

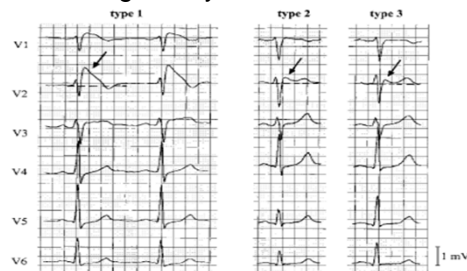
Update on Brugada Syndrome

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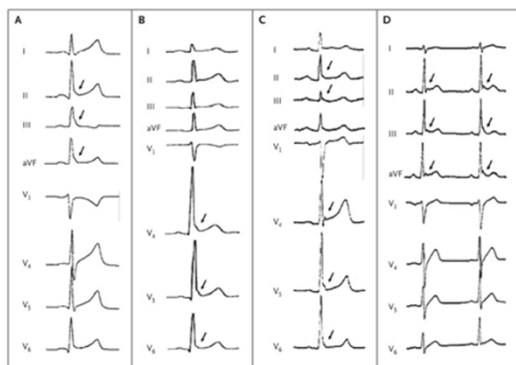
Brugada Syndrome ECG



ST-Segment Abnormalities in Leads V ₁ to V ₆			
	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	saddleback	saddleback
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.

Part of a Spectrum of Early Repolarization



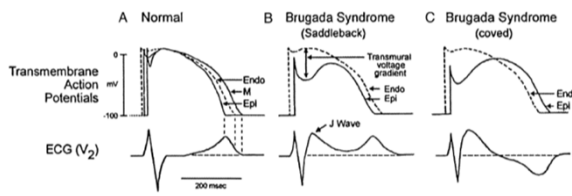
Haissaguerre, et al NEJM May 2008

Classification Scheme

	Inherited	Early repolarization in lateral leads (ERS type 1)	Early repolarization in inferior or inferolateral leads (ERS type 2)	Global early repolarization (ERS type 3)	Brugada syndrome	Acquired	Ischemia-mediated VT/VF	Hypothermia-mediated VT/VF
Anatomic location responsible for chief electrophysiologic manifestations	Anterolateral left ventricle	Inferior left ventricle	Left and right ventricles	Left and right ventricles	Right ventricle	Left and right ventricles	Left and right ventricles	Left and right ventricles
Leads displaying 2 point/3-point abnormalities	I, V ₁ -V ₂	II, III, aVF	Global	Global	V ₁ -V ₂	Any of the 12 leads	Any of the 12 leads	Any of the 12 leads
Response of 2-wave elevation to: Bradycardia or pause	Increase	Increase	Increase	Increase	Increase	N/A	N/A	N/A
Softens channel blockers	Little or no change	Little or no change	Little or no change	Little or no change	Increase	N/A	N/A	N/A
Gender dominance	Male	Male	Male	Male	Male	Male ^{70,71}	Yes	Other gender
VF	Rare; commonly seen in healthy men and athletes ^{72,73,74}	Rare	Yes electrical Storms ^{75,77}	Yes	Yes	Yes	Yes	Yes
Response to quinidine	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Inhibition of VT/VF ⁷⁸
Response to isoproterenol	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF	Normalization of 3-point elevation and inhibition of VT/VF
Gene mutations	CACNA1C, CACNA1C, CACNA2D1	KCNB1 ⁷⁹ , CACNA1C, CACNA2D1	CACNA1C ⁸⁰	CACNA1C ⁸¹	SCN5A, CACNA1C, CACNA2D1, GPD1-L, SCN5B, KCNE1, SCN3B, KCNB1	SCN5A ⁸²	SCN5A ⁸³	N/A

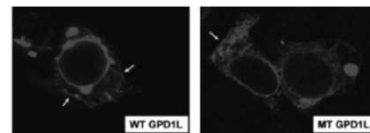
ERS = early repolarization syndrome; N/A = not available; VF = ventricular fibrillation; VT = ventricular tachycardia.

