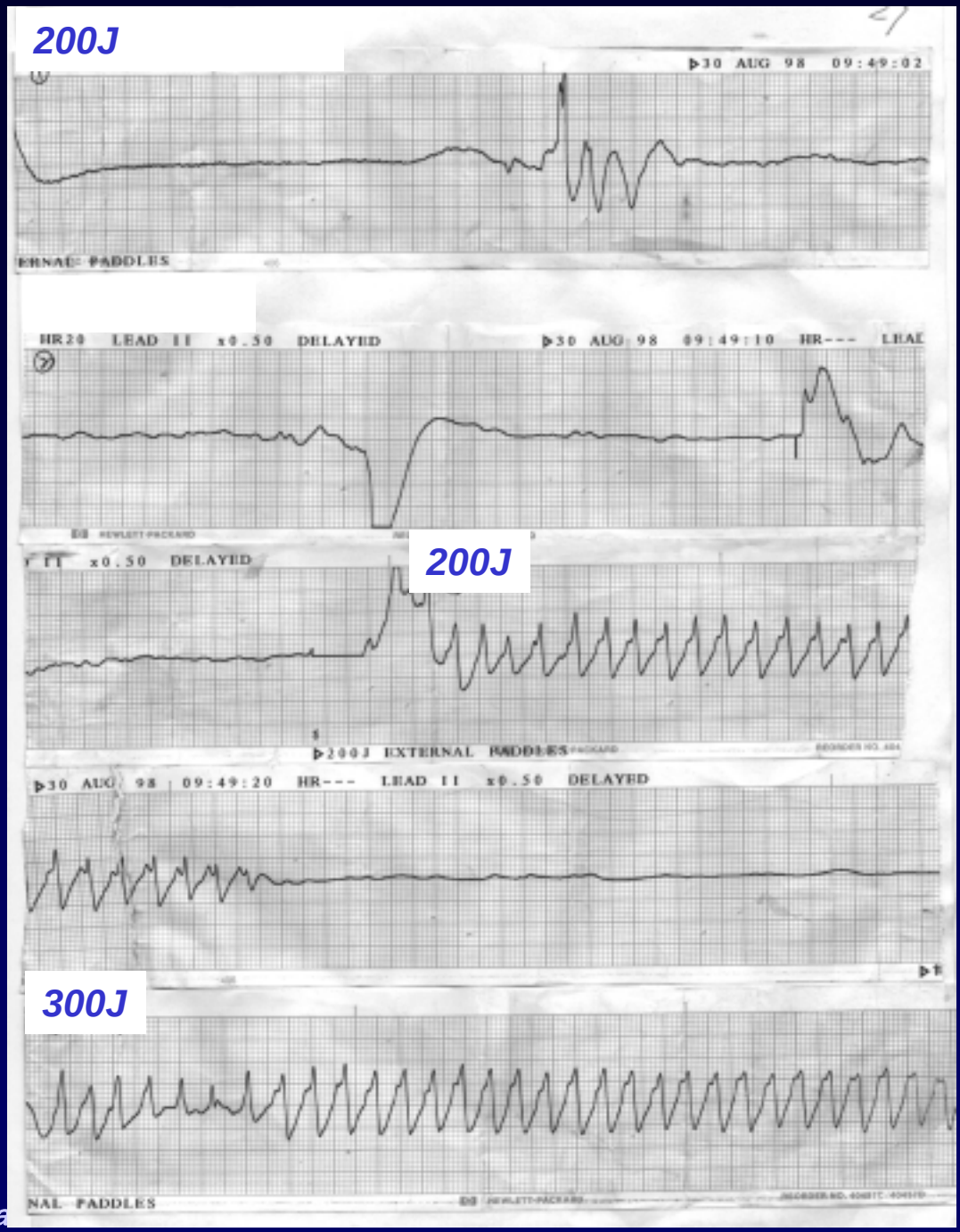
43-year-old Male School teacher

Two episodes of agonal breathing while asleep 1 week apart

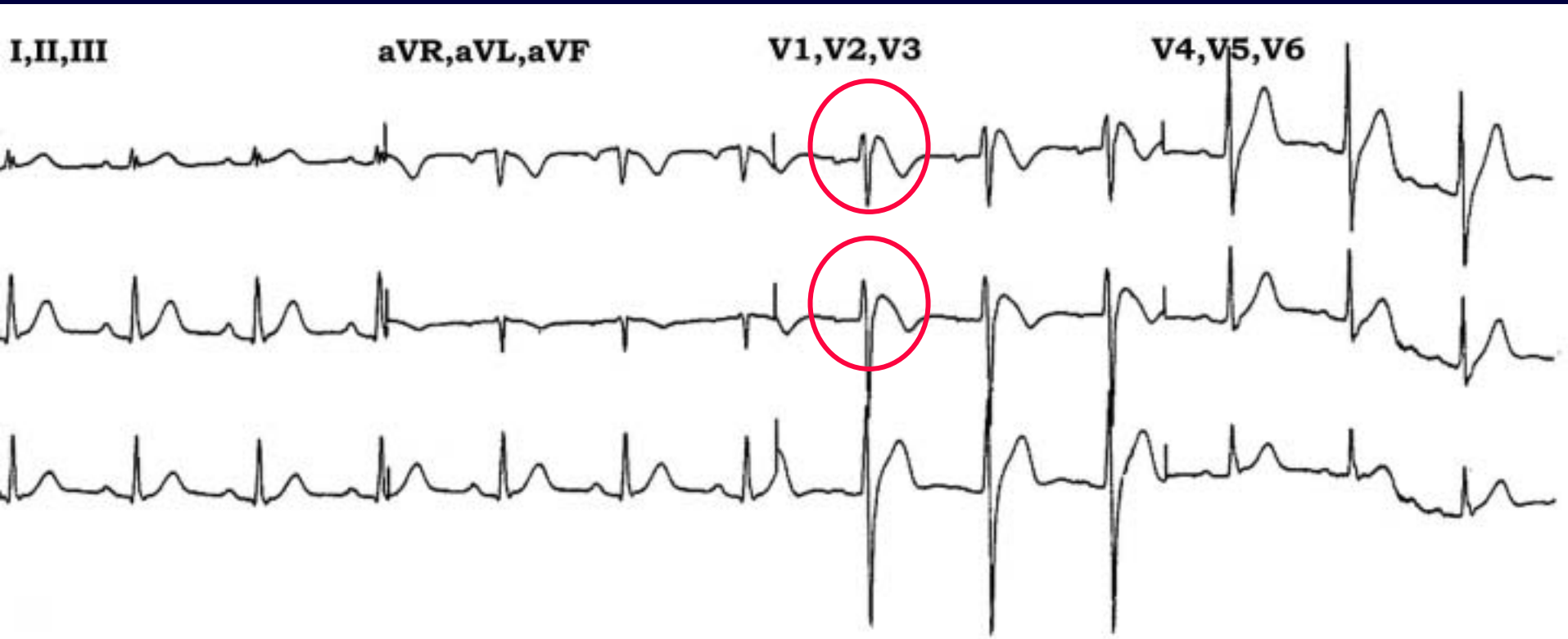
ECG at ER



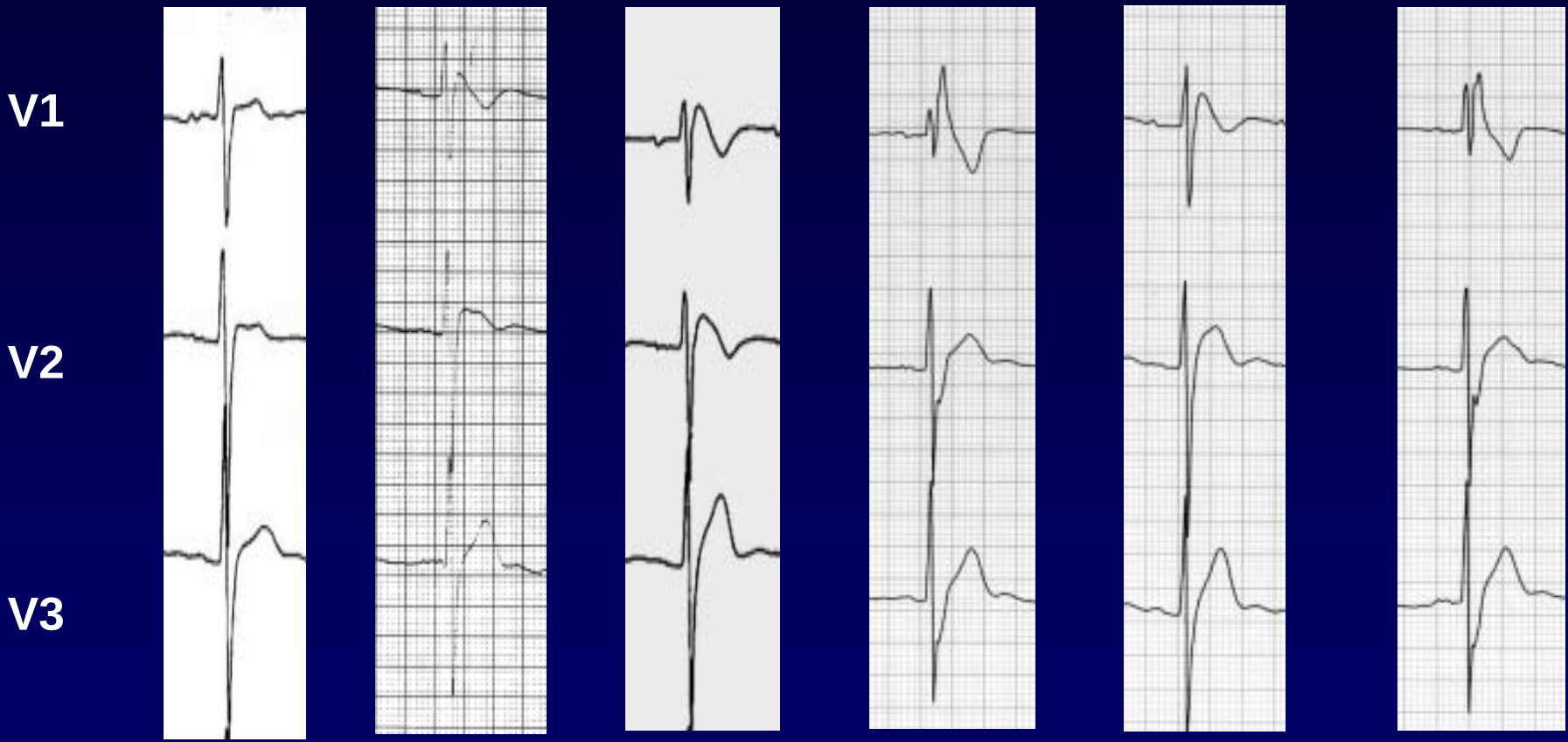



200J
30 AUG 98 09:49:02
HR20 LEAD II x0.50 DELAYED
30 AUG 98 09:49:10 HR--- LEAD
200J
200J EXTERNAL PADDLES
30 AUG 98 09:49:20 HR--- LEAD II x0.50 DELAYED
300J

ECG after Cardioversion



Dynamic ST segment changes



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

A Multicenter Report

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD*†

Aalst, Belgium and Barcelona, Spain

Objectives. The objectives of this study were to present data on eight patients with recurrent episodes of aborted sudden death unexplainable by currently known diseases whose common clinical and electrocardiographic (ECG) features define them as having a distinct syndrome different from idiopathic ventricular fibrillation.

Background. Among patients with ventricular arrhythmias who have no structural heart disease, several subgroups have been defined. The present patients constitute an additional subgroup with these findings.

Methods. The study group consisted of eight patients, six male and two female, with recurrent episodes of aborted sudden death. Clinical and laboratory data and results of electrocardiography, electrophysiology, echocardiography, angiography, histologic study and exercise testing were available in most cases.

Results. The ECG during sinus rhythm showed right bundle branch block, normal QT interval and persistent ST segment elevation in precordial leads V_1 to V_2–V_3 not explainable by electrolyte disturbances, ischemia or structural heart disease. No histologic abnormalities were found in the four patients in whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic ventricular tachycardia initiating after a short coupled ventricular extrasystole. A similar arrhythmia was initiated by two to three ventricular extrastimuli in four of the seven patients studied by programmed electrical stimulation. Four patients had a prolonged HV interval during sinus rhythm. One patient receiving amiodarone died suddenly during implantation of a demand ventricular pacemaker. The arrhythmia of two patients was controlled with a beta-adrenergic blocking agent. Four patients received an implantable defibrillator that was subsequently used by one of them, and all four are alive. The remaining patient received a demand ventricular pacemaker and his arrhythmia is controlled with amiodarone and diphenylhydantoin.

Conclusions. Common clinical and ECG features define a distinct syndrome in this group of patients. Its causes remain unknown.

(J Am Coll Cardiol 1992;20:1391–6)

Additional features associated Brugada Syndrome

1. Male predominance
2. Familial incidence

   Autosomal dominant inheritance
3. Molecular defect :

   Mutation in cardiac Na channel gene (SCN 5A)

   -channelopathy
4. Characteristic response to pharmacologic testing with

   Class IA or IC (procainamide, flecainide, ajmalin)
5. Induction of VF during PES

Sudden Unexplained Death Syndrome (SUDS) in Southeast Asia

1. Sudden unexplained death without preceding distress
2. Young healthy men (20-40 yrs old)
3. Occurring at night while asleep
4. No explainable obvious cardiac pathology
5. Southeast refugees from Laos, Cambodia and Vietnam

- Philippine : “ban gun gut” (moaning during sleep)
- Japan : “Pokkuri” (sudden unexpected death)
- Thailand : “lai tai” (sleep death)
- Annual prevalance
  1/2,500 in Thailand
  1/1,000 in Laos

