

Brugada and Brugada like

The precordial early repolarization syndrome, discovered by Nava, but later called Brugada syndrome (BS).
History and future of a fascinating entity.

Martini Bortolo
Andrea Nava †



ELECTROCARDIOGRAPHIC PATTERN SIMULATING ACUTE MYOCARDIAL INJURY

By HAROLD L. OSHER, M.D.
PORTLAND, MAINE

AND

LOUIS WOLFF, M.D.
BOSTON, MASSACHUSETTS

(From the Electrocardiographic Laboratory, Beth Israel Hospital, the Department of Medicine, Harvard Medical School, Boston, Massachusetts, and the Heart Disease Epidemiology Study, National Heart Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Framingham, Massachusetts.)

ABNORMAL displacement of the S-T segment may be associated with a variety of clinical states. In myocardial injury the typical configuration consists of elevation and upward bowing of the S-T segment with symmetrical inversion of the T waves in leads facing the affected area. We have recently observed a similar electrocardiographic pattern in patients without clinical evidence of any acute myocardial process. The purpose of this paper is to point out the distinguishing characteristics of this pattern and to elucidate the mechanism of its production.

Our attention was first drawn to this pattern by the electrocardiograms reproduced in Figure 1. The patient, a 39-year-old white male, entered the Beth Israel Hospital for study on January 19, 1950, because of an episode, 2 weeks previously, of interscapular pain following exertion, and vague substernal discomfort 2 days prior to admission. Physical examination was entirely within normal limits with blood pressure of 120/80 and a normal sized heart with sounds of good quality and no murmurs. Chest roentgenogram and laboratory examination of urine and blood revealed no abnormalities. His hospital course was afebrile and symptom-free except for anxiety; there was no further chest pain and white

blood cell counts and erythrocyte sedimentation rates remained normal. Initial electrocardiograms showed right bundle branch block (RBBB) with elevation of S-T segments and inversion of T waves in the right precordial leads, and were interpreted as consistent with antero-septal injury. However, subsequent tracings showed persistence of the S-T-T pattern with only minor variations, rather than the serial changes typical of evolution of an acute process. The patient was discharged on February 6, 1950, and remained well for 8 months.

In November, 1950, during a period of emotional turmoil, he was again hospitalized because of mild substernal discomfort lasting one day. Clinical and laboratory examination failed to reveal any abnormality, and his hospital course was uneventful except for a few brief twinges of chest pain related to emotional upsets. The electrocardiograms were essentially unchanged and again failed to show progressive changes. The patient has remained well to date (April, 1953), and presents no objective evidence of heart disease although the unusual electrocardiographic pattern persists.

Figure 2 shows the electrocardiograms of a healthy 43-year-old white male (H.D.E.S. Case Number 4549)

(541)

Osher's
ECG

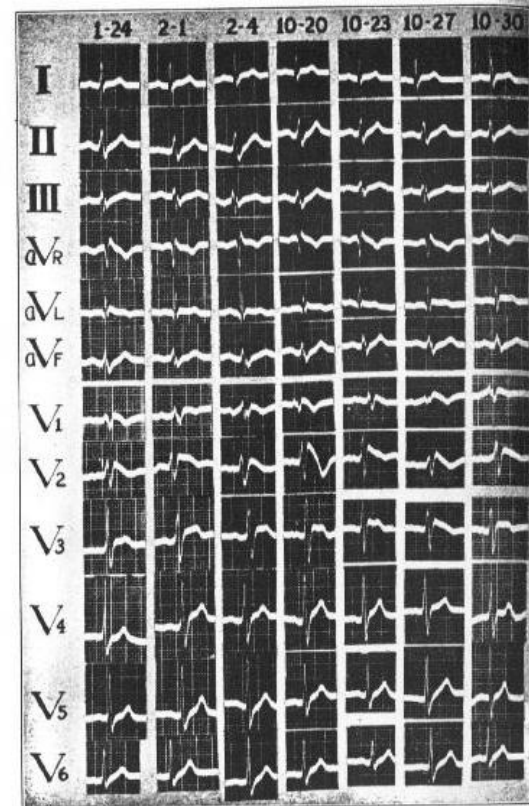


Fig. 1.—Electrocardiograms of a 39-year-old white male with mild atypical chest pain but no clinical evidence of heart disease. Note the wide QRS interval (0.12-0.13 sec.) with features of RBBB, and S-T segment elevation and T wave inversion in the right precordial leads, simulating the pattern of antero-septal injury. The serial tracings show minor variations in the S-T-T configuration, but not the typical evolution seen with myocardial injury.

(542)

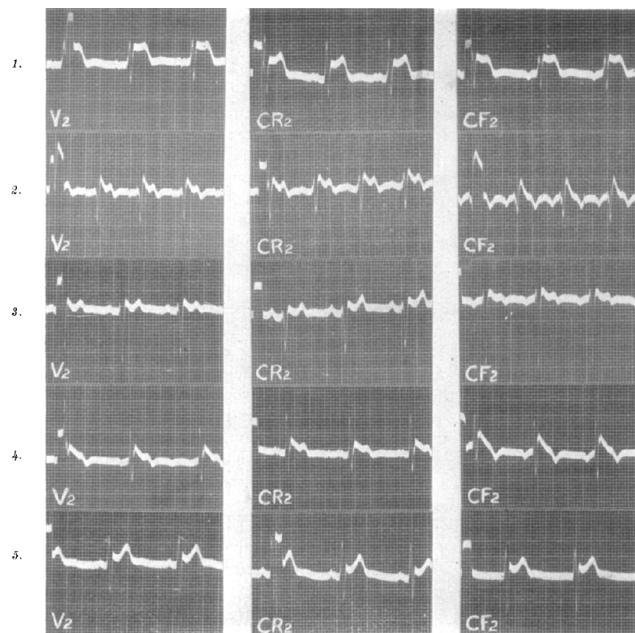
"This is apparently due to prolongation of the depolarization process by right bundle block or possibly focal block with delayed activation of a portion of the right ventricle: unusually early onset of repolarization may also play a role."

Osher HL, Wolff L. Electrocardiographic pattern simulating acute myocardial injury. *Am J Med Sci* 1953; 226: 541-5.

ELEVATION OF THE RS-T SEGMENT, APPARENT OR REAL, IN THE RIGHT PRECORDIAL LEADS AS A PROBABLE NORMAL VARIANT

JOSEPH EDEIKEN, M.D.

1954



Figs. 1 and 2.—Single precordial leads of ten patients showing marked positive RS-T segment deviation. Comparison of V, CR, and CF leads: all were made in the fourth intercostal space to the left of the sternum.

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AMERICAN HEART JOURNAL

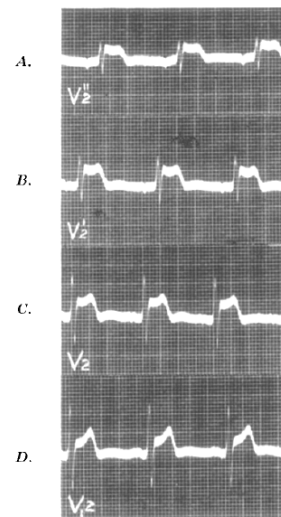


Fig. 4.—Patient No. 1, five years and nine months after the original electrocardiogram showing a change in the configuration with change in the position of the exploring electrode. A, Second intercostal space to the left of the sternum. B, Third intercostal space. C, Fourth intercostal space. D, Fifth intercostal space.

Upper spaces

Clues of an underlying organic substrate in the Brugada Syndrome

Bortolo Martini, Nicolò Martini, Manlio Marquez, Caterina Dorantes, Li Zhang, Guy Fontaine and Andrea Nava
Archivos de Cardiología de México 2017

- On 20 October 1984 a healthy 42 y.o. asymptomatic cook, had a syncope during quite conversation with his post-officer outside his restaurant in Conegliano (the land of the Prosecco wine). An external cardioversion saved his life. The following ECG showed ST elevation on the precordial leads but a brilliant young cardiologist Dr. Piccoli, excluded an AMI and made a diagnosis of “focal block of the right bundle”.

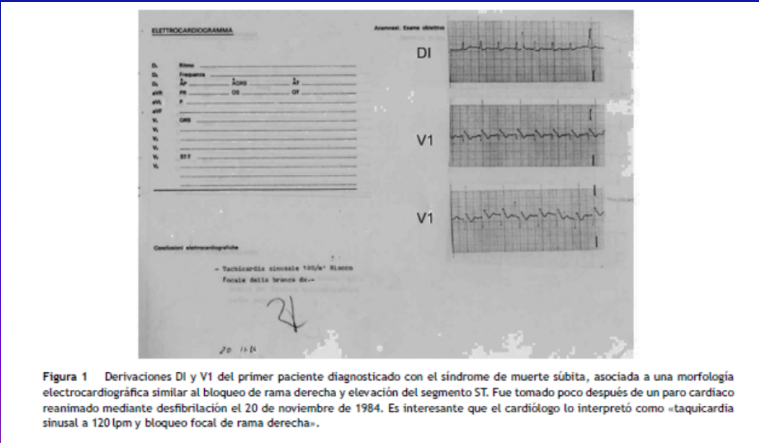
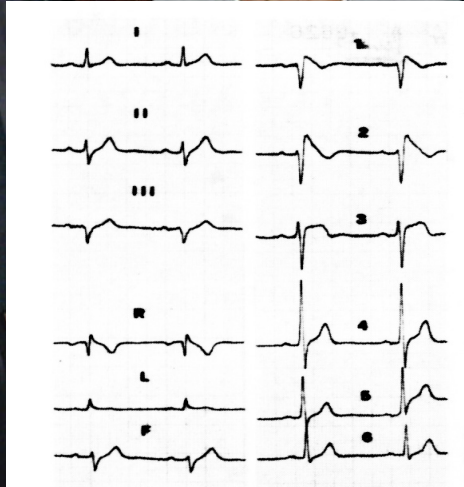
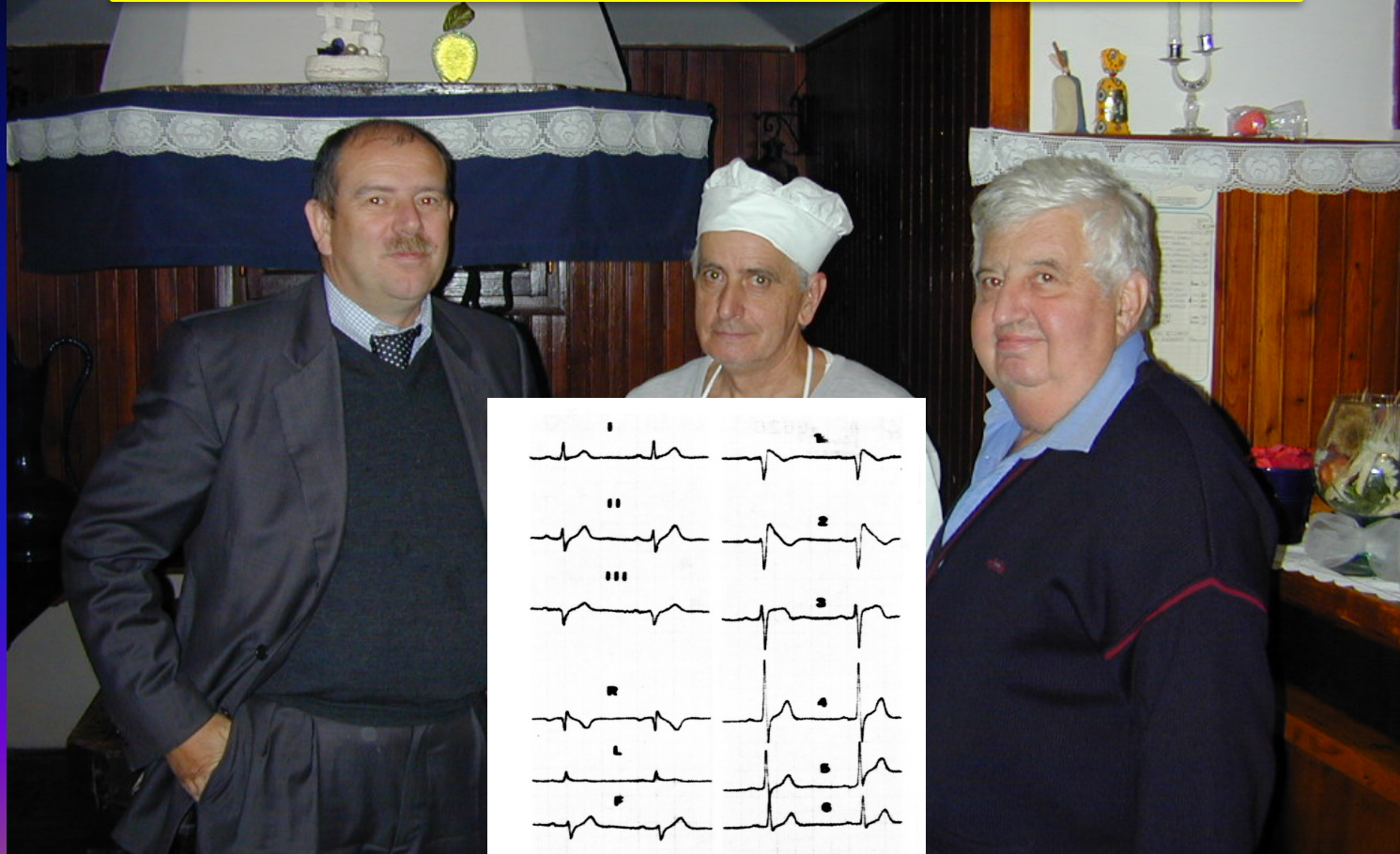
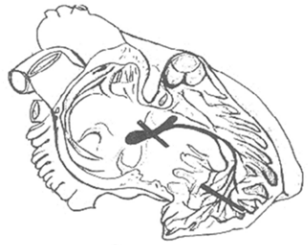


Figura 1 Derivaciones DI y VI del primer paciente diagnosticado con el síndrome de muerte súbita, asociada a una morfología electrocardiográfica similar al bloqueo de rama derecha y elevación del segmento ST. Fue tomado poco después de un paro cardíaco reanimado mediante desfibrilación el 20 de noviembre de 1984. Es interesante que el cardiólogo lo interpretó como «taquicardia sinusal a 120 lpm v bloqueo focal de rama derecha».