Repolarization Hypothesis



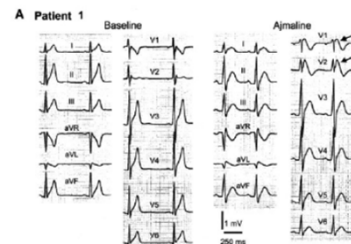
Other Genes

- GPD1-L & (MOG-1) Na channel- Reduced membrane Expression of SCN5a

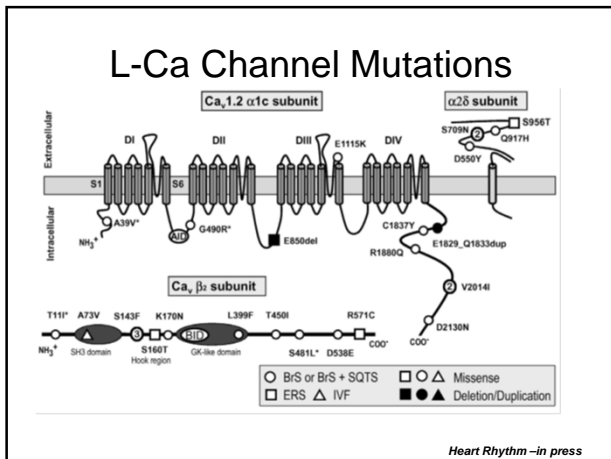


- CACNA1C L type Ca channel BS morphology and short QTc

- KCNE3 & 5 Upregulates Ito



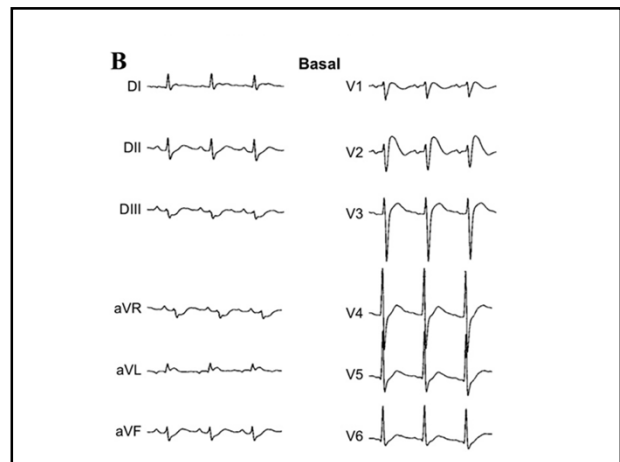
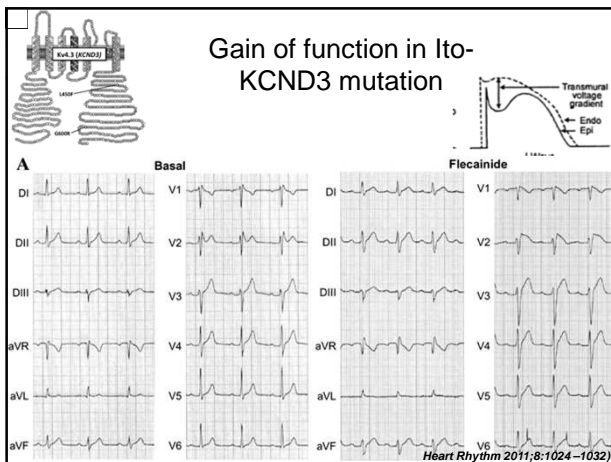
Antzelevitch et al, Circulation 2007.



