Primer elektriksel bozuklukların tedavisinde yeni gelişmeler: Brugada sendromu

Dr.İlknur Can

NE Üni Meram Tıp Fak Kardiyoloji KONYA

4. AF Zirvesi 2015

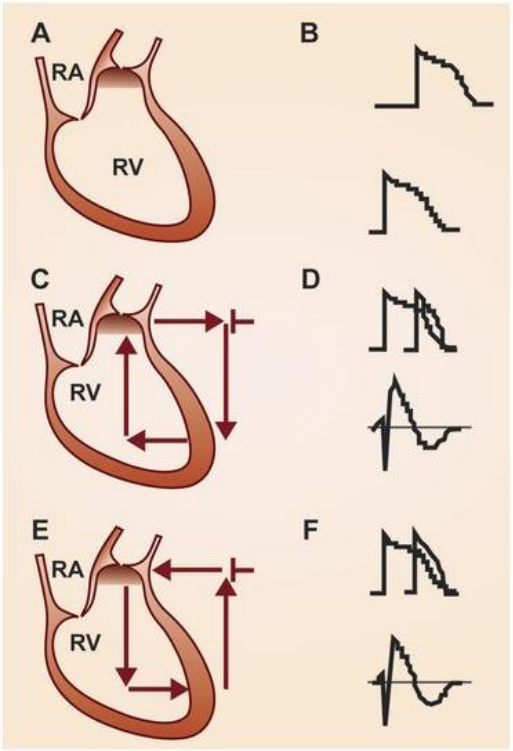
Yeni gelişmeler

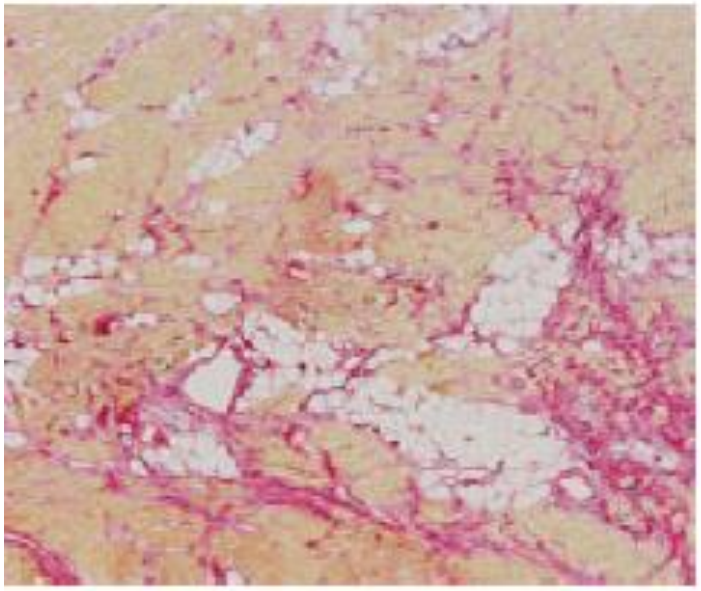
- Ablasyon
  - Endokardiyal
  - Epikardiyal
  - Pulmoner ven izolasyonu
- İlaç
  - Bepridil
  - Cilostazol+bepridil kombinasyonu

Aritmik substrat ile ilgili teoriler

Depolarizasyon bozukluğu teorisi:

RV ye göre RVOT da yavaşlamış ileti





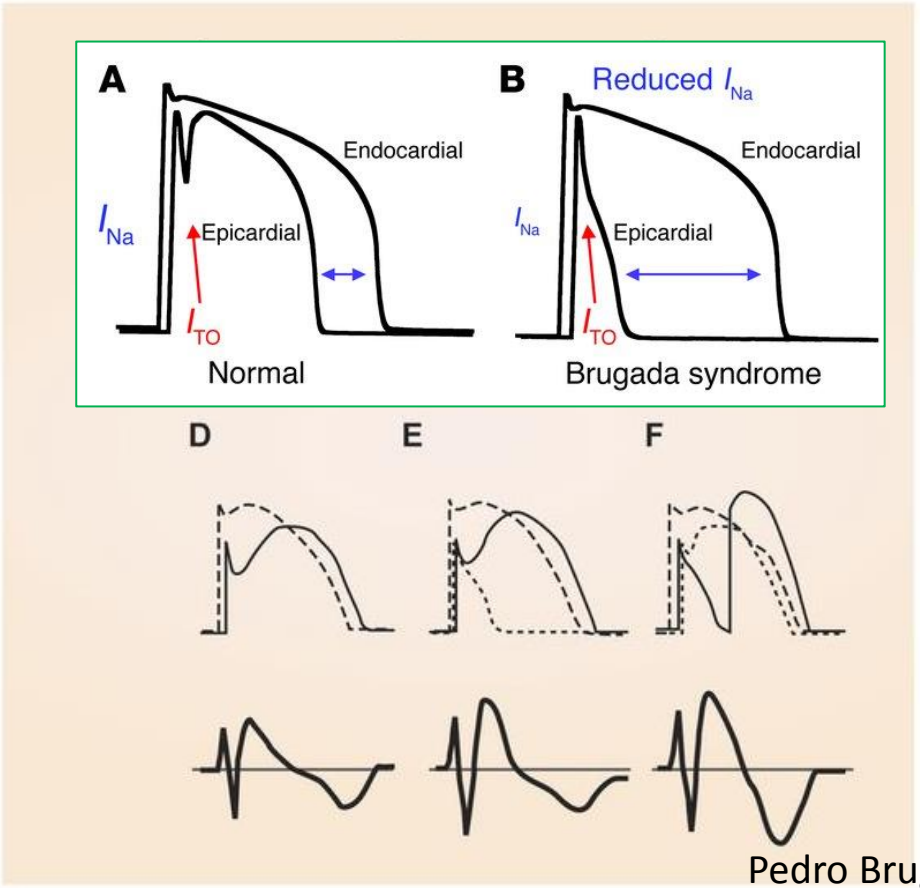
Pedro Brugada. Eur Heart J 2013

Coronel R, Circulation 2005

Aritmik substrat ile ilgili teoriler