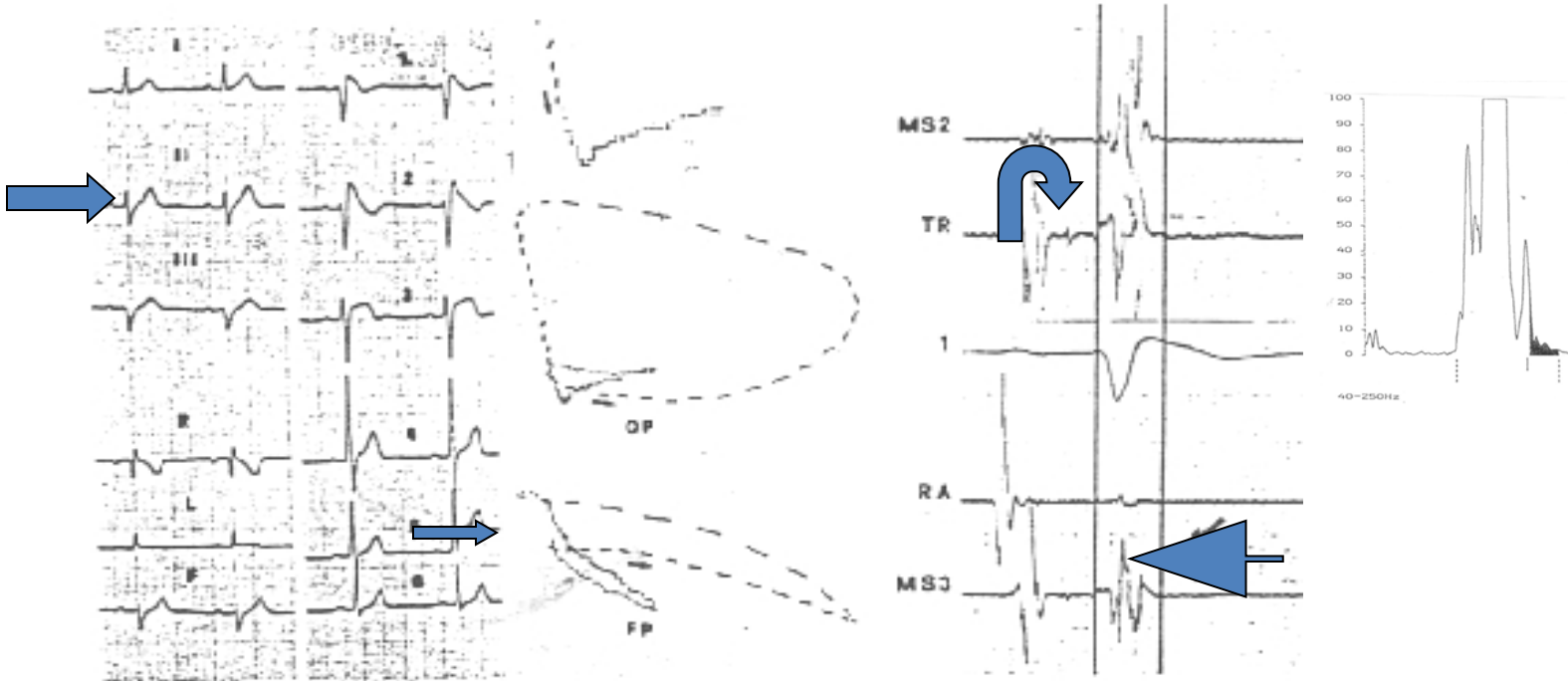
**This patient recently died because of senectus, was always asymptomatic
after a single cardiac arrest that happened on 20.10.2024.
He was initially treated with amiodarone and later with beta blockers**



The first description of a new syndrome due to a structural conduction delay at the Hisian and RVOT level



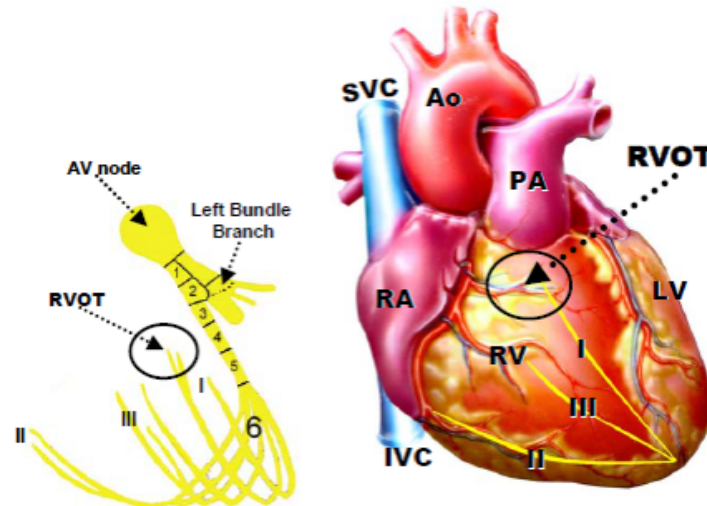
**La Repolarisation Precoce
Precordial. Mises a Jour
Cardiologiques 1988;17:157-9**



- Coved ST in V1-V2
- Inverted t waves
- LAD
- Small or No s in V6
- Prolonged PR and HV
- Delayed depolarization at the RVOT
- Late Potentials
- Structural abnormalities

RIGHT HIS SYSTEM BLOCKS

THE RIGHT HIS SYSTEM COMPONENTS



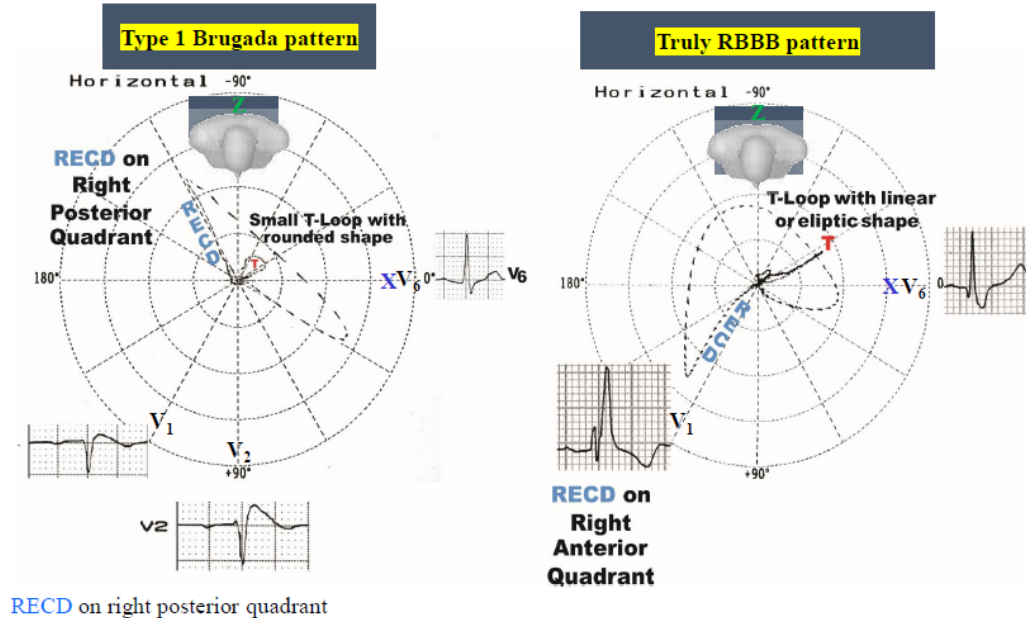
6) DIVISIONAL PORTION OF RIGHT BUNDLE ON FREE WALL OF RIGHT VENTRICLE.

Which originates three divisions in the right ventricle free wall Purkinje.

- I) SUPERIOR DIVISION OF RIGHT BUNDLE-BRANCH;
- II) INFERIOR DIVISION OF RIGHT BUNDLE-BRANCH;
- III) MIDDLE DIVISION OF RIGHT BUNDLE-BRANCH.

Riera Andres: Non è un BBDx

ECG/VCG correlation in the horizontal plane



(Pérez-Riera 2012)

Eco «impuro»
con RECD
ed s in v₆

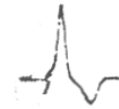
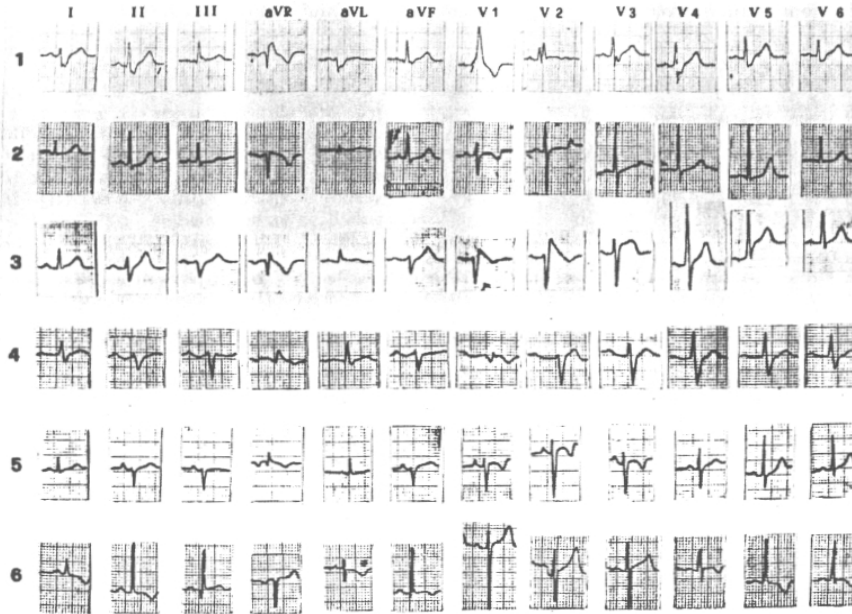
Ventricular fibrillation without apparent heart disease: Description of six cases

Bortolo Martini, MD, Andrea Nava, MD, Gaetano Thiene, MD,
Gian Franco Buja, MD, Bruno Canciani, MD, Roldano Scognamiglio, MD,
Luciano Daliento, MD, and Sergio Dalla Volta, MD. *Padua, Italy*

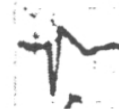
Martini et al.

In this article three typical ECG pattern of the syndrome were described. The fourth probably needs Drug Challenge

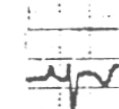
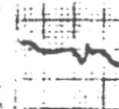
December 1989
American Heart Journal



Brugada



Corrado



Structural (minor) Heart abnormalities detected

Martini et al.