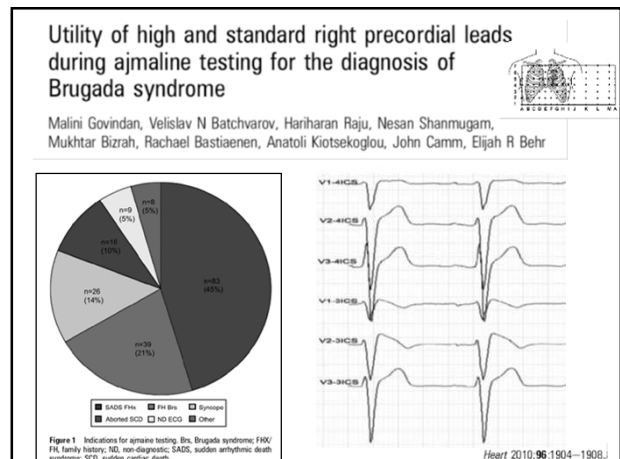
Frequencies

Diagnosis	Brugada Syndrome, BrS/SQT			IVF			ERS		
Number of screened probands	162			19			24		
Subunits	α1	β2	α2δ	α1	β2	α2δ	α1	β2	α2δ
Number of probands with mutations for α1,n	9						1		
Yield%	5.5%						4.1%		
Number of probands with mutations for β2,n		8		1				2	
Yield%		4.9%		5.2%				8.3%	
Number of probands with mutations for α2δ,n			3						1
Yield%			1.8%						4.1%
Total Yield of probands with mutations %	12.3%			5.2%			16%		
Number of probands with rare polymorphism for α1,n	7			1			1		
Yield%	4.3%			5.2%			4.3%		
Number of probands with rare polymorphism for β2,n		2		2				2	
Yield%		1.2%		10.5%				8.3%	
Total Yield of probands with mutations and rare polymorphisms %	17.9%			21%			29.1%		

KCN J8/KATP Channel- <1%



Diagnosis



Vertical Lead Relationship



Table 1 Baseline characteristics of ajmaline subjects (n=183)

	Positive ajmaline tests (n=31)			p Value
	Standard (SL) and high leads (HL) positive (n=18)	High leads (HL) only positive (n=13)	Negative ajmaline test (n=152)	
Age (years)	44 ± 17	42 ± 16	35 ± 14	0.025*
Sex (men)	10 (32%)	8 (26%)	94 (62%)	NS
Weight (kg)	74 ± 13	76 ± 12	75 ± 17	NS
Ajmaline dose (mg)	60 ± 19	65 ± 18	74 ± 17	0.02*
Heart rate (beats/min)	64 ± 10.2	68 ± 12.5	71 ± 14.4	NS
PR (ms)	170 ± 38	160 ± 17	160 ± 28	NS
PR max (ms)	226 ± 40	261 ± 69	213 ± 36	0.04
QRS (ms)	112 ± 23	97 ± 13	100 ± 16	0.01†
QRS max (ms)	158 ± 32	138 ± 17	134 ± 22	0.001†
QTc (ms)	391 ± 47	383 ± 30	394 ± 34	NS
QTcF max (ms)	416 ± 69	402 ± 36	407 ± 39	NS
Family history of Brugada syndrome	6 (33%)	5 (38%)	28 (18%)	0.03*
Family history of sudden cardiac death	7 (39%)	4 (31%)	73 (48%)	NS
His of syncope	3 (17%)	1 (8%)	22 (14%)	NS

*Significance between the positive test group and negative test group but not between standard leads (SL) + high leads (HL) and HL only.

†Significance between (SL + HL) group and HL, and (SL + HL) and negative group but not HL and negative group.

QTcF, corrected QT interval using Fredericia formula.

Differentiating RBBB from Type II and Type III BrS ECG

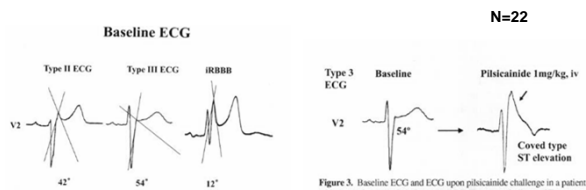


Figure 1. Measuring the terminal QRS angle. The angle between the axis of the upstroke of the S wave and that of the downstroke of the r' wave is measured on the baseline ECG.

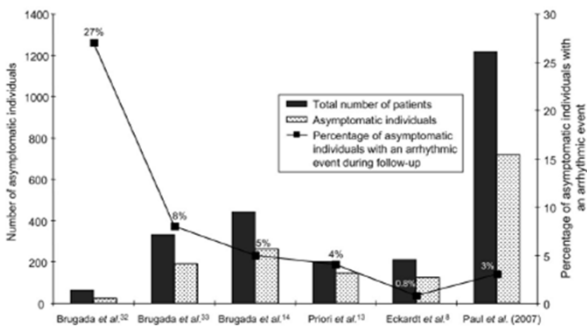
Figure 2. Baseline ECG and ECG upon pilsicainide challenge in a patient with a type 3 (angle: 54°) Brugada ECG. The arrow indicates ST segment elevation after administration of pilsicainide.