Repolarizasyon bozukluğu teorisi

RVOT epikardı



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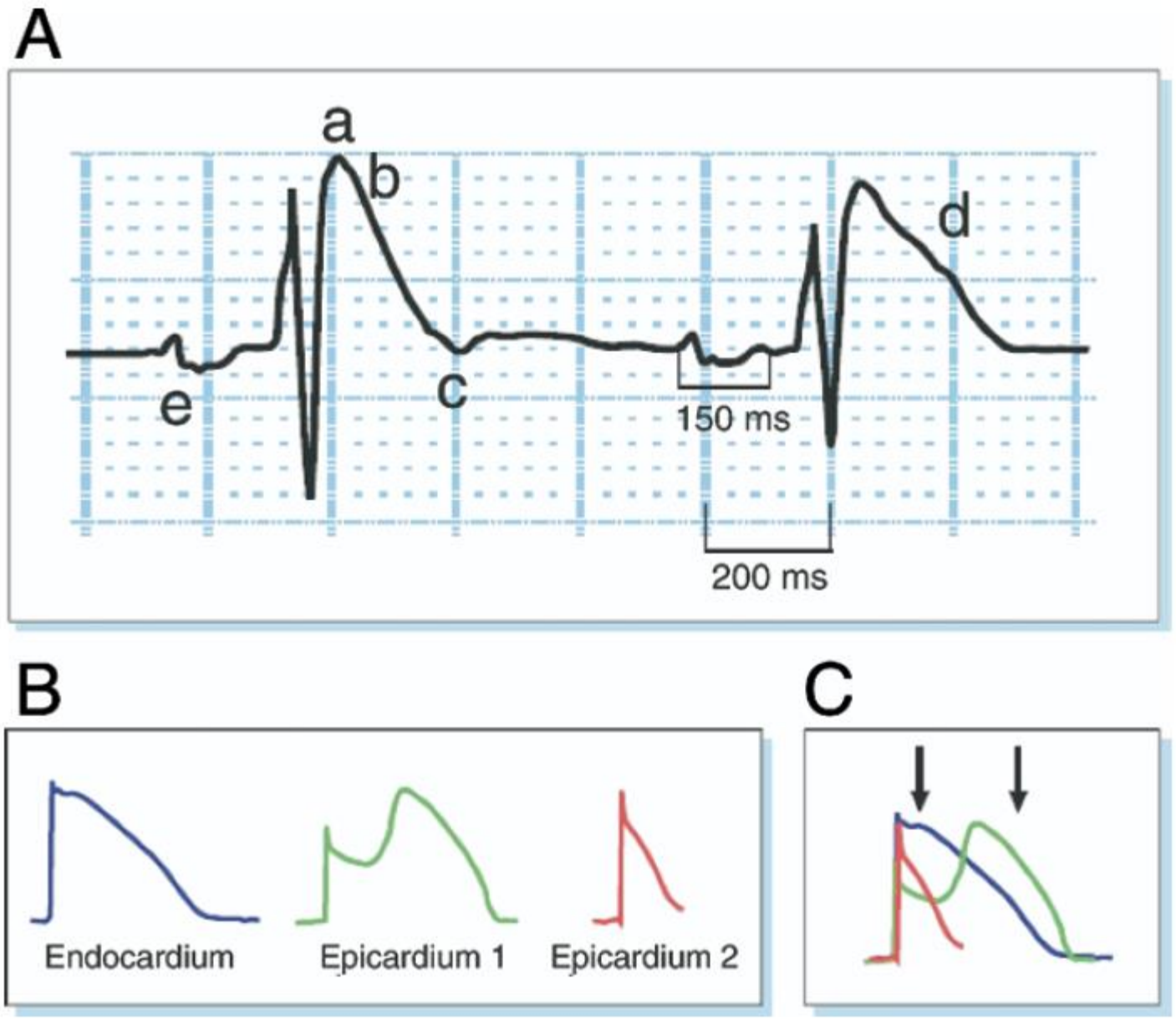
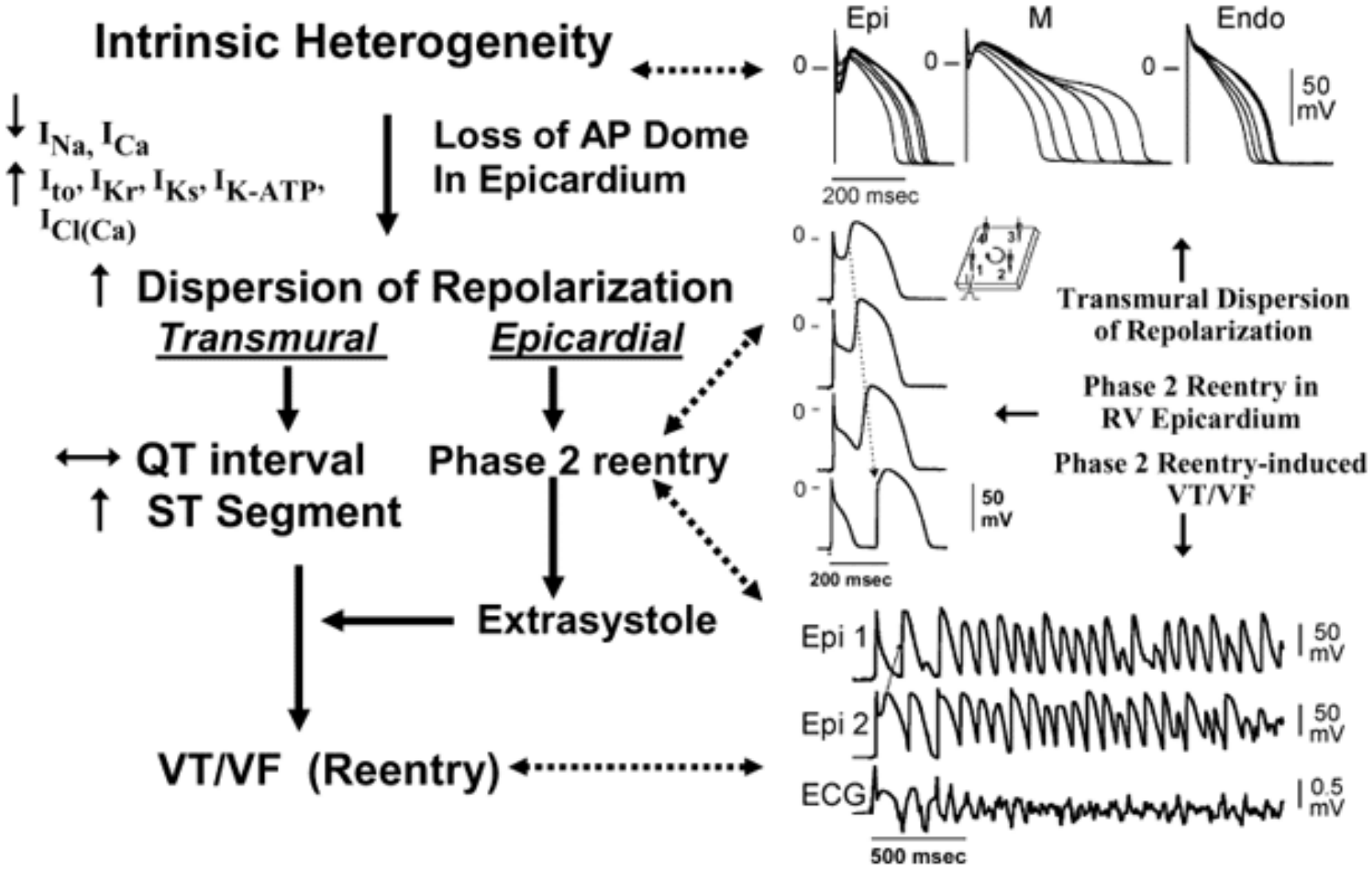