Arrhythmogenic Marker for the Sudden Unexplained Death Syndrome in Thai Men

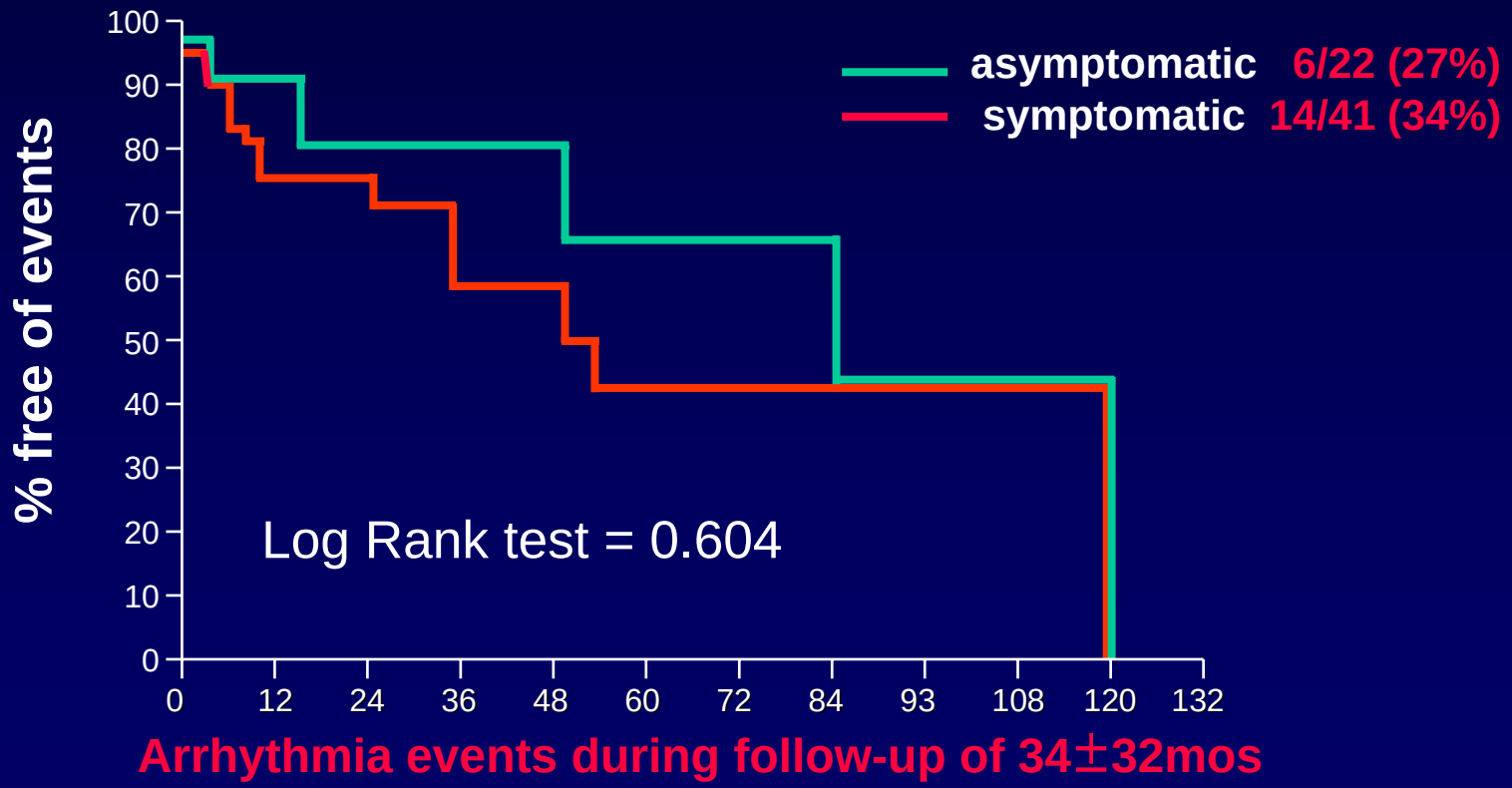
- Characteristics of 27 patients -

	Group 1 Brugada type ECG	Group 2 Normal ECG
No. of patients	16	11
Mean age, yrs	40 ± 12	39 ± 8
History of documented VF, n(%)	14(88)	3(27)
Inducible VT/VF, n(%)	13/14(93)	1/9(11)
Late potential on SAECG, n(%)	11/13(92)	1/9(11)
HV interval	63 ± 11	49 ± 6
Arrhythmia event, n(%) (Follow-up 11.8 ± 8 mos)	10/16(63)	2/11(18)

Nademanee K et al. Circulation 1997;96:2595

RBBB and ST-Segment Elevation in Leads V1 Through V3

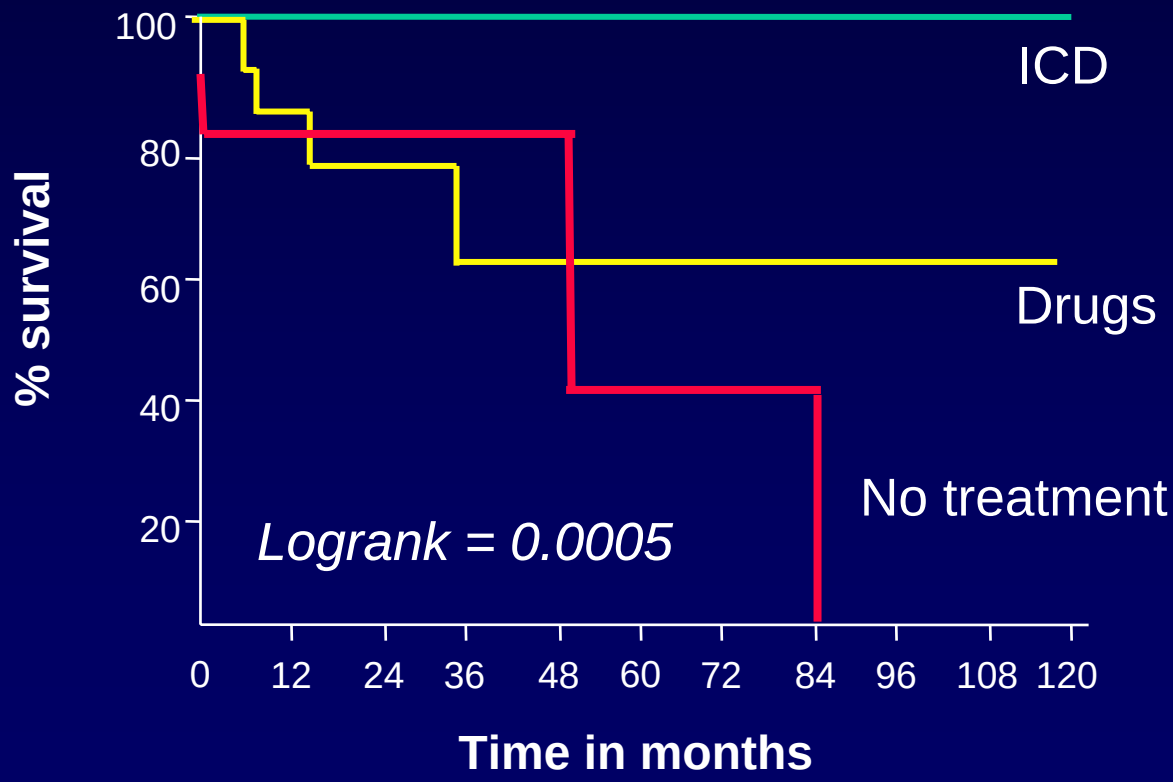
Recurrence of first VT or Sudden death



Brugada J et al. Circulation 1998;97:457

RBBB and ST-Segment Elevation in Leads V1 Through V3

Survival according to treatment



Brugada J et al. Circulation 1998;97:457

Long-Term Follow-up of Individuals With the ECG Pattern of RBBB and ST-Segment Elevation in Precordial Leads V1 to V3

Clinical Presentation	Aborted Sudden Death	Syncope	Asymptomatic	*P*
No.	71	73	190	
Male/female	61/10	59/14	135/55	0.007
Age.yrs	41±16	47±14	40±16	0.03
Basal abnormal ECG	61 (84%)	62 (85%)	111 (58%)	0.0001
Family history of SCD	23 (38%)	26 (39%)	131 (72%)	0.0001
EPS-VF ind	83%	63%	33%	
Arrhythmic event	62%	19%	8%	
Follow-up (mos)	54±54	26±36	27±29	

Brugada J et al. Circulation 2002;105:73

Incidence of Brugada-type ECG in General Population

- Fujimori K et al. Circulation 2000;102(suppl II)–676:3268

  0.48% (140 / 34,520)