23% - PPA of 76%, NPV 100% conversion to Type 1 ECG

Ohkubo et al, Int Heart Journal, 52, 159-63

Prognosis

Brugada registry: asymptomatic individuals with an arrhythmic event during follow-up in different publications



Finger Registry

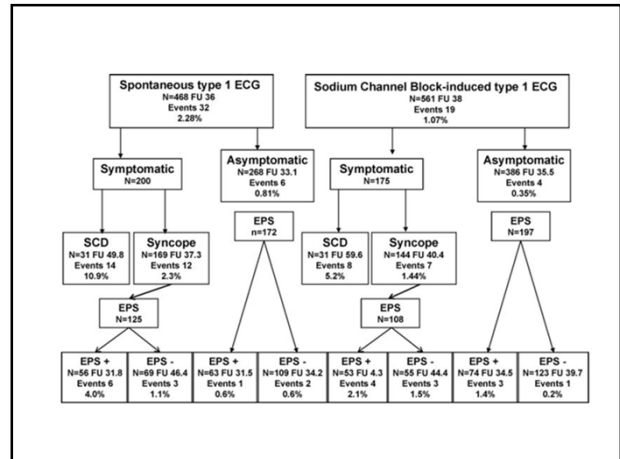
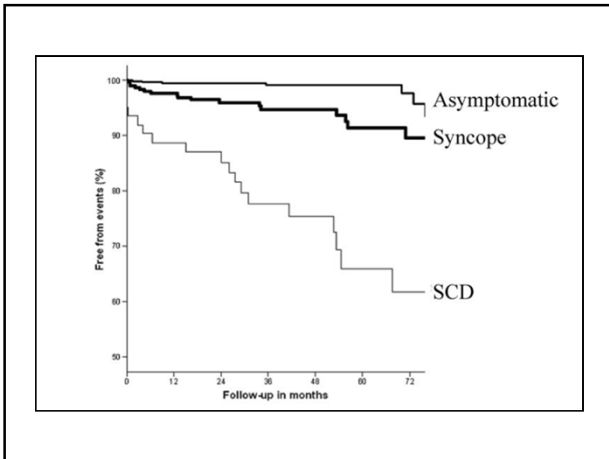
Table. Patient Characteristics According to Their Clinical Presentation

	Cardiac Arrest Group	Syncope Group	Asymptomatic Group	P
No. of patients	62	313	654	
Index patients, %	98	93	70	<0.001
Male, n (%)	55 (89)	238 (76)	452 (69)	0.01
Age at diagnosis, y	43 (35-54)	46 (37-57)	45 (35-55)	0.19
Family history of SCD, n (%)	6 (10)	63 (20)	195 (30)	<0.001
PR, ms	160 (130-190)	180 (158-200)	171 (160-195)	0.01
QRS, ms	106 (95-120)	105 (93-117)	100 (92-115)	0.19
ST elevation, mm	2 (0.4-3)	2 (1-4)	2 (0.2-3)	0.002
Spontaneous type 1 ECG, n (%)	31 (50)	169 (54)	268 (41)	0.001
EPS performed, n (%)	36 (58)	233 (74)	369 (56)	<0.001
Inducible VT/VF, n (%)	16 (44)	109 (47)	137 (37)	0.06
SCN5A mutations, n (%)	12/49 (24)	53/203 (26)	120/398 (30)	0.92
Follow-up, mo	44 (26-68)	34 (14-58)	31 (13-53)	0.01
No. of patients with events during follow-up	22	19	10	<0.001
Mean event rate per year, %	7.7	1.9	0.5	

VT/VF indicates ventricular tachycardia/ventricular fibrillation.

*The follow-up is the time between the first event or the last new date and the diagnosis ECG date.