A
a
b
c
d
e
150 ms
200 ms
B
Endocardium
Epicardium 1
Epicardium 2
C

Brugada Syndrome



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  - Cilostazol+bepridil kombinasyonu

RERKÜRREN VT/VF: *ICD ŞOKLARI*

Regional Substrate Ablation Abolishes Brugada Syndrome

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A 43-year-old man presented with syncope, family history of unexplained sudden death in his 41-year-old father, and unprovoked and consistent electrocardiographic (ECG) features of Brugada syndrome. SCN5A mutation was absent. Two months after the implantation of a defibrillator, he experienced recurrent shocks triggered by frequent episodes of ventricular fibrillation (VF). The ECG recorded between the episodes showed sinus rhythm with unprovoked Brugada pattern in leads V1 and V2 and frequent isolated left bundle branch block morphology ventricular ectopic beats with inferior axis and QRS transition in lead V4. On continuous 12-lead ECG monitoring, the ectopics initiating VF were observed to resemble the isolated ectopics. The patient consented for the ablation of the ectopics triggering VF.

Due to the absence of clinical ectopics during invasive electrophysiology study, endocardial ablation was performed focally on the septal and the anterolateral right ventricular outflow tract (RVOT) under the guidance of pace mapping.Initial ablation of these foci triggered flurry of non-sustained episodes of VF. Later, ectopics disappeared and ablation was reinforced in a wider area surrounding both foci (total ablation time—56 minutes). This led to the disappearance of Brugada pattern in leads V1–V2, and the ECG normalized. The ECG remained normal during the subsequent hospital stay and at every follow-up visit thereafter. The patient has not experienced any arrhythmia and the ECG has no evidence of Brugada pattern 6.5 years after ablation.

To our knowledge, this is the first clinical report of long-term abolition of ventricular arrhythmias and ECG pattern of Brugada syndrome by the ablation of the RVOT substrate. Arrhythmogenic substrate ablation has a potential to cure and impact the natural course of primary electrical disorders like Brugada syndrome.

J Cardiovasc Electrophysiol, Vol. 22, pp. 1290-1291, November 2011.

No disclosures.

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doi: 10.1111/j.1540-8167.2011.02054.x