December 1989
American Heart Journal

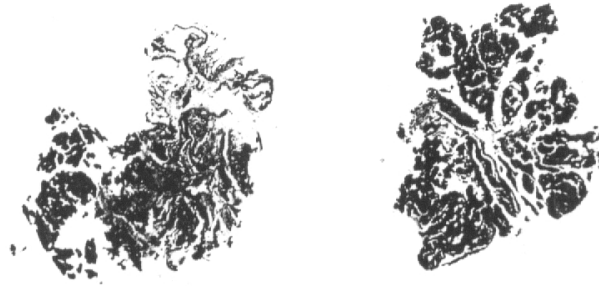


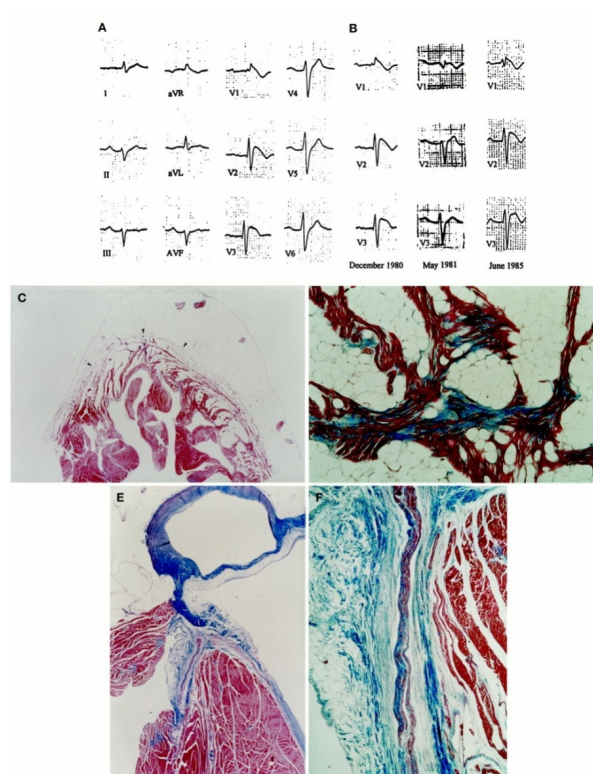
Fig. 3. Endomyocardial biopsy from patient 1: moderate fibrosis is visible in two fragments. (Azan Mallory stain; original magnification $\times 10$.)

Table III. Investigational data derived from ultrasonic, hemodynamic, and histologic study

Patient	RVEDV (cc/m ²)	RVEF (%)	LVEDV (cc/m ²)	LVEF (%)	RVWMA	LVWMA	RVOT (mm)	MVP	TVP	HBE	Histology
1	103	44	68	67	+++	0	45	+	+	VF	F ++
2	124	60	96	61	+++	+	35	+	+	NSVT	F +++ A +
3	(94)	(52)	(62)	(63)	++	0	45	0	0	PRR	ND
4	(105)	(48)	70	60	+++	0	45	0	0	SRR	F +++ A +
5	110	42	79	62	+++	+	45	0	0	ND	ND
6	76	67	80	84	0	0	25	0	0	SRR	0



A 35-year-old man who died suddenly at rest.



Corrado D et al. *Circulation* 2001;103:710-717

The 2nd paper on the syndrome was published in Japan!



第2回 心臓性急死研究会

特発性心室細動の臨床
および電気生理学的特徴

相原直彦* 大江 透* 松久茂久雄*
鎌倉史郎* 栗田隆志* 高木 洋*
下村克朗*

*国立循環器病センター内科心臓部門
(〒565 吹田市藤白台 5-7-1)

Clinical and electrophysiologic characteristics
of idiopathic ventricular fibrillation
Naohiko Aihara*, Tohru Ohe*,
Shiro Kamakura*, Mokuo Matsuhisa*,
Takashi Kurita*, Hiroshi Takagi*,
Katsuro Shimomura*.
*National Cardiovascular Center,
Internal Medicine, Division of Cardiology.

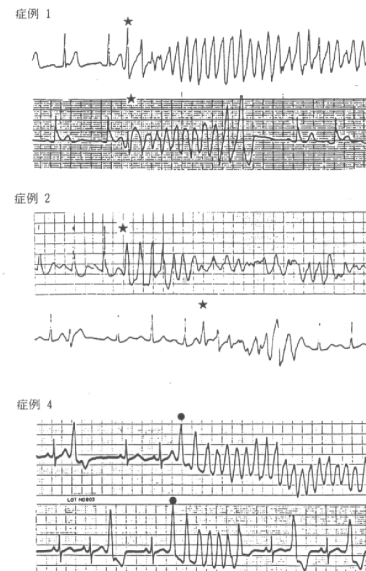
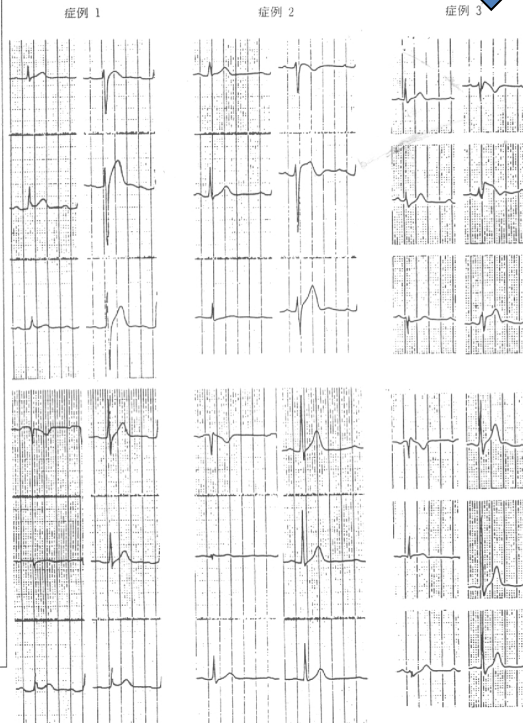


図3 症例1, 2, 4での心室細動(上段)および多形性非持続型の心室頻拍(下段)の出現様式

症例1, 2では、下向きの緩やかな初期成分をもつ心室性期外収縮から心室細動および多形性非持続型心室頻拍が出現している。症例4では、下向きの成分は認められず、比較的急峻な初期成分をもつ心室性期外収縮より出現している。

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

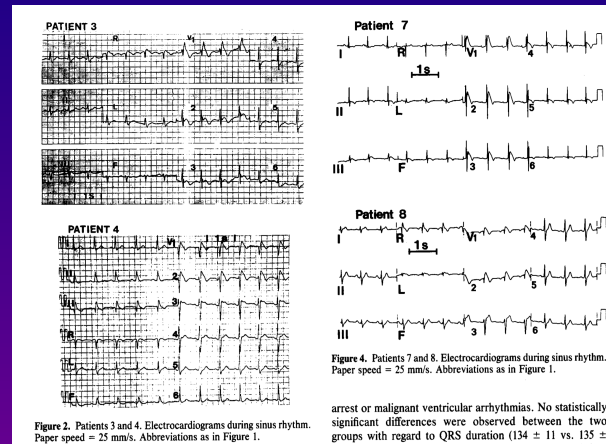
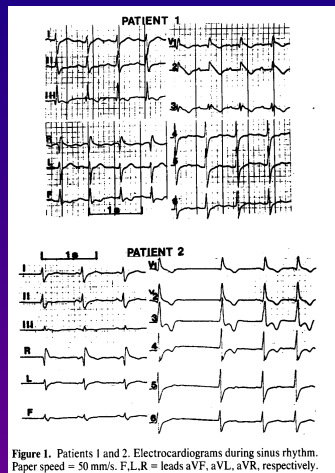
whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic ventricular tachycardia initiating after a short coupled ventricular extrasystole. A similar arrhythmia was initiated by two to three ventricular extrastimuli in four of the seven patients 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.

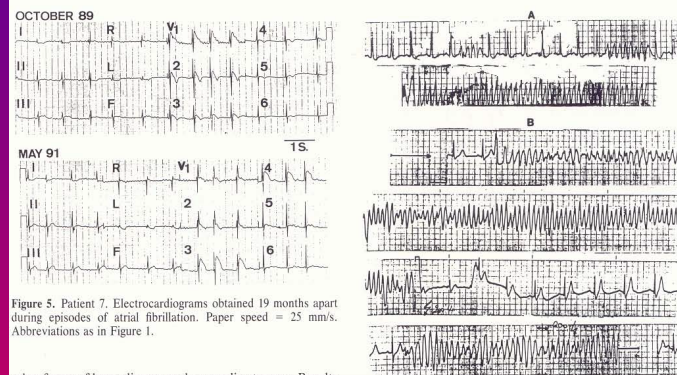
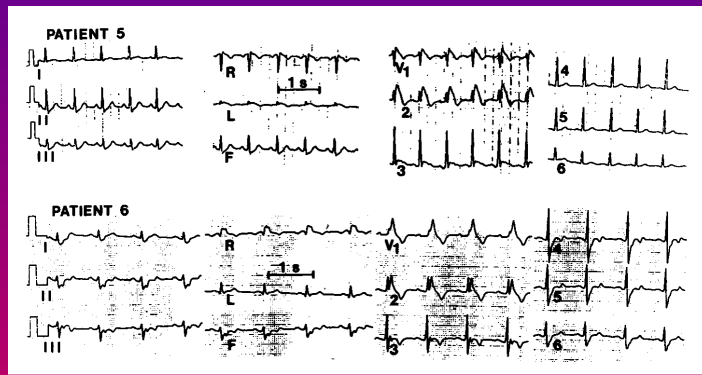
(J Am Coll Cardiol 1992;20:1391-6)



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



arrest or malignant ventricular arrhythmias. No statistically significant differences were observed between the two groups with regard to QRS duration (134 ± 11 vs. $135 \pm$



The eponim Brugada syndrome. Where did it came from?

140—(3166)

—臨床と研究・71巻12号(平成6年12月)—

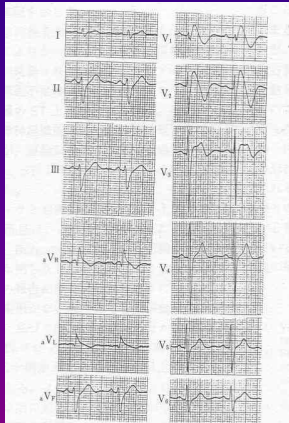
心電図のページ

心電図一例一話

[203]

— Brugada 症候群様の心電図所見を示した77歳男性 —

森 博 愛* 土 橋 哲 夫**



QRS 間隔は0.13秒。V₁-V₃でST部が著しく上昇し、ことにV₁, V₂ではQRS波終末部とST部が一体化し、陰性T波に移行し、一見、急性心筋梗塞の際のST上昇に類似する。

図4 典型的な Brugada 症候群の心電図 (自験例)

Nava explanation of the ECG

Martini, B.; Nava, A.; Thiene, G.; Buja, G.F.; Canciani, B.; Scognamiglio, R.; Dalla Volta, S. Ventricular fibrillation without apparent heart disease: Description of six cases. *Am. Heart J.* **1989**, 118, 1203–1209.

- Depolarization abnormality of the His and RVOT conduction, due to structural abnormalities.

Brugada explanation of the ECG

Brugada, P.; Brugada, J: A distinct clinical and electrocardiographic syndrome. A multicenter report. *J. Am. Coll. Cardiol.* 1992, 20, 1391–1396.

- “It is either a marked dispersion of refractoriness of cardiac tissue or extreme anisotropic properties of the conduction system and the ventricular muscle”



LETTERE AL DIRETTORE

FORUM

G Ital Cardiol 1994; 24: 797-799

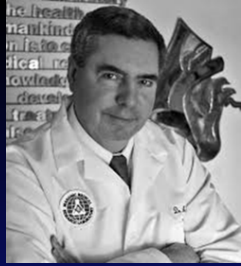
Let us do not get confused, please!...

2). The case presented by Dr. Proclemer and coworkers has all the features of the new syndrome which we described (3): Aborted sudden death, right bundle branch block, persistent ST segment elevation in leads V1 to V3 and a *completely normal heart*. Dr. Naccarella argues that this case is similar to cases previously reported by Martini et al. (4) and suggests that this is a case of right ventricular dysplasia. We fully disagree with his comments and interpretations.