Circulation. 2010;121:635-643

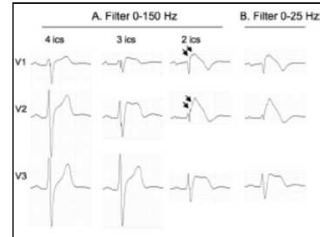


The Question of VF Inducibility

Japanese Study		Europe FINGER Study		Both studies	
Spontaneous type I	Drug-induced type I	Spontaneous type I	Drug-induced type I	Spontaneous type I	Drug-induced type I
57	34	172	197	229	231
Inducible VF	Inducible VF	Inducible VF	Inducible VF	Inducible VF	Inducible VF
32 (56%)	20 (59%)	63 (37%)	74 (37%)	95 (42%)	94 (41%)
Spontaneous VF at 4 years	Spontaneous VF at 5 years	Spontaneous VF at 4 years	Spontaneous VF at 5 years	Spontaneous VF at 4 years	Spontaneous VF at 5 years
1/29=3%	0/20=0%	1/63=2%	3/74=4%	2/95=2%	3/94=3%
1/52 = 1.9%		4/137 = 2.9%		5/189 = 2.6%	
Spontaneous type I	Drug-induced type I	Spontaneous type I	Drug-induced type I	Spontaneous type I	Drug-induced type I
25	14	109	123	134	127
Negative EPS	Negative EPS	Negative EPS	Negative EPS	Negative EPS	Negative EPS
2/25=8%	0/14=0%	2/109=2%	1/123=1%	4/134=3%	1/127=1%
2/29 = 5.1%		3/232 = 1.3%		5/271 = 1.8%	

Viskin, Rosso JACC 2010;1585-8

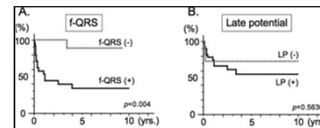
Fragmented QRS and Prognosis



n=115 cases

SCN5A pos in 33% with fQRS vs 5% without.

58% fQRS pos=VF
6% fQRS neg =VF



Morita et al, Circulation 2008;118;1697-1704

Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients With Brugada Syndrome

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Saita and Osaka, Japan

(J Am Coll Cardiol 2010;56:1576-84)

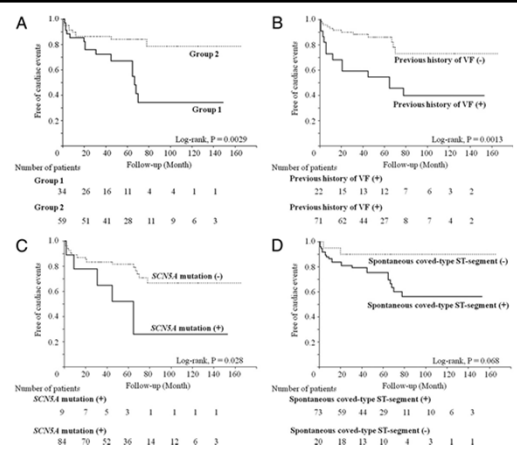
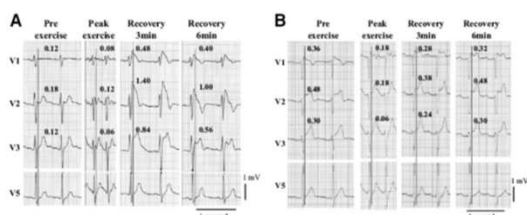


Table 4 Incidence of Cardiac Events According to Symptoms Before Exercise Testing

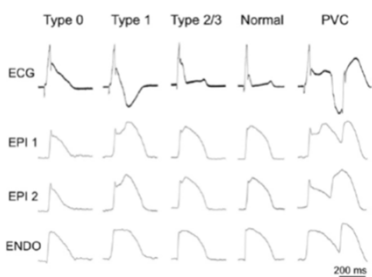
Type	n	Treadmill Exercise Test	n	VF Occurrence	p Value (vs. Group 1)
Documented VF	22	Group 1	7	6 (86%)	0.14
		Group 2	15	7 (47%)	
Syncope alone	35	Group 1	12	6 (50%)	0.016
		Group 2	23	3 (13%)	
Asymptomatic	36	Group 1	15	3 (20%)	0.039
		Group 2	21	0 (0%)	