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43 y erkek hasta

ICD- 2 ay sonra rekürren VF atakları

RVOT orijinli izole ektopikler-VF

RVOT da ***endokardiyal ablasyon***-işlem sırasında ektopi yok

Pace mapping-Süreksiz VF atakları

Septal-AL duvarda 56 dak ablasyon

İşlem sonunda EKG düzelmiş

6.5 yıl takip. EKG düzgün-aritmi yok

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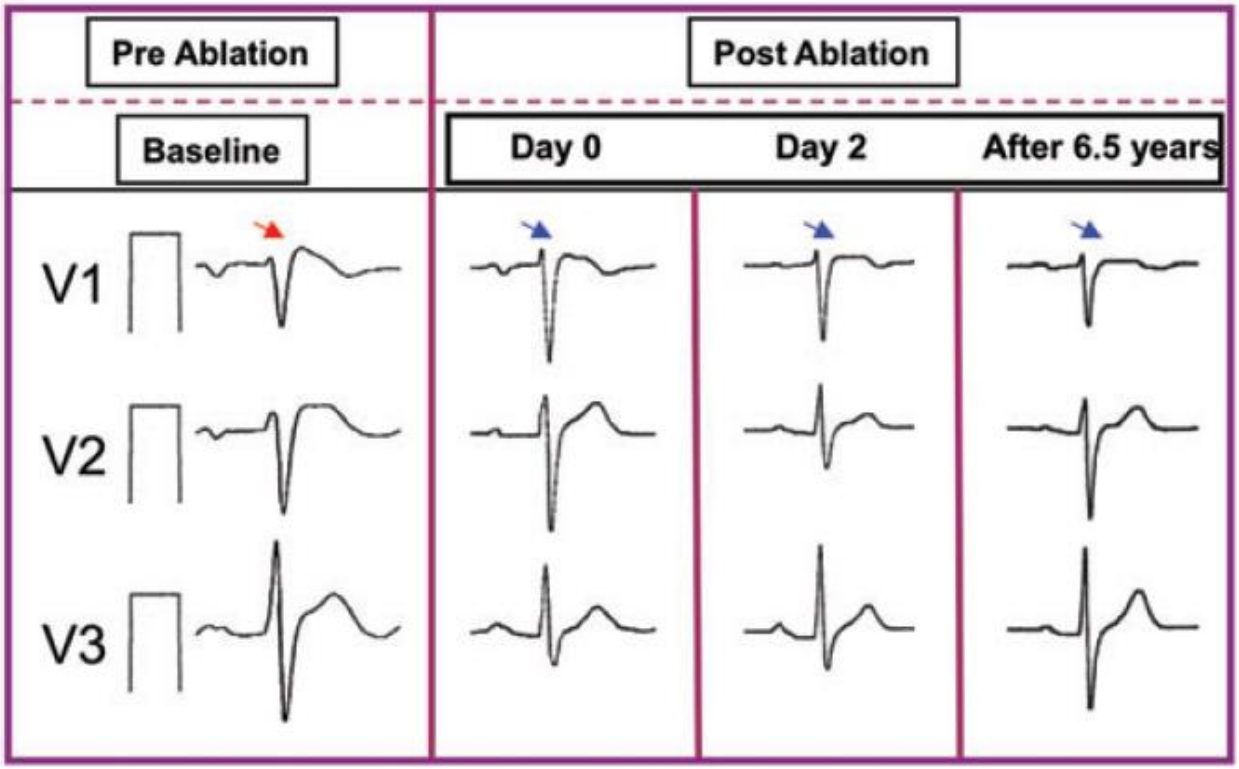
Abolition of Brugada syndrome ECG by Regional Ablation



Endocardial Mapping and Catheter Ablation for Ventricular Fibrillation Prevention in Brugada Syndrome

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SUTHASINEE THAMAREE, M.D.,‡ and SHU ZHANG, M.D., PH.D.†

From the *Division of Cardiology, Department of Medicine, Faculty of Medicine, Cardiac Center, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand; †Clinical EP Lab and Arrhythmia Center, Fuwai Hospital and Cardiovascular Institute of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China; and ‡Department of Medicine, Faculty of Medicine, Naresuan University Hospital, Pitsanulok, Thailand

Endocardial Mapping and Ablation of Brugada Syndrome. *Introduction:* **Brugada syndrome (BS) is characterized by ST-segment elevation in the right precordial electrocardiogram (ECG) leads and episodes of ventricular fibrillation (VF). This study aimed to observe the feasibility of substrate modification by radiofrequency catheter ablation and its effects on VF storm.**

Methods and Results: **Ten BS patients (all men; median age 36.5 years) with VF storm (group I, n = 4) and no VF storm (group II, n = 6) were enrolled in the study between August 2007 and December 2008. All patients underwent electrophysiological study using noncontact mapping. The multielectrode array was placed in the right ventricular outflow tract (RVOT). The isopotential map was analyzed during sinus rhythm and the region that had electrical activity occurring during J point to +60 (J+60) milliseconds interval of the V1 or V2 of surface ECG was considered as the late activation zone (LAZ) and also the substrate for ablation. LAZ was found in RVOT with variable distribution in both groups. Endocardial catheter ablation of the LAZ modified Brugada ECG pattern in 3 of 4 patients (75%) and suppressed VF storm in all 4 patients in group I during long-term follow-up (12–30 months). One patient had complete right bundle branch block from the ablation procedure.**