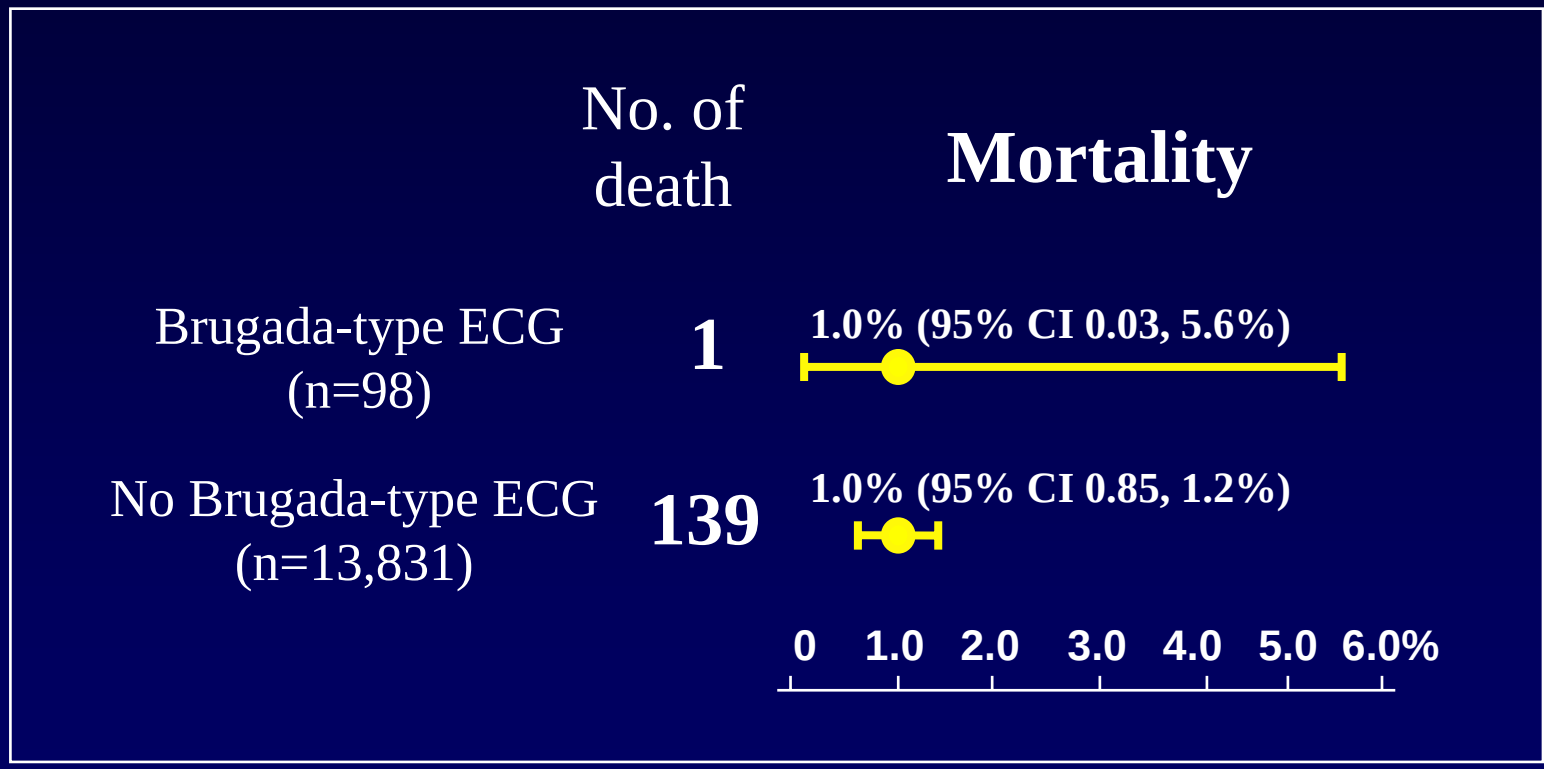
- Atarashi H et al. JACC 2001;37:1916

  0.16% (16 / 10,000)

- Miyasaka Y et al. JACC 2001;38:771

  0.7% (98 / 13,929)

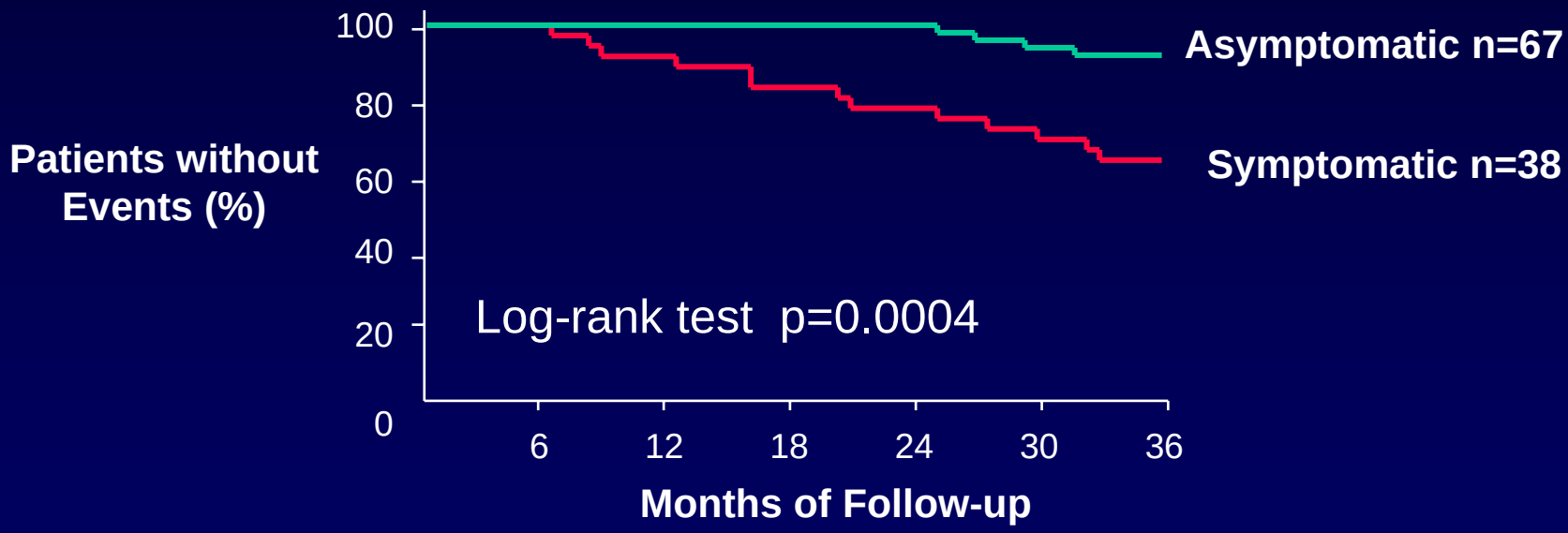
Prevalence and Mortality of the Brugada-Type ECG in One City in Japan



The total mortality of subjects with the Brugada-type ECG did not differ from the mortality of those without the Brugada-type ECG in a community-based population.

Miyasaka Y et al. JACC 2001;771

Three-year Prospective Follow-Up of Patients With RBBB and ST Segment Elevation in the Right Precordial Leads



Arrhythmia event during 3 years follow-up

Symptomatic : 25.7%

Asymptomatic : 1.5%

Atarashi H et al. JACC 2001;37:1916

Clinical and Genetic Heterogeneity of RBBB and ST-Segment Elevation Syndrome
- A Prospective Evaluation of 52 Families -

60 patients with typical Brugada ECG pattern

(45 males, mean age 40±15 yrs)

- VF recurrence during 33±38 mos follow-up

  Symptomatic patients 5/30 (16%)

  Asymptomatic patients 0/30 (0%)

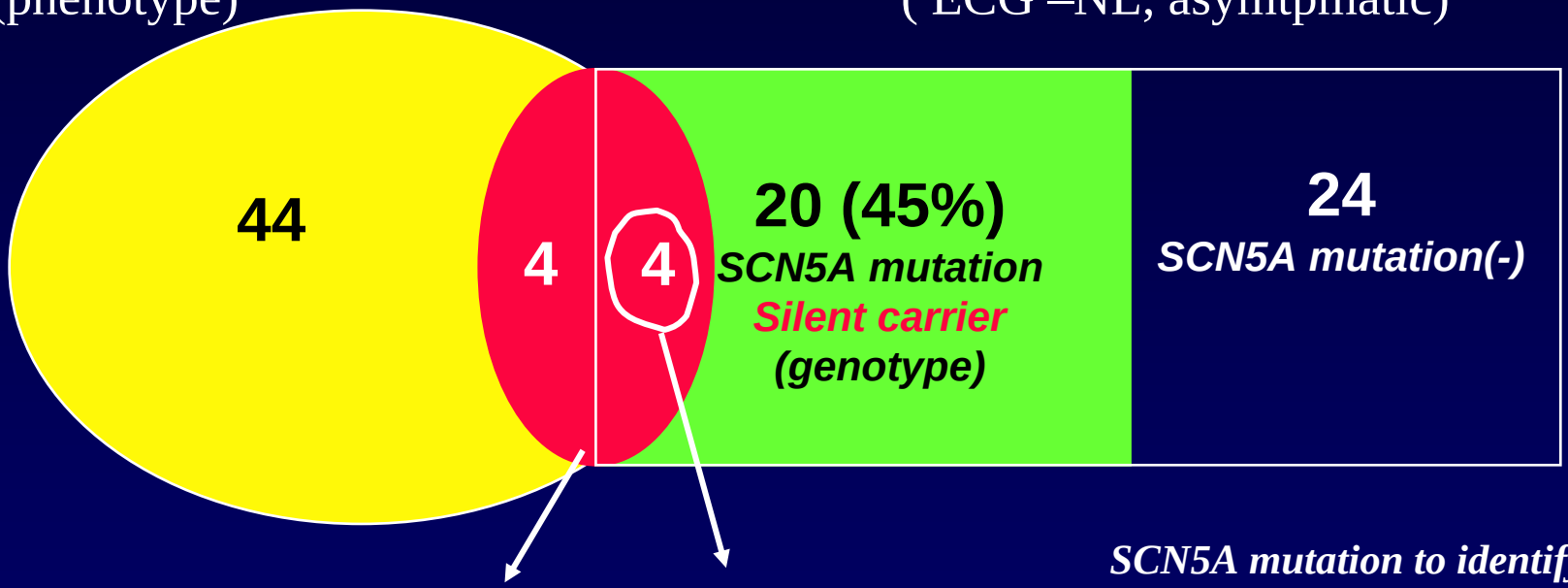
- EPS : Positive predictive value : 50%

  Negative predictive value : 46%

- Drug test positive predictive value : 35%

Priori S et al. Circulation 2000;102:2509

Genetic Analysis in 52 Probands



8/52 (15%)
SCN5A
mutation
Prevalence

4/24 (16%)
SCN5A
penetrance

SCN5A mutation to identify Pt with cardiac arrest
Sesitivity 32%
Specificity 57%

Priori S et al. Circulation 2000;102:2509

Clinical Profile of ICD implanted Patients in YUMC (1997-2004)