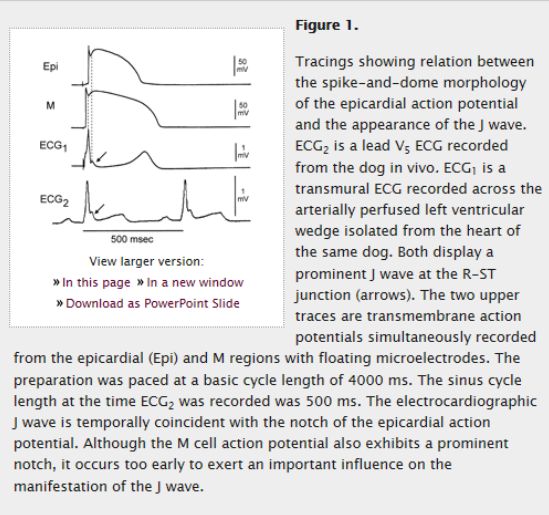
The «30 years ST war» between Repolarization army and Depolarization partisans

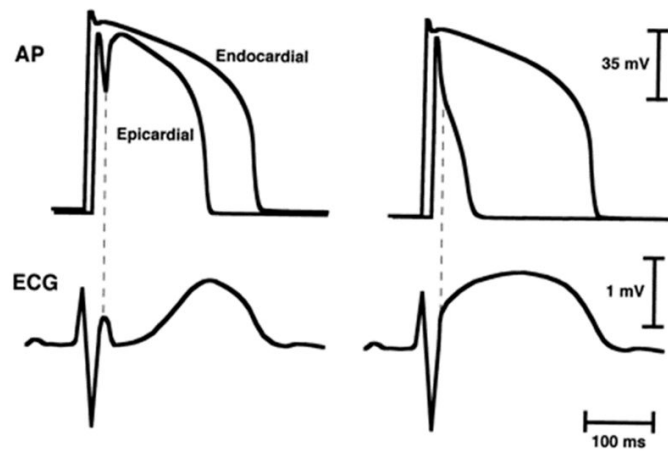
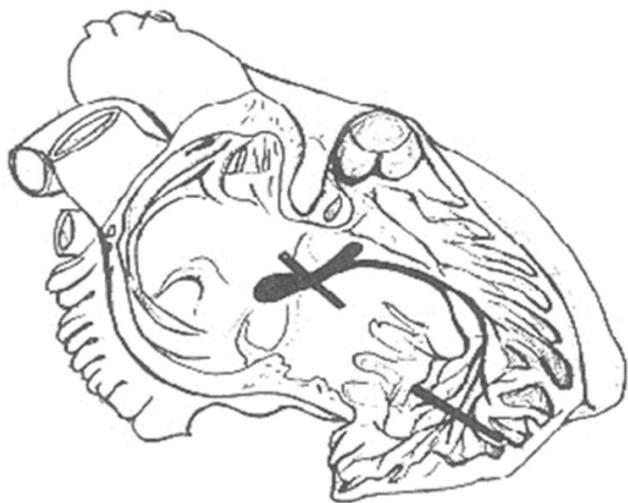


Circulation. 1996;93:372-379



- **Cellular Basis for the Electrocardiographic J Wave**
- *Gan-Xin Yan, MD, PhD; Charles Antzelevitch, PhD*
From the Masonic Medical Research Laboratory, Utica, NY.





Genetic basis and molecular mechanism for idiopathic ventricular fibrillation

Guoyun Chen¹, Glenn E. Kirsch¹, Danmel Zhang¹, Ramon Brugada², Josep Brugada³, Pedro Brugada⁴, Domenico Potenza⁵, Angel Moya⁶, Martin Borggrefe⁷, Günter Breithardt⁸, Rocio Ortiz-Lopez⁹, Zhiqing Wang¹⁰, Charles Antzelevitch¹¹, Richard E. O'Brien¹², Eric Schatz-Gaber¹³, Mark T. Keating¹⁴, Jeffrey A. Towbin¹⁵ & Qing Wang¹⁶

¹ Department of Pediatrics (Cardiology), a Medicine (Cardiology),

¹¹ Cardiovascular Sciences, b Molecular and Human Genetics,

¹² Baylor College of Medicine, Houston, Texas 77030, USA

¹³ The Ramon Llull Center for Research, Menéndez Pidal Campus,

¹⁴ Case Western Reserve University, Cleveland, Ohio 44105, USA

¹⁵ Arrhythmia Unit, Cardiovascular Institute, Hospital Clinic,

University of Barcelona, 08036 Barcelona, Spain

¹⁶ The Cardiovascular Center, Cleveland Clinic, 9300 Euclid, Delton

¹⁷ Cardiology Department, IRCCS Casa Sollievo della Sofferenza, S. Giovanni

Rotondo, Italy

¹⁸ Department of Cardiology, Hospital Vall d'Hebron, 08035 Barcelona, Spain

¹⁹ Department of Cardiology and Angiology, Institute of Anesthesiology Research,

Hospital of the University of Münster, D-48129 Münster, Germany

²⁰ Mason Medical Research Laboratory, Utica, New York 13504, USA

²¹ Howard Hughes Medical Institute, Department of Human Genetics and

Medicine, University of Utah, Salt Lake City, Utah 84143, USA

²² These authors contributed equally to this work.

Ventricular fibrillation causes more than 300,000 sudden deaths each year in the USA alone^{1,2}. In approximately 5–12% of these cases, there are no demonstrable cardiac or non-cardiac causes to account for the episode, which is therefore classified as idiopathic ventricular fibrillation (IVF)^{3–5}. A distinct group of IVF patients has been found to present with a characteristic electrocardiographic pattern^{6–8}. Because of the small size of most pedigrees and the high incidence of sudden death, however, molecular genetic studies of IVF have not yet been done. Because IVF causes cardiac rhythm disturbance, we investigated whether malfunction of ion channels could cause the disorder by studying mutations in the cardiac sodium channel gene *SCN5A*. We have now identified a missense mutation, a splice-donor mutation, and a frameshift mutation in the coding region of *SCN5A* in three IVF families. We show that sodium channels with the missense mutation recover from inactivation more rapidly than normal and that the frameshift mutation causes the sodium channel to be non-functional. Our results indicate that mutations in cardiac ion-channel genes contribute to the risk of developing IVF.

Ventricular fibrillation is the most common cause of sudden cardiac death. When it occurs, there is no cardiac output, peripheral pulses and blood pressure are absent, and the patient loses consciousness. Death is imminent unless the arrhythmia is immediately controlled. IVF patients account for 3% of survivors of out-of-hospital cardiac arrest⁹. For patients who survive an episode of IVF, the rate of recurrence can be as high as 25–30% (ref 7, 17). A distinct electrocardiogram (ECG) pattern, with right bundle branch block (RBBB) and elevation in ST segment in leads V1 to V3, has been described for some patients with sudden and aborted cardiac death due to IVF^{10–12}. Although the exact prevalence of IVF associated with RBBB and ST segment elevation is not known, clinical experience in Belgium and Spain suggests that it accounts for 40–60% of all IVF cases (data not shown).

We studied six small families and two sporadic patients with IVF by using single-strand conformation polymorphism (SSCP) and

DNA sequence analyses to identify mutations in known ion channel genes, including the cardiac sodium channel gene *SCN5A*. Two aberrant SSCP conformers were identified in all affected members in family K005, one in exon 21 of *SCN5A* (data not shown) and the other in exon 28 (Fig. 1a, b)¹⁴. Neither of the SSCP anomalies was seen in unaffected individuals (Fig. 1b) or in DNA samples from more than 150 control individuals (data not shown). DNA sequence analysis revealed two C-to-T base substitutions, one in exon 21 and the other in exon 28 (Fig. 1c); these mutations lead to substitution of an arginine by a tryptophan at codon 1,232 (represented as R1232W; data not shown), which lies in the extracellular loop between transmembrane segments S1 and S2 of domain III, and to substitution of a highly conserved threonine by a methionine at codon 1,620 (T1620M; Fig. 1c) in the extracellular loop between S3 and S4 of domain IV. Studies with sodium-channel-specific toxins indicated that the extracellular loop between DIVS3 and DIVS4 is important for coupling channel activation to fast inactivation^{15–18}.

Additional *SCN5A* mutations were found in two IVF families, K007 and K2823. Aberrant SSCP conformers were identified in affected individuals of K007 (Fig. 2a) and K2823 (Fig. 2b), but not in DNA samples from more than 150 control individuals (data not shown). DNA sequencing revealed that the abnormal SSCP band identified in K007 contained an insertion of two nucleotides, AA, which disrupted the splice-donor sequence of Intron 7 (ref 18, 22) (Fig. 2a). The abnormal band identified in K2823 contained a deletion of a single nucleotide (A) at codon 1,397 (Fig. 2b). This deletion results in an in-frame stop codon that eliminates DIVS6, DIVS1–S6, and the carboxy-terminal portion of the cardiac sodium channel (Fig. 2b).

The potential contribution of R1232W and T1620M mutations to the mechanism of IVF was determined by heterologous expression

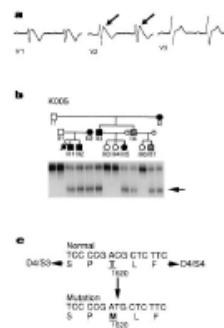


Figure 1 *SCN5A* missense mutation co-segregating with IVF in family K005. **a**, Electrocardiogram of an affected individual (II-1). Note the ECG pattern of RBBB and ST-segment elevation (diagonal arrows) in leads V1–V3. **b**, Pedigree structure and SSCP analysis with primers amplifying exon 28 of *SCN5A*. Affected individuals are filled circles (females) and filled squares (males). Unaffected individuals are empty symbols, and individuals without clinical data are shown as hatched. The individual who suffered sudden death from IVF is identified. **c**, DNA and amino-acid sequences of the *SCN5A* missense mutation associated with IVF in K005. DNA sequence analysis revealed a C-to-T substitution which causes the T1620M mutation in the extracellular loop between DIVS3 and DIVS4.

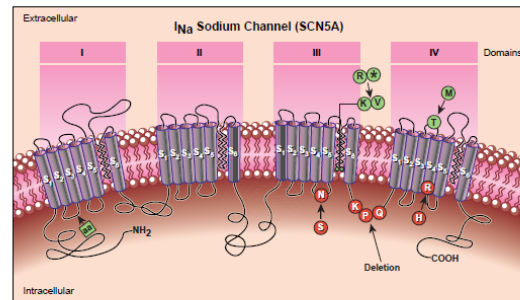


Figure 4 The predicted secondary structure of the cardiac sodium channel and locations of mutations causing IVF and chromosome-3-linked long-QT syndrome (LQT). The channel consists of four putative transmembrane domains (DI–DIV), with each domain containing six transmembrane segments (S1–S6). IVF mutations are shown in green and LQT-associated mutations are in red.

Received 29 September; accepted 23 December 1997.

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The syndrome has a genetic background, but which chromosome/s?, which genes?

CORRADO ET AL.
FAMILIAL CARDIOMYOPATHY AND SUDDEN DEATH

JACC Vol. 27, No. 2
February 1996:443-8

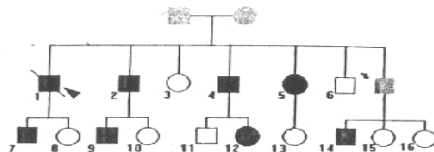
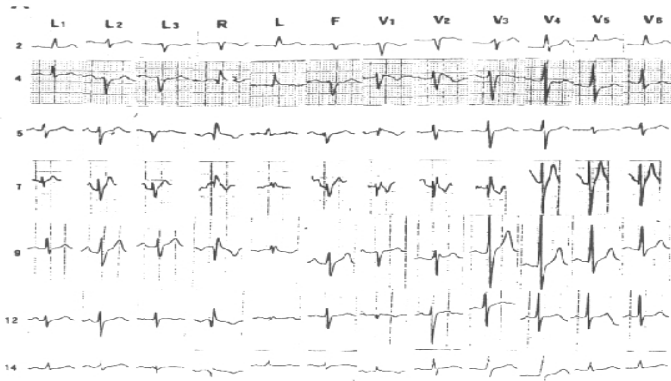


Figure 1. Family pedigree. Numbers indicate cases. Circles represent women and squares represent men. Arrowhead indicates the proband. Diagonal bars indicate deceased family members. Affected members are represented by solid circles and squares. Nonaffecting and noninvestigated members are represented by open and gray symbols, respectively.



Males predominance
Familial involvement
Autosomal with incomplete
penetrance heart disease

JACC Vol. 27, No. 2
February 1996:443-8

443

Familial Cardiomyopathy Underlies Syndrome of Right Bundle Branch Block, ST Segment Elevation and Sudden Death

DOMENICO CORRADO, MD, ANDREA NAVA, MD, GIANFRANCO BUJA, MD,
BORTOLO MARTINI, MD, GIUSEPPE FASOLI, MD, LUCA OSELLADORE, MD,
PIETRO TURRINI, MD, GAETANO THIENE, MD, FESC

Padua, Italy

The real world

- 80% phenotype + genotype -
- 15% phenotype + genotype +
- 5% genotype + phenotype -

Let's go back to the ECG and later to the syndrome (if in time!)

- Dynamic ST elevation mainly coved or saddle-like
- Different patterns also for type 1

Dinamic ST behaviour (Sumiyoshi 1993)

30-50% of pts with ths syndrome. How many healthy subject with the ecg???