Conclusions: **LAZ on RVOT identified by noncontact mapping may serve as potential VF substrate in BS patients with VF episodes. Radiofrequency ablation on LAZ normalized ECG, suppressed VF storm, and reduced VF recurrence. The procedure is safe and may prevent VF occurrence.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. S10-S16, November 2012)*

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10 hasta, 2 grup (VF fırtınası olanlar grup 1, n:4)

RVOT Multielektrod array

Geç aktivasyon bölgesi (LAZ: V1-V2 deki J noktası+60 ms)

-Bu bölgeler hedef ablasyon bölgesi-

12-30 ay takip, grup 1, 3 hastada EKG modifiye, VF fırtınası suprese.

Endocardial Mapping and Catheter Ablation for Ventricular Fibrillation Prevention in Brugada Syndrome

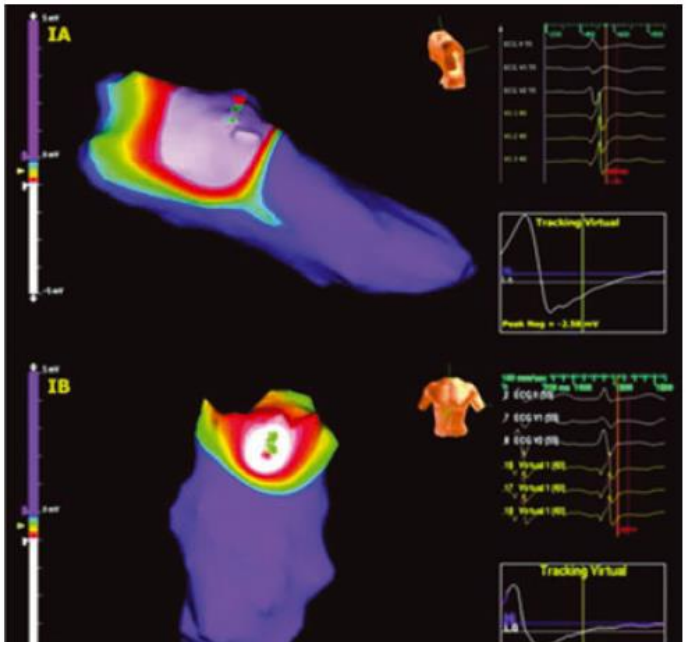

TABLE 3

Electrocardiographic Pattern, Ventricular Fibrillation (VF), and VF Storm Occurrence Before and After Ablation in Group I

Patient No.	Change of ST Elevation*	No. VF Shocks		No. VF Shocks		No. VF Storms	
		Before	After	1–6 m	7–30 m	Before	After
1	Major	47	24	24	0	6	2
2	Major to CRBBB	23	32	28	4	2	0
3	Minor	15	0	0	0	1	0
4	Major	57	0	0	18†	8	0

CRBBB = complete right bundle branch block; m, months; VF = ventricular fibrillation.

*Change of ST elevation: major, ST elevation decreased by >60%; minor, ST elevation decreased between 20 and 60%; unchanged, ST elevation decreased by <20%; †7–12 months after ablation.

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

Koonlawee Nademanee, MD; Gumpanart Veerakul, MD; Pakorn Chandanamattha, MD; Lertlak Chaothawee, MD; Aekarach Ariyachaipanich, MD; Kriengkrai Jirasirirojanakorn, MD; Khanchit Likittanasombat, 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 (BrS) remains unelucidated. 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 BrS 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 BrS (all men; median age 38 years) who had recurrent VF episodes (median 4 episodes) per month, necessitating implantable cardioverter defibrillator discharge. Electroanatomic 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=0.008). 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 BrS 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 BrS. (***Circulation*. 2011;123:1270-1279.**)

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9 hasta, rekürren ICD şokları (VF atakları 4/ay)