No of Patients	34
Gender (M : F)	29 : 5
Age (yrs)	48 ± 16 (14-74)
Underlying heart disease	
Brugada syndrome	10 (29.4%)
No structural heart disease	8 (23.5%)
CAD	6 (17.6%)
HCMP	5 (14.7%)
DCMP	3 (8.8%)
Non specified CMP	1 (2.9%)
Valvular heart disease	1 (2.9%)

Brugada Syndrome in YUMC (1997-2004)

N = 12

Sex : all male

Mean age = 44 ± 14 years (range 22 – 74)

Clinical manifestation

- 6 : Syncope
- 3 : Aborted SD with preceding syncope
- 1 : Aborted SD without preceding syncope

Brugada Syndrome in YUMC (1997-2004)

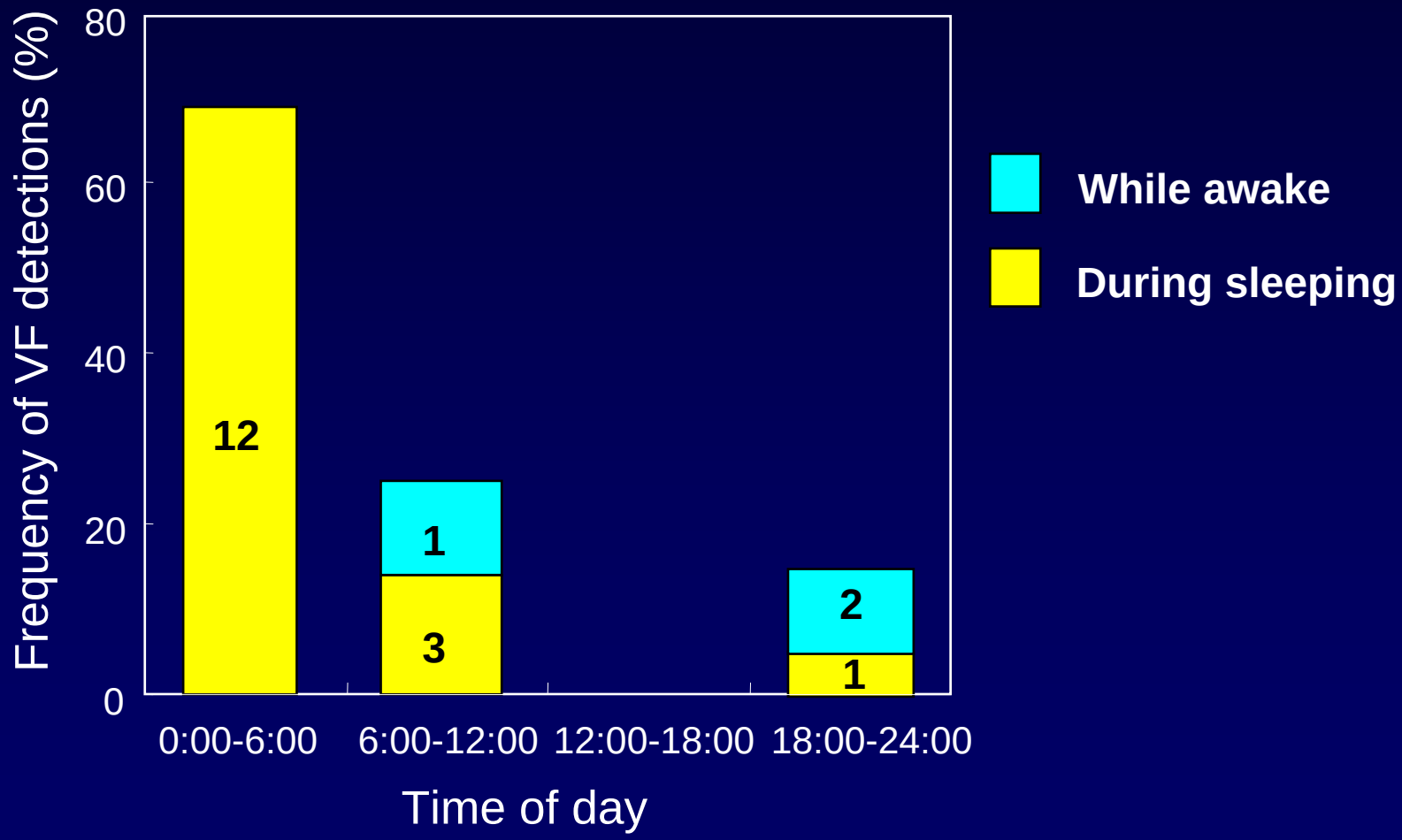
Activity at time of event : sleeping 5/10

Family Hx : 6/12

EPS : VF induced 10/10

Recurrence : 3/10 (within 1 year)

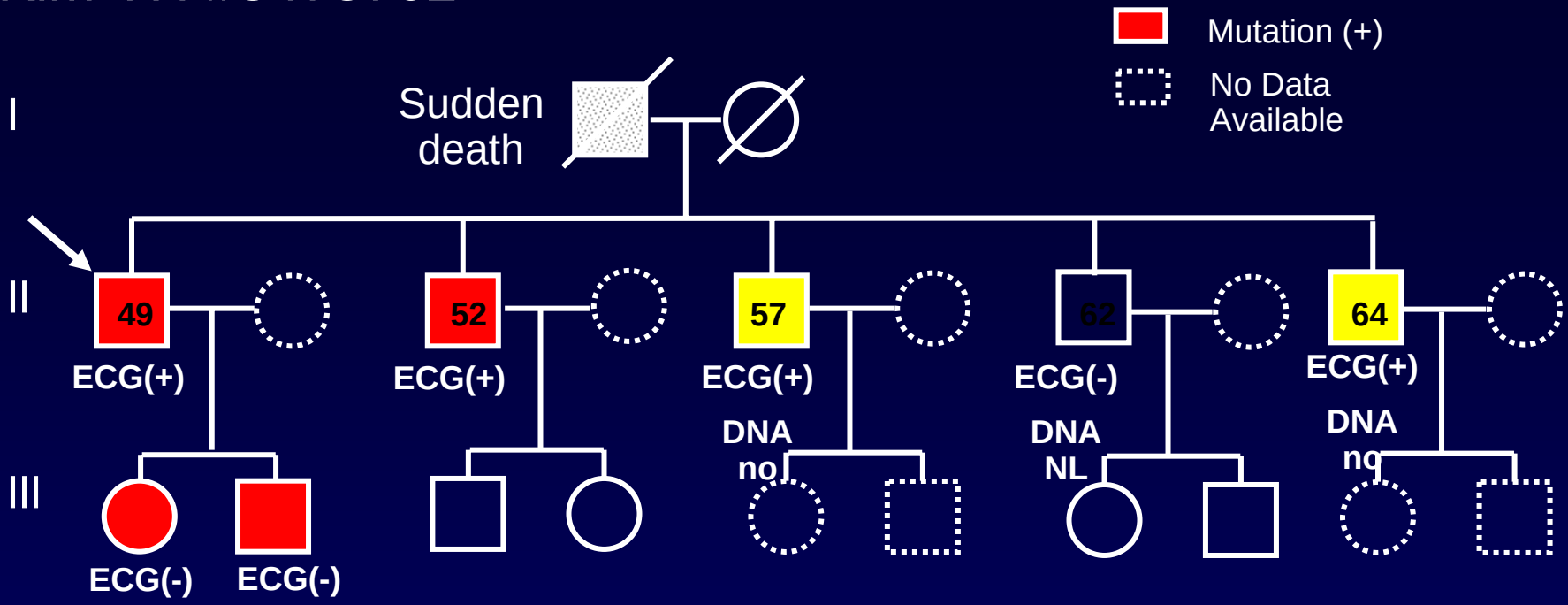
The Circardian Pattern of three Patients with ICD