ST elevation

Coved

Saddle-like

Dome shaped

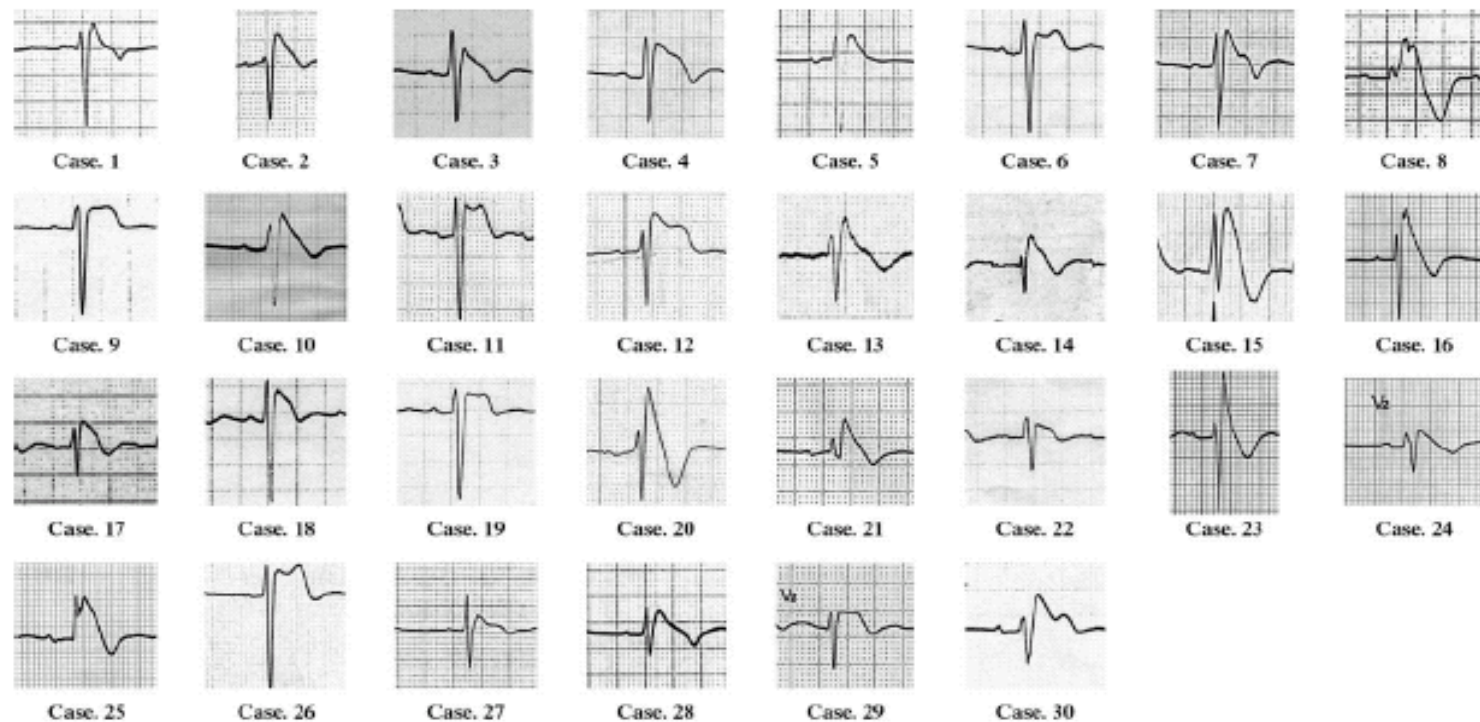
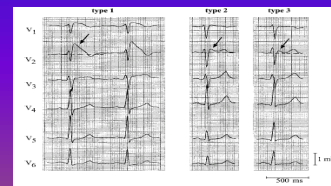
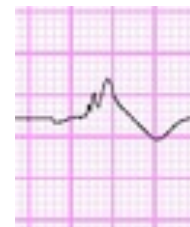


Fig 1. Lead V₂ ECGs in patients with the characteristic Brugada syndrome ECG at the time of presentation. Twenty-four patients had the 'coved type' ST-segment elevation and 6 patients had 'saddle-back type' ST-segment elevation.



v1



b

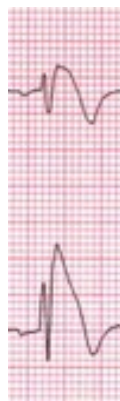
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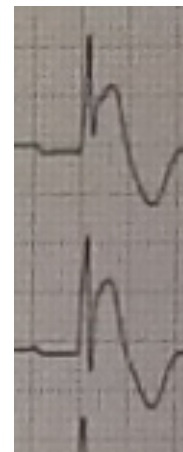
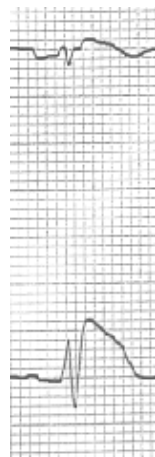
e

f

v1



v2



g

h

i

l

m

n

Table 1 ST segment abnormalities in leads V_1 - 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 configuration	Coved type	Saddle back	Saddle back
ST segment (terminal portion)	Gradually descending	Elevated ≥ 1 mm	Elevated <1 mm

1 mm=0.1 mV, the terminal portion of the ST-segment refers to the latter half of the ST-segment.

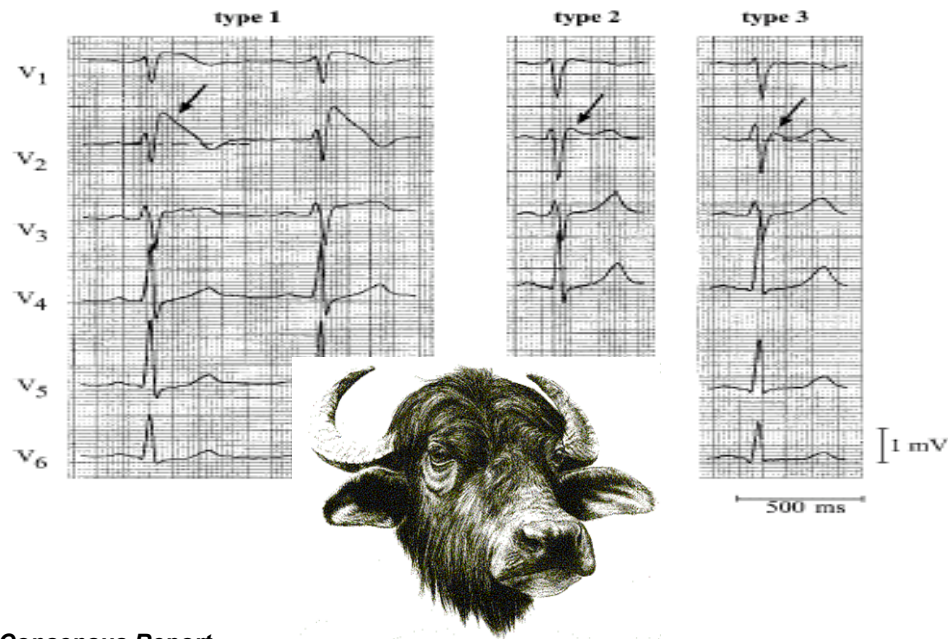


Figure 1 Precordial leads of a resuscitated patient with Brugada

syndrome. Note the dynamic ECG changes in the course of a couple of days. All three patterns are shown. Arrows denote the J-wave. The left panel shows a clear type 1 ECG.

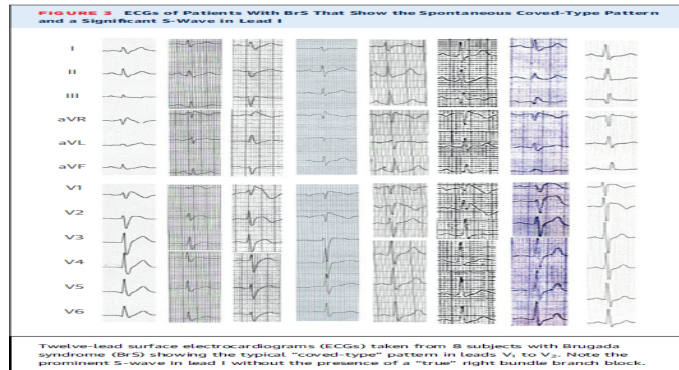
Between 7 February 1999 and 13 February 1999 types 2 and 3

Consensus Report

Proposed Diagnostic Criteria for the Brugada Syndrome
Wilde et al Circulation 2002

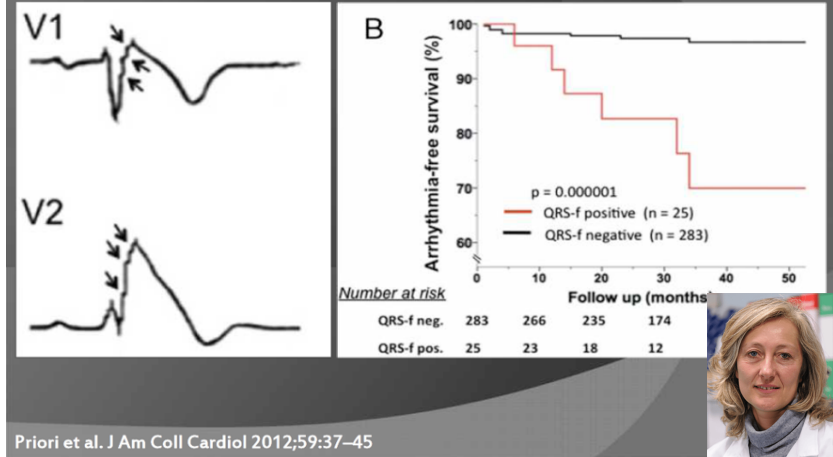
This was not a classification but a case report!!

First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome
Federico Migliore 2018



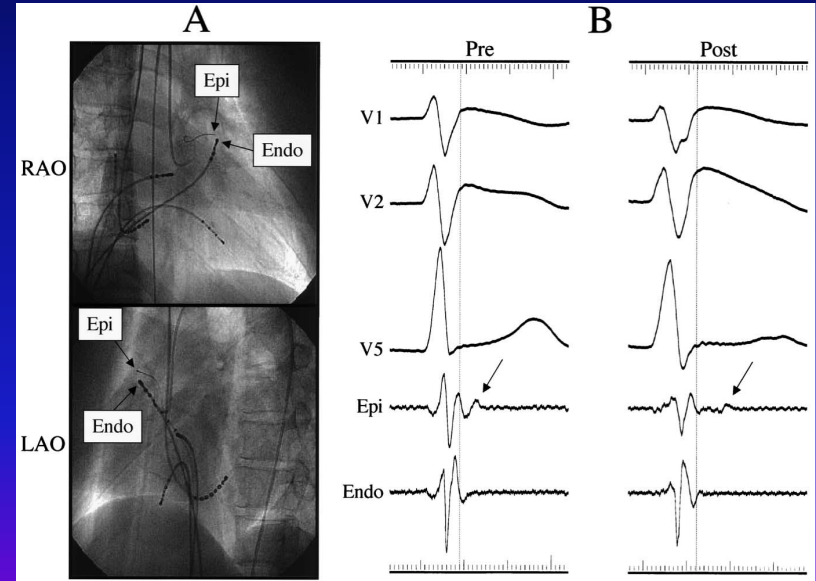
Calò 2018

QRS-fragmentation: Data from the PRELUDE registry

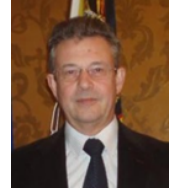
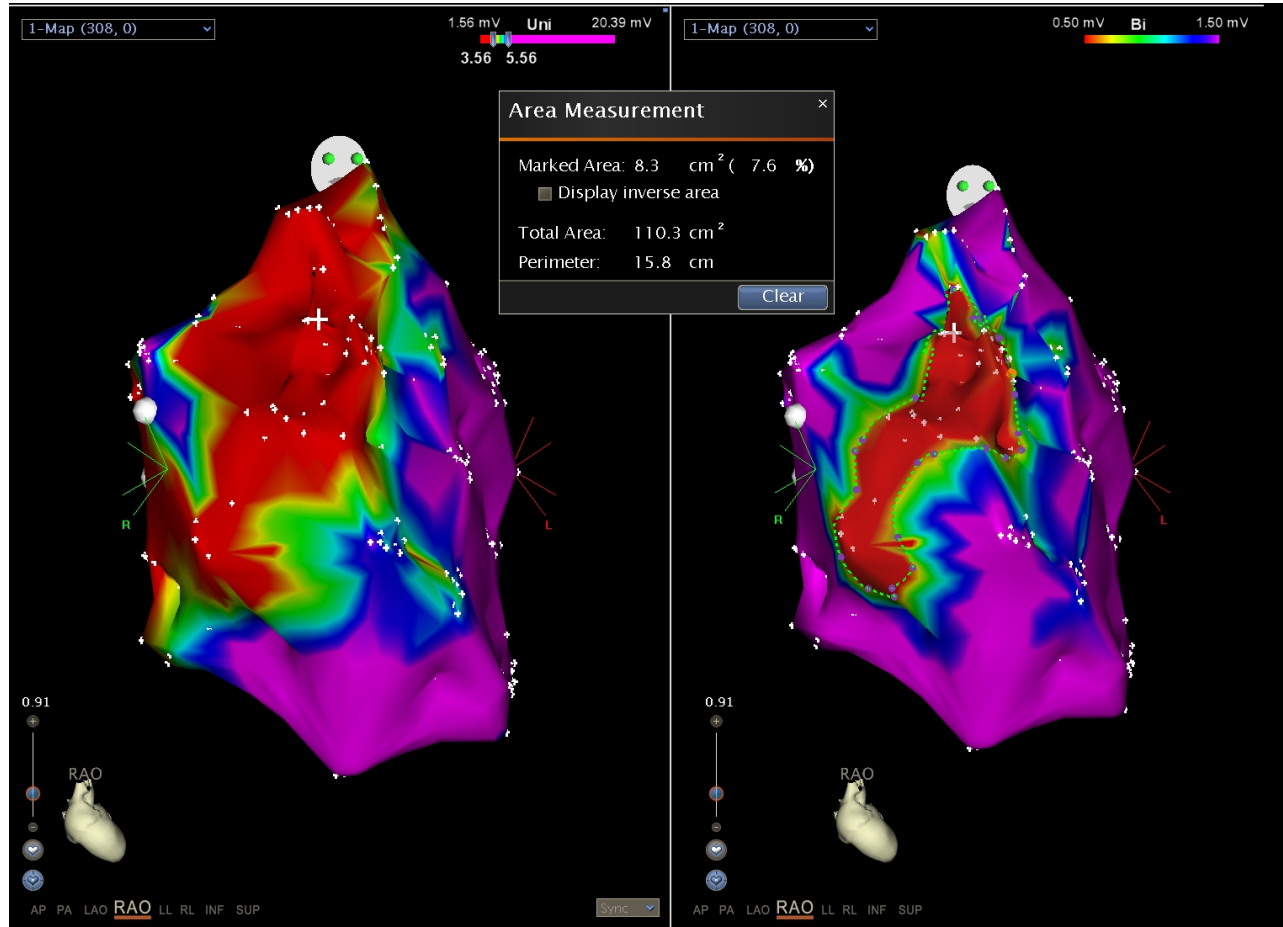