Predictive Capabilities of Cardiac Events

	Positive, n (%)	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	p Value	HR (95% CI)	p Value
Previous episodes of VF	22 (24%)	3.40 (1.54-7.53)	0.003	3.25 (1.43-7.37)	0.005
Augmentation of ST-segment elevation at early recovery phase	34 (37%)	3.17 (1.42-7.09)	0.005	3.17 (1.37-7.33)	0.007
SCNSA mutation	9 (10%)	2.86 (1.07-7.66)	0.037		
Spontaneous coved-type ST-segment	72 (77%)	3.51 (0.83-14.9)	0.089		
Late potential	56/91 (64%)	2.25 (0.84-5.99)	0.11		
VF inducible in EPS	59/78 (76%)	0.73 (0.30-1.75)	0.48		
Family history of SCD or BrS	23 (25%)	1.19 (0.47-3.02)	0.72		

HR = Brugada syndrome; CI = confidence interval; EPS = electrophysiologic study; HR = hazard ratio; other abbreviations as in Table 2.

Spontaneous ECG Alterations Predict VF



Take et al, Heart Rhythm 2011;8:1014-102

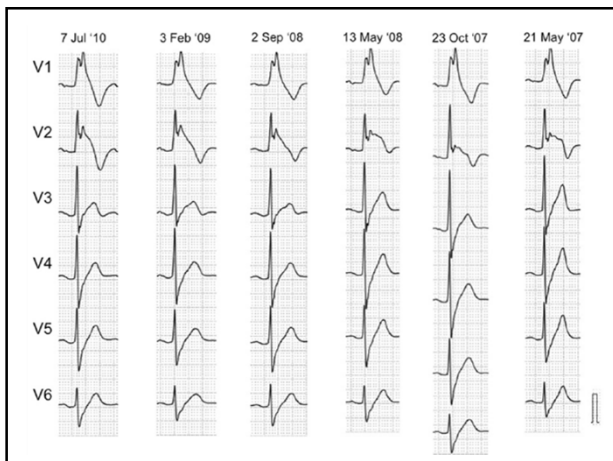
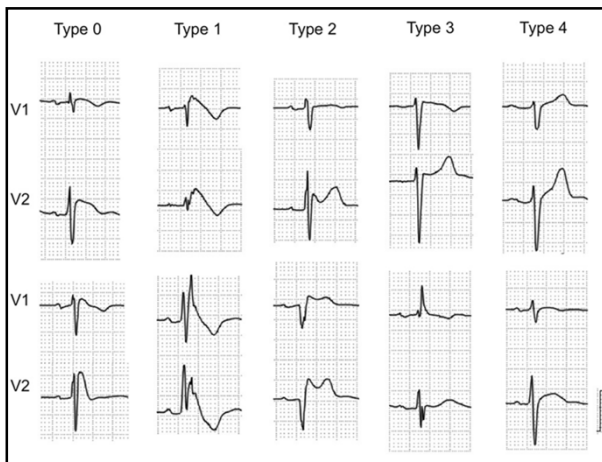


Table 1 Clinical and ECG parameters in patients with Brugada syndrome

	Asymptomatic	VF	P
Patients background			
n	41	33	—
Female	3	1	NS
Age	68 ± 6	48 ± 11	<.001
Follow-up period	60.8 ± 37.6	75.7 ± 53.9	NS
Family history	8 (19)	11 (35)	NS
SCNSA mutation (n = 43) (%)	4 (15)	4 (24)	NS
PES induced VF (n = 46) (%)	3 (10)	19 (46)	.0008
ECG alterations (%)			
ECG type	18 (44)	32 (97)	<.0001
ST change ≥2 mm	6 (15)	30 (91)	<.0001
Spontaneous appearance of ECG type during follow-up (%)			
Type 0	2 (5)	23 (70)	<.0001
Type 1	24 (59)	30 (91)	.0014
Type 2	29 (71)	25 (76)	NS
Type 3	6 (15)	11 (33)	NS
Normal	5 (12)	20 (61)	<.0001
ECG Parameters			
II			
RR, ms	949 ± 188	958 ± 168	NS
PQ, ms	193 ± 42	183 ± 38	NS
QRS, ms	105 ± 13	118 ± 17	.0007
V1			
QT, ms	377 ± 43	405 ± 39	.0048
ST level, mV	0.16 ± 0.10	0.25 ± 0.16	.0026
Spikes	2.4 ± 0.8	2.9 ± 1.0	.0189
V2			
QT, ms	386 ± 35	407 ± 51	.0495
ST level, mV	0.29 ± 0.16	0.39 ± 0.25	.0393
Spikes	2.6 ± 0.9	3.3 ± 1.1	.0064
V3			
QT, ms	385 ± 30	391 ± 40	NS
ST level, mV	0.19 ± 0.11	0.25 ± 0.15	NS
Spikes	1.7 ± 0.8	2.1 ± 1.1	NS
V5			
QT, ms	386 ± 34	376 ± 24	NS
ST level, mV	0.03 ± 0.05	0.06 ± 0.06	.0368
Spikes	1.2 ± 0.5	1.3 ± 0.5	NS
QRS			
Total spikes (V1-3)	6.6 ± 1.7	8.3 ± 2.3	.0011
Spikes/min (V1-3)	37 (44)	32 (43)	.0001