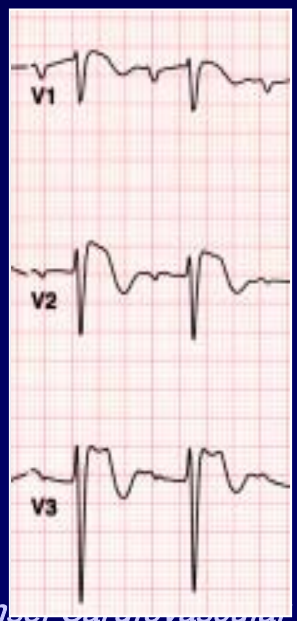


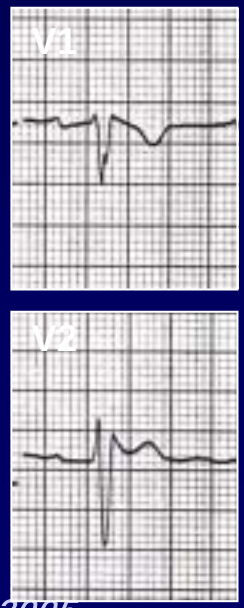
Genetic study

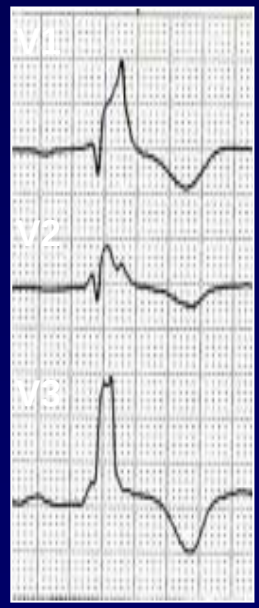
- *SCN5A* genetic abnormality was found in one out of 10 probands and three out of 14 family members.
- One brother, son, and daughter of this proband showed same *SCN5A* genetic abnormality among 8 family members who underwent genetic study.

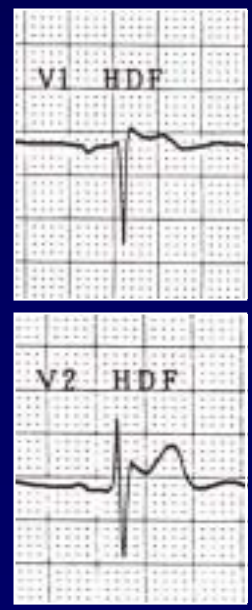
Kim YH #3478762









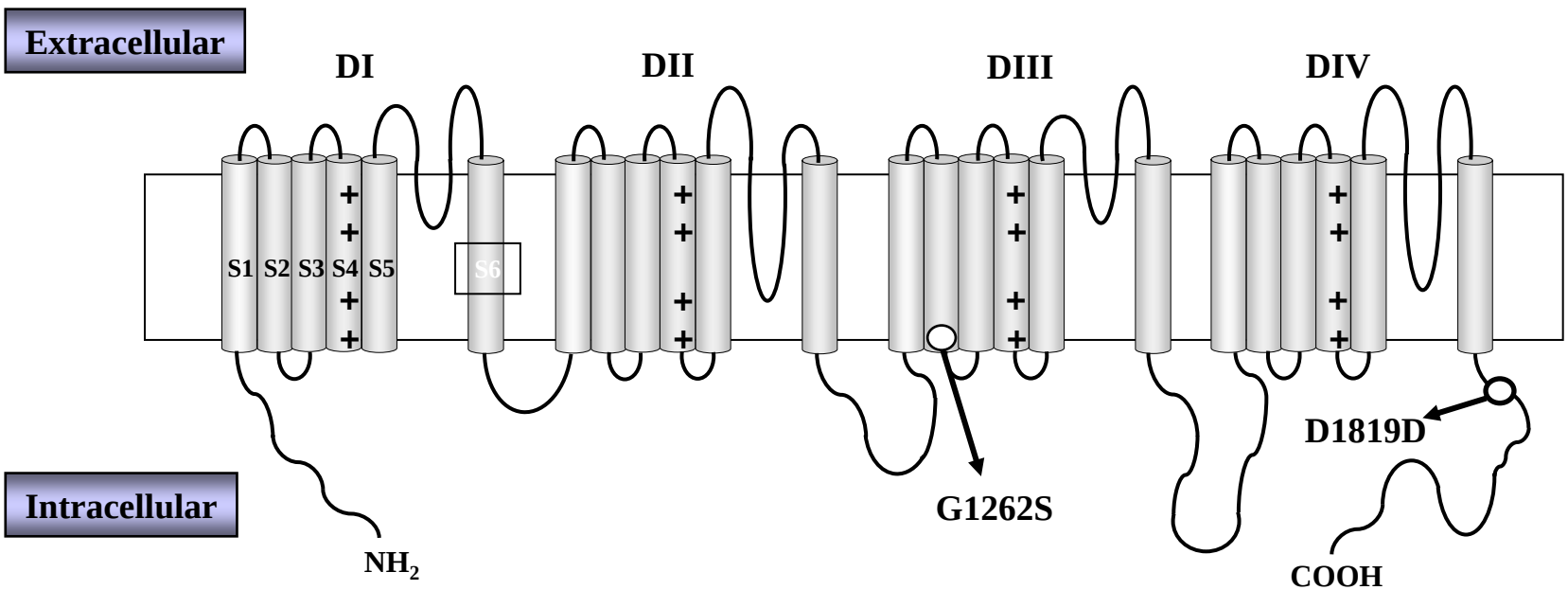


SCN5A (Human cardiac sodium channel α subunit gene)

- Localization : 3p21
- 28 exons (2,016 amino acid, 6,048bp)
- Mutations in SCN5A have been linked to Brugada syndrome.

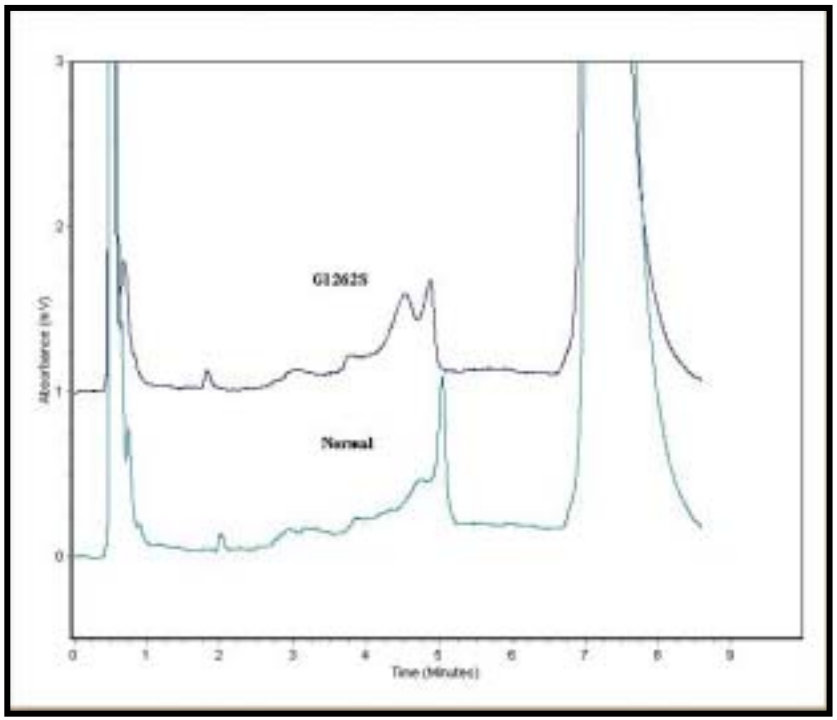
(Chen et al. Nature 1998;392:293)