Nagase, S., Kusano, K. F., Morita, H., et al. Epicardial electrocardiogram of the right ventricular outflow tract in patients with Brugada syndrome using the epicardial lead.
JACC. 2002; 39:1992–5

- In five patients with a Brugada-type electrocardiogram (ECG), local unipolar electrograms were recorded at the epicardium and endocardium of the RVOT. The duration of the local electrogram after termination of the QRS complex (DP) was measured before and after class IC anti-arrhythmic drug administration.
- **RESULTS** A definite DP was observed at the epicardium, but not at the endocardium.
- After administration of a class IC anti-arrhythmic drug, the DP at the epicardium was prolonged from 38 ± 0 ms to 67 ± 24 ms.



Delise 2007: The first report of an E.A.M.



Type 1 ECG recorded in different sites or drug induced

- Upper spaces
- drugs

Electroanatomical Correlation of Repolarization Abnormalities in Brugada Syndrome
 Detection of Type 1 Electrocardiogram in the Right Ventricular Outflow Tract
 Nagase 2010. Letter to JACC

In summary, our results show that positioning of ECG electrodes at the RVOT can detect type 1 ECG in patients with BrS.

The Inter Costal Space, that is associated with the RVOT, can be different in each patient

PS: the first observations were made by Eideken (1954) Calo (1955) and Naccarella (1993)

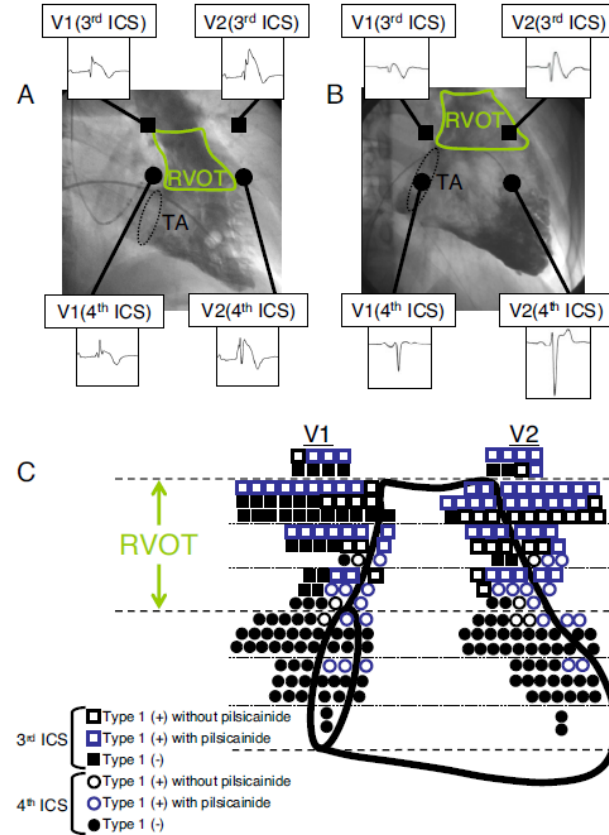


Figure 1 Detection of Type 1 ECG in the RVOT

(A) A 62-year-old male patient with recurrent unknown syncope attacks. (B) A 17-year-old male patient without any symptoms. (C) Position of electrocardiogram (ECG) leads in all patients. The lead location in front of the right ventricular outflow tract (RVOT) determined the manifestation of type 1 ECG. The lead position manifesting type 1 ECG coincided with the location of the RVOT in 34 of 44 (77.3%) V₁ leads and in 58 of 71 (81.7%) V₂ leads. ICS = Intercoastal space; TA = tricuspid annulus.

**Prevalence of Brugada-type
electrocardiogram pattern by recording
right precordial leads at
higher intercostal spaces**

*Burak Humuk, Alper Kepez, and Okan Erdogan
2012*

Healthy male volunteers (n 504) between 18 and 55 years of age (37.3 ± 10.7 years) without known cardiac or metabolic disorders were enrolled into the study. After the standard ECG recording, two other recordings were obtained by placing the right precordial leads to the third and second ICS.

There were 15 subjects (3%) who displayed BTEP on their standard ECG recordings. Number of cases displaying BTEP increased to 25 (5%) and 38 (7.5%) when the right precordial leads were moved to third and second ICS, respectively. Although none of the subjects displayed type 1 BTEP on their standard ECGs, three subjects displayed type 1 BTEP on the third and four subjects displayed type 1 BTEP on the second ICS

- Our study revealed that the prevalence of type 1-3 ECG in healthy male subjects was 7.5% by placing the right precordial leads to higher ICS.

Type 1 ECG recorded in different sites or drug induced

- Upper spaces
- **drugs**

CLINICAL STUDIES

ELECTROPHYSIOLOGY

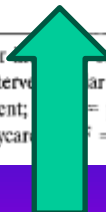
Autonomic and Antiarrhythmic Drug Modulation of ST Segment Elevation in Patients With Brugada SyndromeTOSHIHISA MIYAZAKI, MD, HIDEO MITAMURA, MD, SHUNICHIRO MIYOSHI, MD,
KYOKO SOEJIMA, MD, YOSHIFUSA AIZAWA, MD,* SATOSHI OGAWA, MD

Tokyo, Japan

Table 1. Clinical and Electrocardiographic Characteristics of Four Male Study Patients

Pt No./ Age (yr)	Syncope	Arrhythmias		ST Segment Elevation	QTc Interval (ms)	CAG (Ach test)	LVG (EF)	RVG	Biopsy
		Documented	Induced						
1/29	+	SVT	VF/SVT	V ₂ -V ₄	410	Normal (negative)	Normal (62%)	NP	NP
2/47	-	PVCs	VF	V ₁ -V ₄	390	Normal (negative)	Normal (60%)	NP	NP
3/41	+	-	VF	V ₁ -V ₄	430	Normal (negative*)	Normal (74%)	NA	NA
4/38	+	VF	-	V ₁ -V ₂	404	Normal (negative)	Normal (59%)	NP	NP

Ach test = acetylcholine provocation test for coronary spasm (*ergonovine was used instead of acetylcholine); biopsy = histologic examination of endomyocardial biopsy specimens taken from interventricular septum; CAG = coronary angiogram; EF = ejection fraction; LVG = left ventriculogram; NA = not available; NP = no particular findings; Pt = patient; PVCs = premature ventricular complexes; QTc interval = corrected QT interval; RVG = right ventriculogram; SVT = sustained monomorphic ventricular tachycardia; VF = ventricular fibrillation.



During drug infusion

Drugs tested:

- norepinefrina
- metoxamina
- isoproterenolo
- propanololo
- edrofonio
- neostigmina
- acetilcolina
- Disopiramide
- Procainamide
- nicorandil
- mexiletine
- verapamil

No adverse events.
The only possible conclusion is:

The subjects with this ecg resist to all drugs!!



Brugada 1996

212

Sudden death

1219 Ajmaline unmasks apparent right bundle branch block and ST segment elevation in V1–V3 in patients with 'idiopathic ventricular fibrillation'

J. Brugada, P. Brugada¹, R. Brugada². Arrhythmia Unit, Hospital Clinic, University of Barcelona, Spain; ¹ Cardiovascular Center, OLV Hospital, Aalst, Belgium; ² Baylor College of Medicine, Houston, TX, USA

It has been described that an electrocardiographic (ECG) pattern of apparent Right Bundle Branch Block (RBBB) and ST segment elevation in leads V1 to V3 is associated with sudden cardiac death (SD) in patients (pts) without demonstrable structural heart disease. It has also been described that these ECG abnormalities can transiently normalize during follow-up. To study whether these ECG abnormalities can be unmasked by pharmacological interventions, we studied the effects of a single dose of i.v. ajmaline in the ECG of pts with the described syndrome and transient normalization of the ECG and we compared it with the effects on pts previously classified as "idiopathic ventricular fibrillation" and with normals.

Methods: A single i.v. dose of 1 mgr/kg of ajmaline was administered during 5 min to: Group A) 5 pts with the RBBB + ST elevation + SD during transient normalization of the ECG; Group B) 7 pts previously classified as "idiopathic ventricular fibrillation"; and; Group C) 10 control pts with no history of syncope or SD and no structural heart disease.

Results: Ajmaline administration reproduced the ECG abnormalities previously observed but now transiently normalized in all pts in group A. Ajmaline administration produced a similar abnormal ECG pattern in 4 out of the 7 pts in group B with "idiopathic ventricular fibrillation". In none of the 10 control pts in group C this pattern was observed after ajmaline administration.

Conclusions: Ajmaline administration is a simple tool to unmask the RBBB + ST segment elevation in pts previously diagnosed as idiopathic ventricular fibrillation. Pending confirmation in a larger study group, these data suggest that some of the pts previously diagnosed as "idiopathic ventricular fibrillation" might suffer the RBBB + ST segment elevation + SD syndrome.

5/5 intermittent
Type 1
4/7 idiopathic VF
0/10 controls

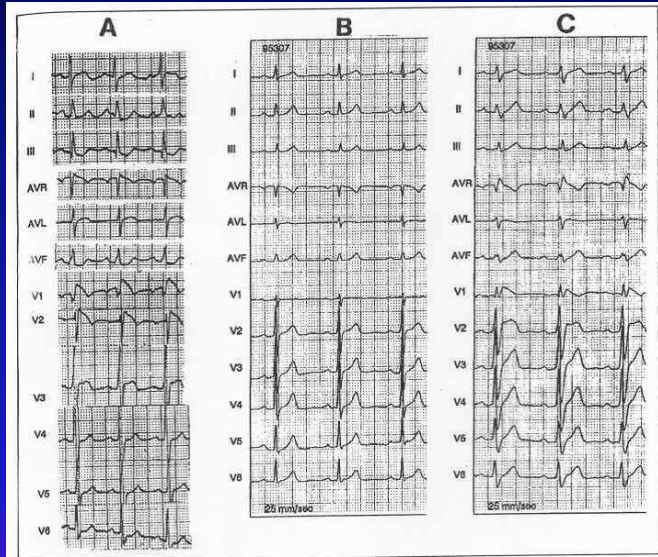
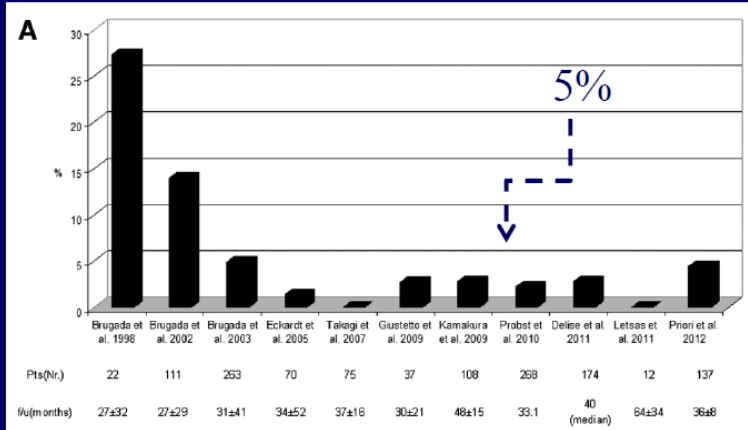
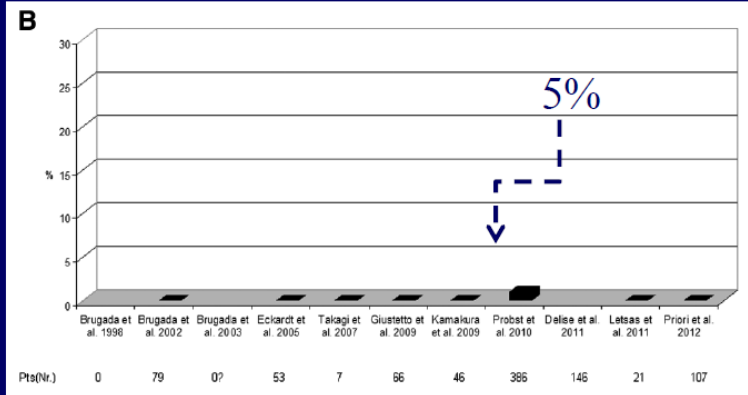


Fig. 5. A patient with the Brugada syndrome who suffered from aborted sudden death. Panel A shows the typical electrocardiogram. In panel B the electrocardiogram has normalized a few months later. Administration of intravenous ajmaline (panel C) uncovers the abnormalities again. Patients with "idiopathic" ventricular fibrillation must be challenged with ajmaline or procainamide to uncover this syndrome

Incidence of events (VT/VF ICD recorded +SD) in patients without previous cardiac arrest ((Mizusawa and Wilde 2012)



Spontaneous
Type 1



Drug-induced
Type 1

Everybody has Brugada syndrome until proven otherwise?