Treatment

Arrhythmia/Electrophysiology

Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

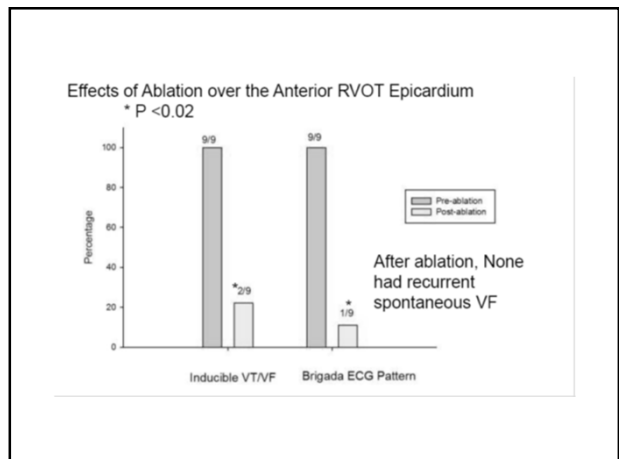
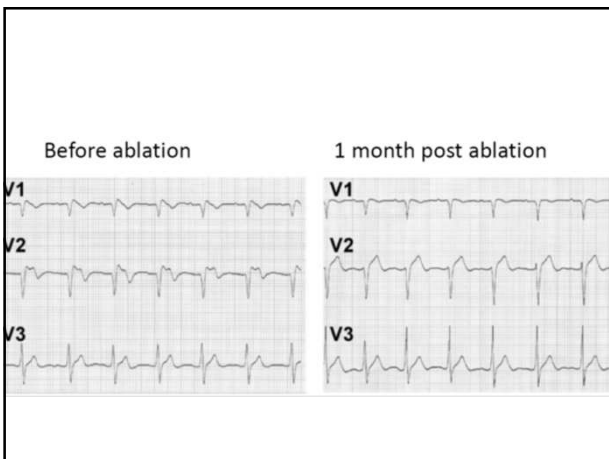
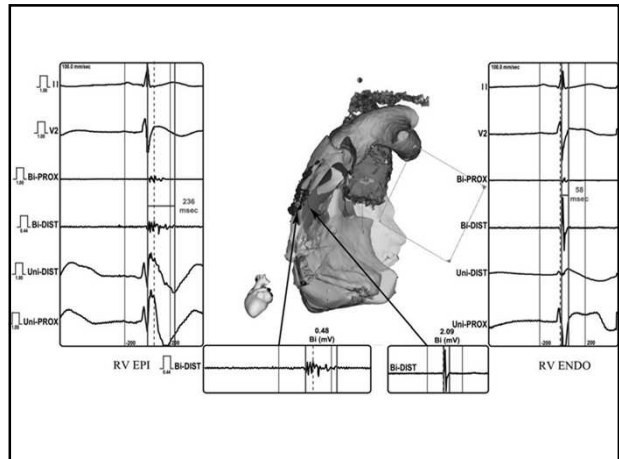
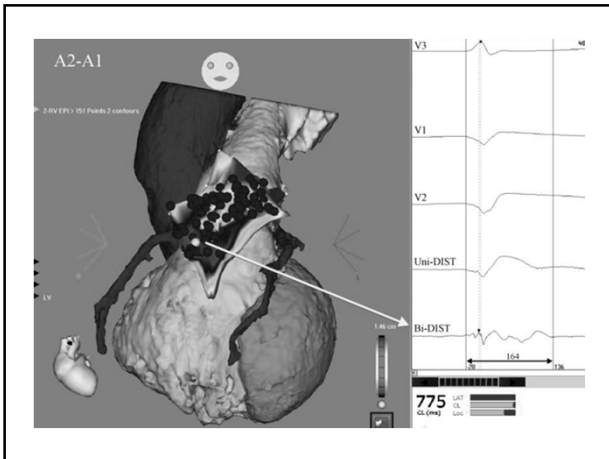
Koonlawee Nademanee, MD; Gumparnat Veerakul, MD; Pakorn Chandanamattha, MD; Lertlak Chaohawee, MD; Aekarach Ariyachaijanich, MD; Kriengkrai Jirasirojanakorn, MD; Khanchit Likittansombat, MD; Kiertijai Bhuripanyo, MD; Tachapong Ngarmukos, MD