- More than 60 mutations

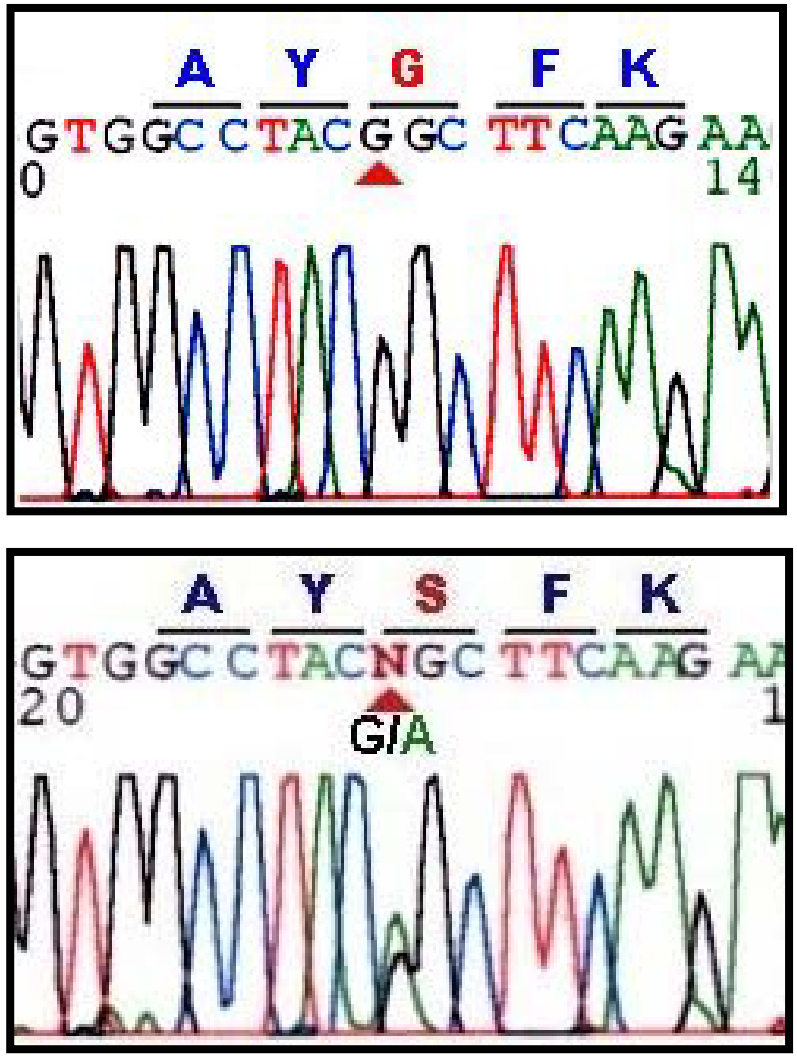


Mutation Detection (#3478762)

G1262S(G→A) at exon 21

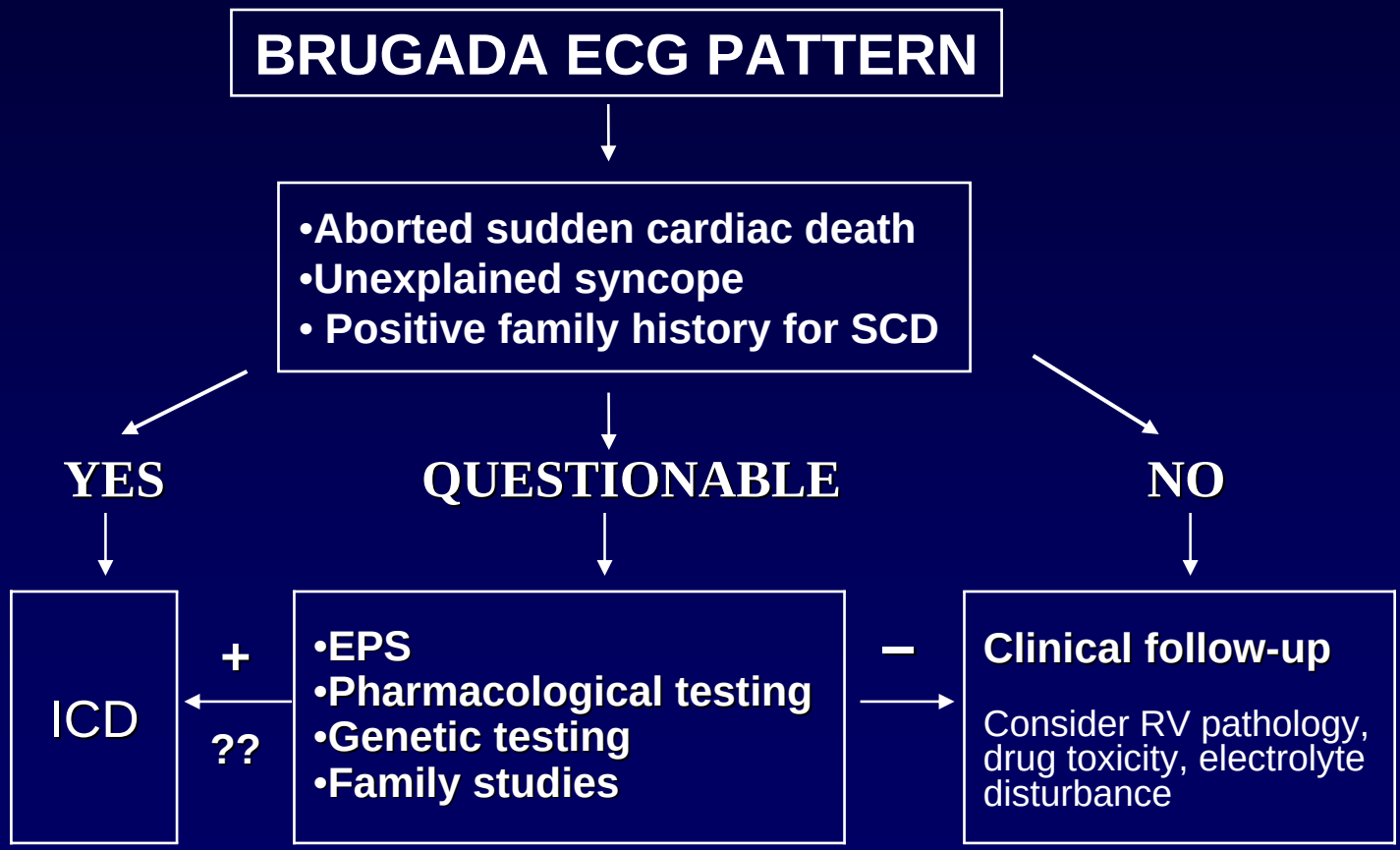


DHPLC analysis showed abnormal band migration in affected individuals among family members.
No variation in 100 controls.



DNA sequence analysis of the PCR product identified a G to A transition in exon 21 of SCN5A, causing substitution of glycine by serine at codon 1262 (G1262S).

Suggested Diagnostic-Therapeutic Algorithm



Littmann L et al. Am Heart J 2003;145:768

Long-Term Prognosis of individuals With Right Precordial ST Elevation Brugada Syndrome (n=212)

Follow-up duration: 40 ± 50 months

	Aborted SD	Syncope	Asymptomatic
No(M/F)	24(22/2)	65(46/19)	123(84/39)
VT/VF(%)	15/22(62)	40/65(68)	38/98(39)
SCN5A	3/24	16/56	38/103
Events(%)	4(17)	4(6)	1(1)

Previous syncope and a spontaneous type I ECG indicate a worse prognosis.
PES has a low positive predictive value but a high negative predictive value.
All asymptomatic, noninducible individuals remained asymptomatic.