Sami Viskin, MD,^{*} Raphael Rosso, MD,^{*} Limor Friedensohn, MD,^{*} Ofer Havakuk, MD,^{*}
Arthur A.M. Wilde, MD, PhD[†]

From the ^{}Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University,
Tel Aviv, Israel, and [†]Heart Center, Academic Medical Center, Amsterdam, The Netherlands.*

- In Europe, 70% of patients diagnosed with “asymptomatic Brugada syndrome” received this diagnosis after a positive ajmaline test. Today, the most common reason for implantable cardioverter-defibrillator (ICD) implantation for Brugada syndrome in asymptomatic patients is “a positive ajmaline test with inducible VF during electrophysiologic studies.”

Drugs Proscription In BS

- **Drugs to be avoided by Brugada syndrome patients**
- *The following drugs have been associated with arrhythmias and the typical (type-1) Brugada syndrome ECG. Therefore the BrugadaDrugs.org Advisory Board strongly advises to avoid these drugs in Brugada syndrome patients or to use these drugs only after extensive consideration and/or in controlled conditions.*



Please cite as
Postema et al. Heart Rhythm 2009;6:1335-41 (PubMed ID 19716089)
and/or Postema et al. Europace 2013;15:1042-9 (PubMed ID 23533266)

Drugs and Brugada syndrome patients: Review of the literature, recommendations, and an up-to-date website
(www.brugadadrugs.org)

Pieter G. Postema, MD,* Christian Wolpert, MD,[†] Ahmad S. Amin, MD,[‡] Vincent Probst, MD, PhD,[¶] Martin Borggrefe, MD, PhD,[†] Dan M. Roden, MD,[§] Silvia G. Priori, MD, PhD,^{||} Hanno L. Tan, MD, PhD,^{**} Masayasu Hiraoka, MD, PhD,^{**} Josep Brugada, MD, PhD,^{††} Arthur A. M. Wilde, MD, PhD^{*‡}

- RESULTS The literature search yielded 506 reports for consideration.
- Drugs were categorized into one of four categories: (1) drugs to be avoided (n 18); (2) drugs preferably avoided (n 23); (3) antiarrhythmic drugs (n 4); and (4) diagnostic drugs (n 4).
- **Level of evidence for most associations was C (only consensus opinion of experts, case studies, or standard-of-care)** as there are no randomized studies and few non-randomized studies in Brugada syndrome patients
- **“Our study does not provide information about the incidence of drug induced Brugada syndrome. Publication bias may have resulted in significant overestimation of the mortality”**

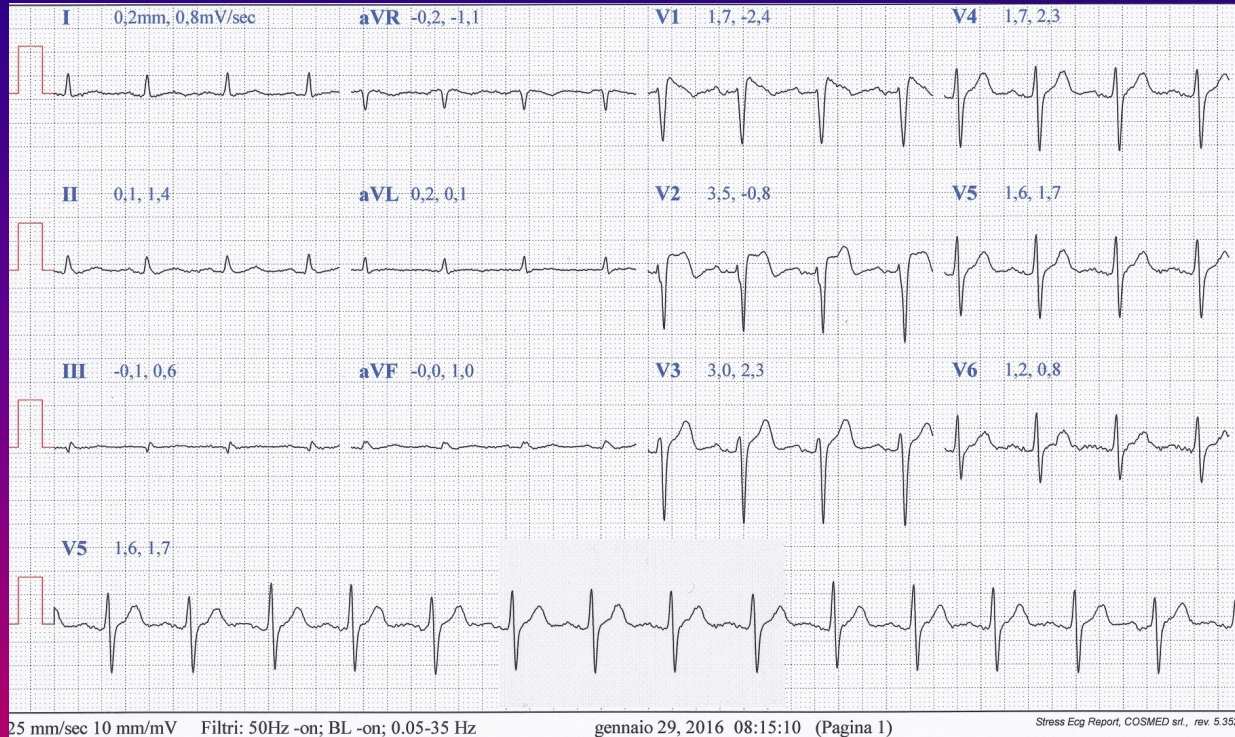
Drug-induced Brugada ECG

- - ECG pattern induced by drugs, often at toxic level.
- -

Use of Nonrecommended Drugs in Patients
With Brugada Syndrome: A Danish
Nationwide Cohort Study
Camilla H. B. Jespersen 2023

- No significant association between any non recommended BrS drug use after diagnosis and risk of all-cause mortality was identified (OR, 3.39 [95% CI, 0.7–19.6], $P=0.14$);

xx. propafenone 425 x 2 da 30 anni per FA su prescrizione Prof. Furlanello!!



Let's go back to the syndrome

- Fibrosis of the RV myocardium and of the conduction system

1976

KOH GOTOH

Fibrosis with a significant reduction of conduction fibers was observed in the sinoatrial node and junction between the node and atrial muscle fibers in 6 cases. Abnormal course and branching of the sinus node artery was seen in 6 cases of which 3 had no penetration of its main branch into the node. Some pathological lesions existed in the atrioventricular conduction system in 4 cases: 2 had fibrotic lesion in the distal bundle of His and proximal left and right bundle branches which were sandwiched between the abnormal conal muscle and the summit of ventricular septum. Remaining 2 had lipomatous partial interruption in the mid- and distal bundle of His. Simultaneous involvement of sinoatrial node and the atrioventricular conduction system was observed in 4 cases. One of such cases showed abnormal ECG consisted of a left axis deviation and right bundle branch block.

As a conclusion, pathological lesions in the conduction system are revealed in more than half of cases of "Pokkuri disease". The pathogenesis seems to be related to minor anomalies such as abnormal sinus node artery, abnormal conal muscle situation.

Histopathology of Conduction System of the "Pokkuri Disease"

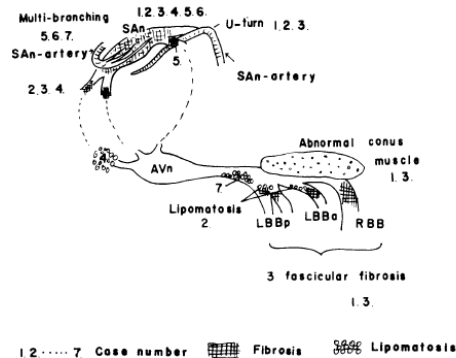


Fig.12. Changes of the cardiac conduction system found in 7 autopsy cases of Pokkuri disease.
Case 1, 2, 3, 4, 5 and 6 show the fibrosis at the SA-node.

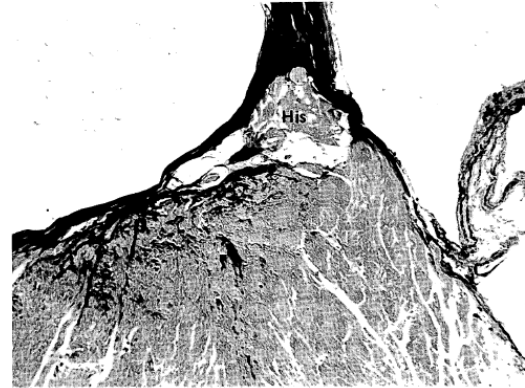


Fig.7. Mild to moderate replacement of the conduction cells by adipose tissue of the distal portion of the bundle of His.

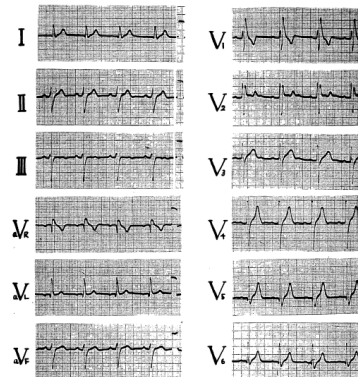
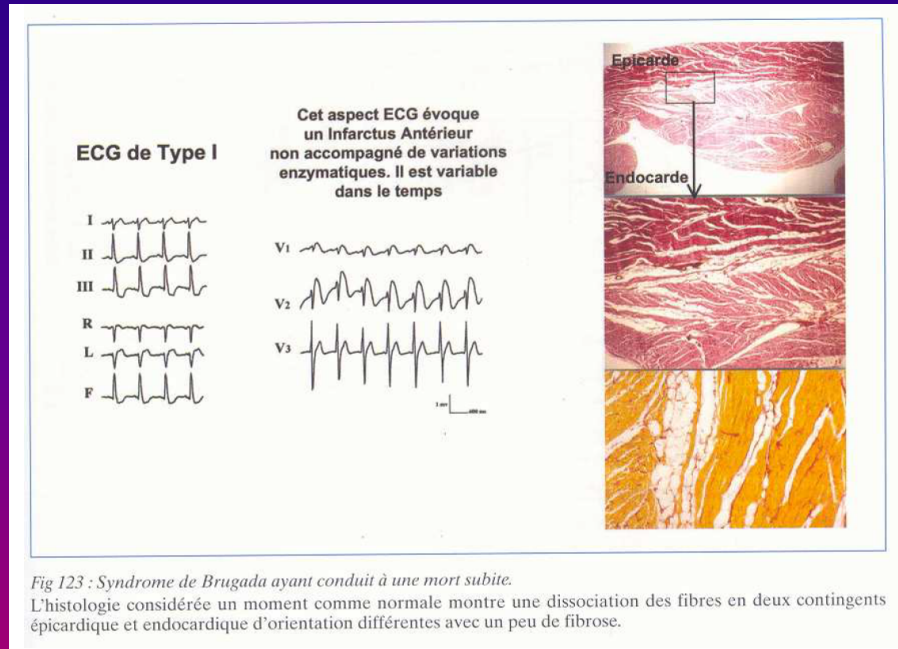


Fig.1. Sinus rhythm with left axis deviation of the QRS vector of over -30° and complete RBBB.