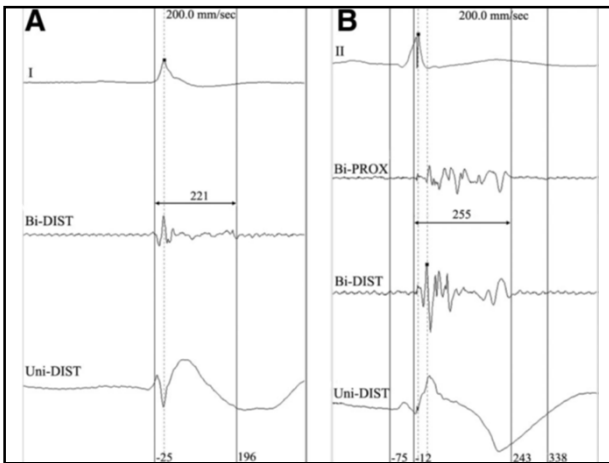
Background—The underlying electrophysiological mechanism that causes an abnormal ECG pattern and ventricular tachycardia/ventricular fibrillation (Vt/VF) in patients with the Brugada syndrome (BS) remains undeciphered. However, several studies have indicated that the right ventricular outflow tract (RVOT) is likely to be the site of electrophysiological substrate. We hypothesized that in patients with BS who have frequent recurrent VF episodes, the substrate site is the RVOT, either over the epicardium or endocardium; abnormal electrograms would be identified at this location, which would serve as the target site for catheter ablation.

Methods and Results—We studied 9 symptomatic patients with the BS (all men; median age 38 years) who had recurrent VF episodes (median 4 episodes per month, necessitating implantable cardioverter defibrillator discharge). Electromechanical mapping of the right ventricle, both endocardially and epicardially, and epicardial mapping of the left ventricle were performed in all patients during sinus rhythm. All patients had typical type 1 Brugada ECG pattern and inducible Vt/VF; they were found to have unique abnormal low voltage (0.94±0.79 mV), prolonged duration (132±48 ms), and fractionated late potentials (96±47 ms beyond QRS complex) clustering exclusively in the anterior aspect of the RVOT epicardium. Ablation at these sites rendered Vt/VF noninducible (7 of 9 patients [78%]; 95% confidence interval, 0.40 to 0.97, $P=0.015$) and normalization of the Brugada ECG pattern in 89% (95% confidence interval, 0.52 to 0.99; $P=0.003$). Long-term outcomes (20±6 months) were excellent, with no recurrent Vt/VF in all patients off medication (except 1 patient on amiodarone).

Conclusions—The underlying electrophysiological mechanism in patients with BS is delayed depolarization over the anterior aspect of the RVOT epicardium. Catheter ablation over this abnormal area results in normalization of the Brugada ECG pattern and prevents Vt/VF, both during electrophysiological studies as well as spontaneous recurrent Vt/VF episodes in patients with BS. (*Circulation*. 2011;123:1270-1279.)

Key Words: Brugada syndrome ■ catheter ablation ■ arrhythmia ■ electrophysiology ■ mapping





Conclusions