Eckardt L et al. Circulation 2005;111:257

Efficacy of Quinidine in High-Risk Patients With Brugada Syndrome (N=25/38)

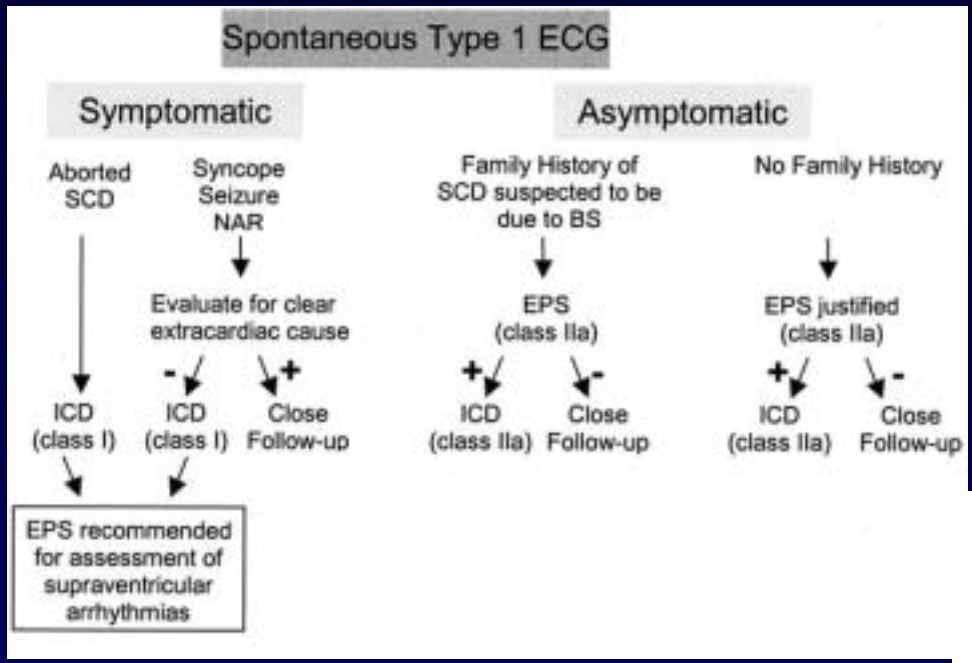
15/15 symptomatic and 10/23 asymptomatic Brugada syndrome

Inducible VF in all patients by PES (up to triple stimuli)

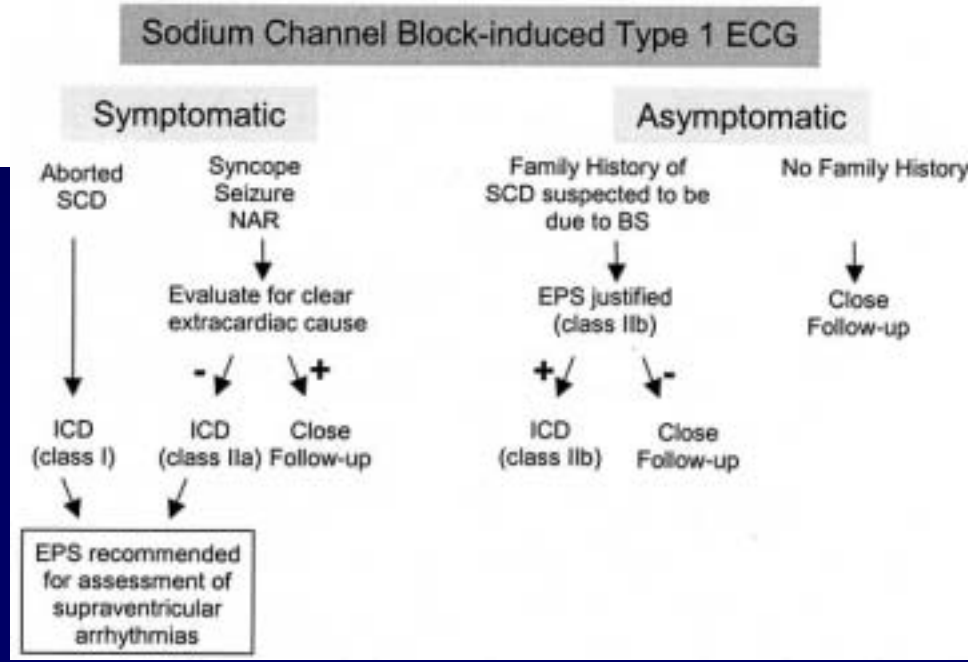
- Quinidine is highly effective for preventing VF induction in Brugada patients inducible VF. 22/25(88% efficacy)
  - 16: quinidine (15 responder, 1 non-responder)
    - 6: ICD
    - 3: ICD + quinidine
- Quinidine appears to be effective in preventing spontaneous VF for 6 to 219 months. (11 symptomatic, 8 asymptomatic)
- 9 ICD
  - 2 quinidine non responder, 5 side effects, 1 syncope, 1 patient's wish

Belhassen B et al. Circulation 2004;110:1731

Brugada Syndrome 2003
Report of the Second Consensus Conference



Antzelevitch C et al. Circulation 2005;111:659



Conclusion

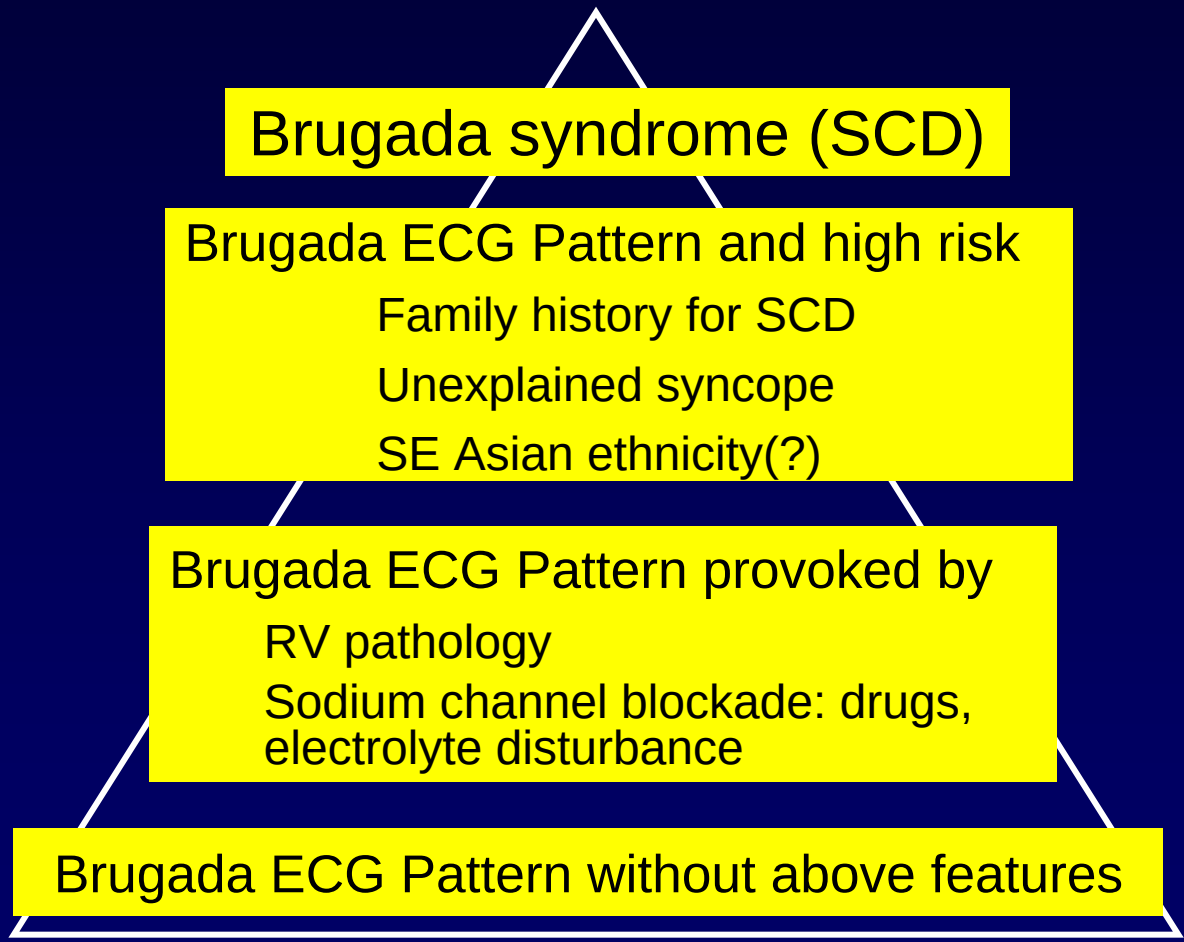
- Brugada syndrome is a distinct form of ventricular fibrillation associated with characteristic ECG and clinical picture.

- Asymptomatic patients with Brugada type ECG pattern raise a clinical dilemma for the practicing physicians.

- Further research is needed to clarify the clinical features of the condition and to establish guideline on how to handle those asymptomatic patients.

- New cardioselective and I_{to} specific blockler would be a powerful arms to combat this agonal disease in near future.

Suggested Diagnostic-Therapeutic Algorithm



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