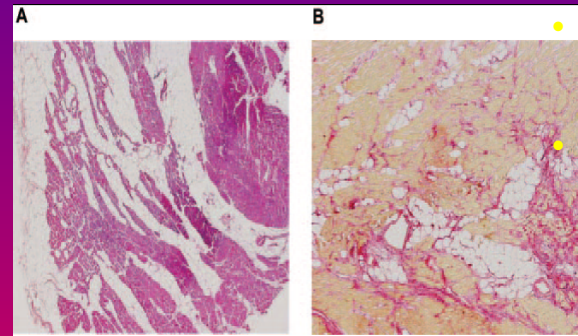
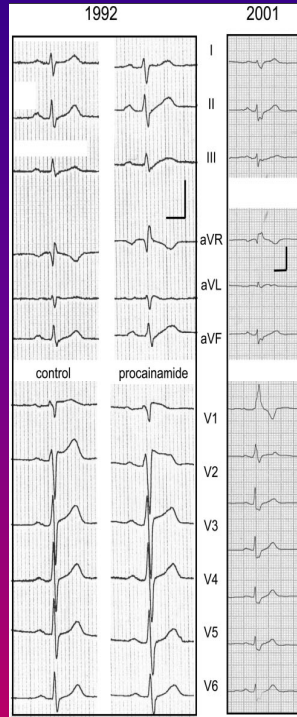
Guy Hughes Fontaine raccontava che nel 1999..



La morte subite dans le Jeune et de l'athlete. G. Fontaine 2010

**Right Ventricular Fibrosis and Conduction Delay in a
Patient With Clinical Signs of Brugada Syndrome
A Combined Electrophysiological, Genetic, Histopathologic,
and Computational Study. (Circulation. 2005;112:2769-2777.)**

R Coronel, S Casini, T Koopmann, F J G Wilms-Schopman, A O Verkerk, J R de Groot,
Z Bhuiyan, C R Bezzina, M W Veldkamp, A C Linnenbank, A C van der Wal, H L Tan, Pedro Brugada, Arthur A M Wilde, J M T de Bakker,

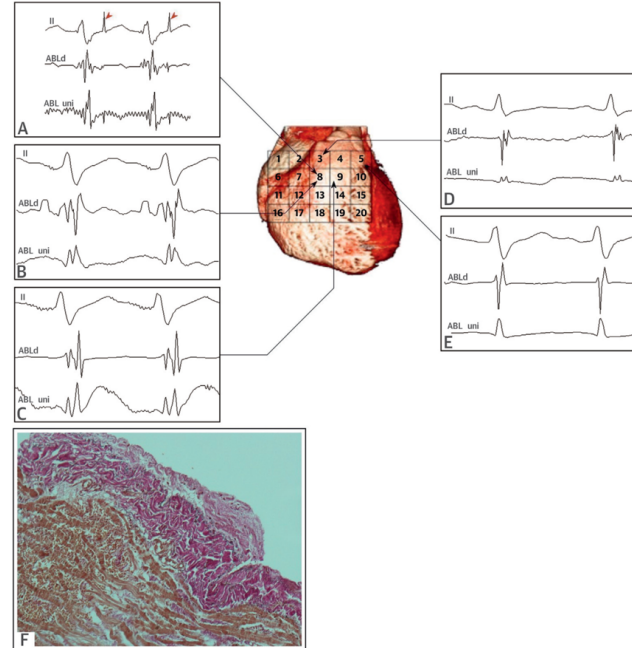


- In this patient with BS, conduction slowing based on interstitial fibrosis, but not transmural repolarization differences, caused the ECG signs .
- **Conclusions**
- At least in some cases of BS, subtle structural interstitial changes that are undetectable by routine diagnostic procedures may underlie both the ECG changes and the propensity for life-threatening arrhythmias. Our study provides evidence in support of the delayed-activation hypothesis for BS.
- Localized conduction delay in the RVOT epicardium may provoke the Brugada sign.

Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome. Jacc 2015

Koonlawee Nademanee, MD,* Hariharan Raju, PHD,y Sofia V. de Noronha, PHD,y Michael Papadakis, MD,y
Laurence Robinson, MBBs,y Stephen Rothery, BSc,z Naomasa Makita, MD,x Shinya Kowase, MD,k
Nakorn Boonmee, MD,{ Vorapot Vitayakitsirikul, MD,{ Samreng Ratanarapee, MD,# Sanjay Sharma, MD,y
Allard C. van der Wal, MD,** Michael Christiansen, MD,yy Hanno L. Tan, MD,** Arthur A. Wilde, MD,**zz
Akihiko Nogami, MD,xx Mary N. Sheppard, MD,y Gumpantart Veerakul, MD,{ Elijah R. Behr, MDy

- **METHODS** Six whole hearts from male post-mortem cases of unexplained sudden death (mean age 23.2 years) with negative specialist cardiac autopsy and familial BrS. An in vivo study was undertaken on 6 consecutive BrS patients (mean age 39.8 years, all men) during epicardial RVOT ablation for arrhythmia via thoracotomy. Abnormal late and fractionated potentials indicative of slowed conduction were identified, and biopsies were taken before ablation.
- **RESULTS** Collagen was increased in BrS autopsy cases compared with control hearts. Fibrosis was greatest in the RVOT and the epicardium. Autopsy and in vivo RVOT samples identified epicardial and interstitial fibrosis. This was collocated with abnormal potentials in vivo that, when ablated, abolished the type 1 Brugada electrocardiogram.
- **CONCLUSIONS** BrS is associated with epicardial surface and interstitial fibrosis and reduced gap junction expression in the RVOT. BrS is also associated with increased collagen throughout the heart. Abnormal myocardial structure and conduction are therefore responsible for BrS.



Subepicardial Cardiomyopathy: A Disease Underlying J-Wave Syndromes and Idiopathic Ventricular Fibrillation

Chris Miles, Bastiaan J. Boukens, Chiara Scrocco, Arthur A.M. Wilde, Koonlawee Nademanee, Michel Haissaguerre, Ruben Coronel, and Elijah R. Behr. 2023

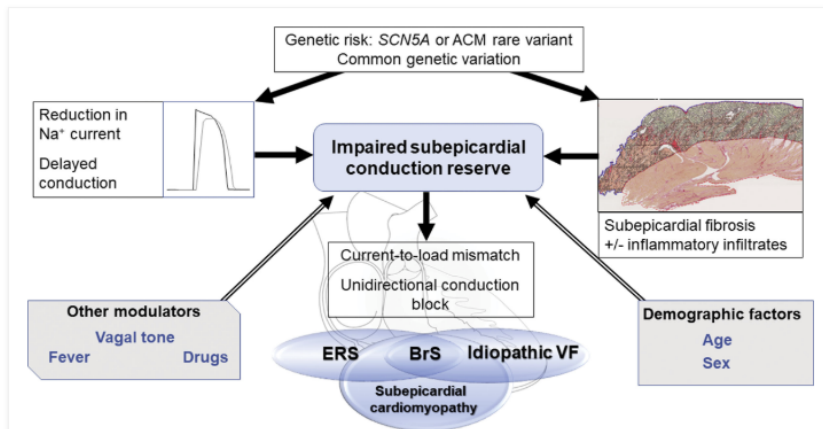


Figure 1. Proposed mechanisms and modulating factors underlying arrhythmogenesis in the subepicardial cardiomyopathy, giving rise to BrS, ERS, and idiopathic VF. ACM indicates arrhythmogenic cardiomyopathy; BrS, Brugada syndrome; ERS, early repolarization syndrome; and VF, ventricular fibrillation.

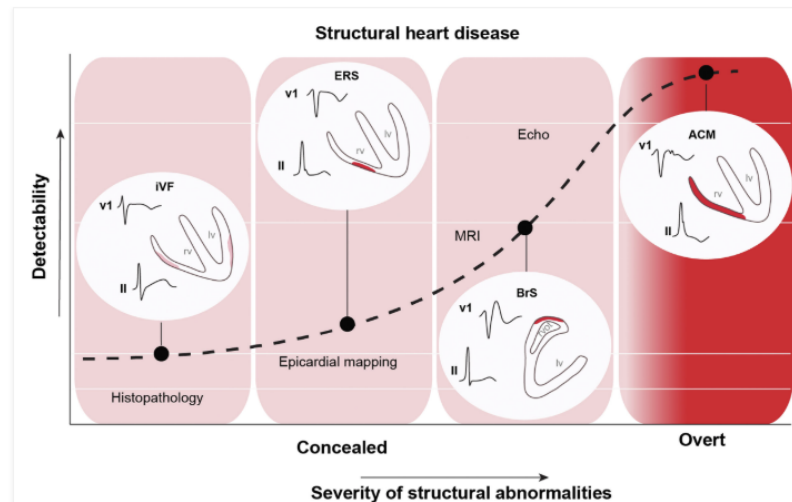


Figure 3. Detectability and severity of structural abnormalities in BrS, ERS, and ACM with respect to cardiac diagnostic modalities. ACM indicates arrhythmogenic cardiomyopathy; BrS, Brugada syndrome; ERS, early repolarization syndrome; iVF, idiopathic ventricular fibrillation; and MRI, magnetic resonance imaging. Adapted from Boukens et al⁹⁴ with permission. Copyright © 2020 Elsevier.

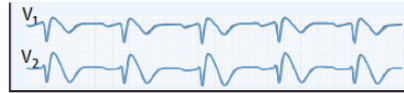


Left Ventricular Abnormal Substrate in Brugada Syndrome

Ghassen Cheniti, Michel Haissaguerre 2023

CENTRAL ILLUSTRATION Left Ventricular Substrate in Brugada Syndrome

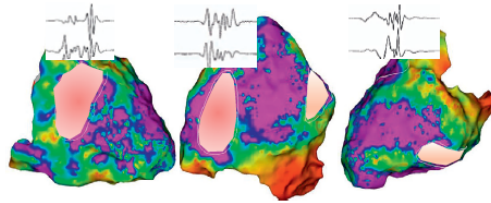
22 patients with Brugada syndrome
High-density epicardial biventricular mapping
Wide genetic screening to identify
SCN5A mutation and common risk variants



Anterior RV/RVOT

Inferior RV

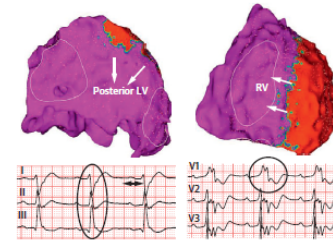
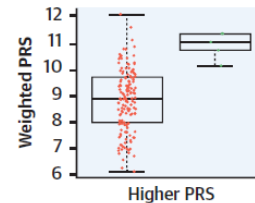
Inferolateral LV



Abnormal left ventricular substrate = 10 (45%)

SCN5A mutation = 70%

Larger RV substrate with inferior RV involvement in all cases



Atrioventricular and intraventricular
conduction abnormalities

Cheniti G, et al. J Am Coll Cardiol EP. 2023;9(10):2041-2051.

(Top) Electrocardiogram showing type 1 Brugada pattern. (Bottom Left) Epicardial anterior, inferior and left lateral views showing abnormal epicardial substrate. (Bottom Middle) Polygenic risk score showing higher score in patients with left ventricular substrate. (Bottom Right) Abnormal conduction identified in a subset of patients with left ventricular involvement. The arrows show areas of expected epicardial exits from the right and left posterior fascicles. LV = Left ventricle; PRS = polygenic risk score; RV = right ventricle.



**Local Depolarization Abnormalities
Are the Dominant Pathophysiologic Mechanism
for Type 1 Electrocardiogram in Brugada Syndrome**

A Study of Electrocardiograms, Vectorcardiograms, and
Body Surface Potential Maps During Ajmaline Provocation
Postema, Wilde A, JACC 2010



- **Conclusions: The type 1 BrS ECG is characterized predominantly by localized depolarization abnormalities, notably (terminal) conduction delay in the RV.**
- **The BS is a cardiomyopathy**

War is over!

Hippocratic Oath: not only a
superstitious gesture but a
serious scientific commitment
for all the following Medical and
scientific work

Delos Island, september 1968

Andrea Nava, Raffaello Chioin, Luciano
Schivazappa, Paolo Stritoni



*Isola di DELOS settembre 1968
Giuramento di Ippocrate*

Andrea Nava, the father of modern clinical arrhythmology. Chapeu!

Last and Final paper on the Nava syndrome



- Good morning bortolo, I have now read your manuscript and as you may anticipate I agree with you. This has been the case, maybe not from the very beginning, but early enough. My take home message from this type of cases is that a syndrome should not be named after someone but should have a descriptive title (like Long QT syndrome). Otherwise, researchers become blind for development (or they are emotionally too much involved as the Brugada brothers are). They are not open anymore to any other thoughts, and that is why they don't accept BrS as a disease in the CMP spectrum, despite the overwhelming evidence we have today
- Very best
- Arthur A. Wilde