Sinüs ritmi sırasında RVOT endo/epi, LV epi haritalması

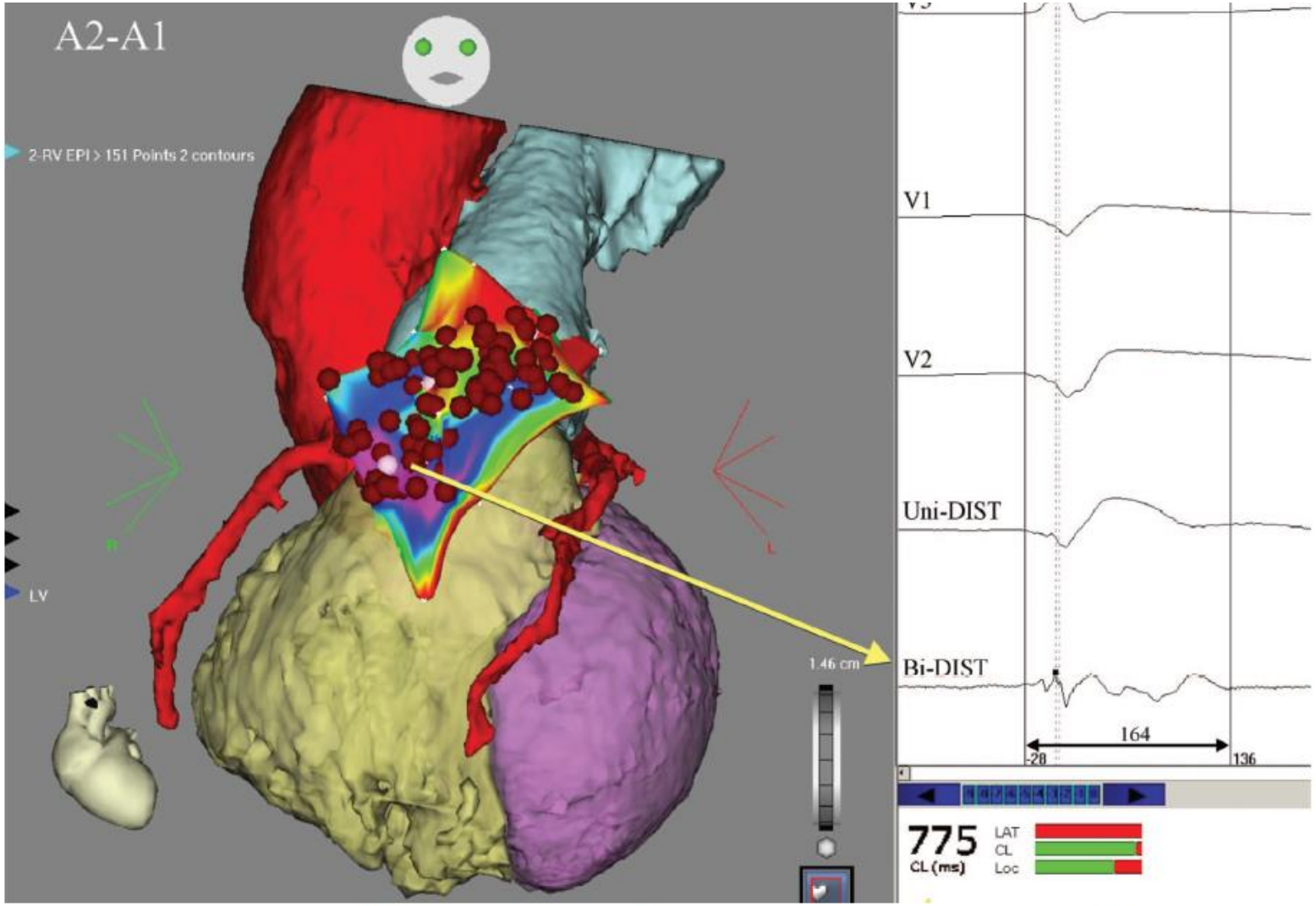
Tüm hastalarda VT/VF inducible

Tüm hastaların ***RVOT ant. epikardında*** düşük voltaj (0.94±0.79 mv), uzun süreli (132±48 ms), fraksiyone geç potansiyeller (QRS den 96±47 ms sonra)

Ablasyon: %78 VT-VF non-inducible, %89 EKG normal

Takip (20±6 ay), tüm hastalar VT-VF free (ilaçsız)

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



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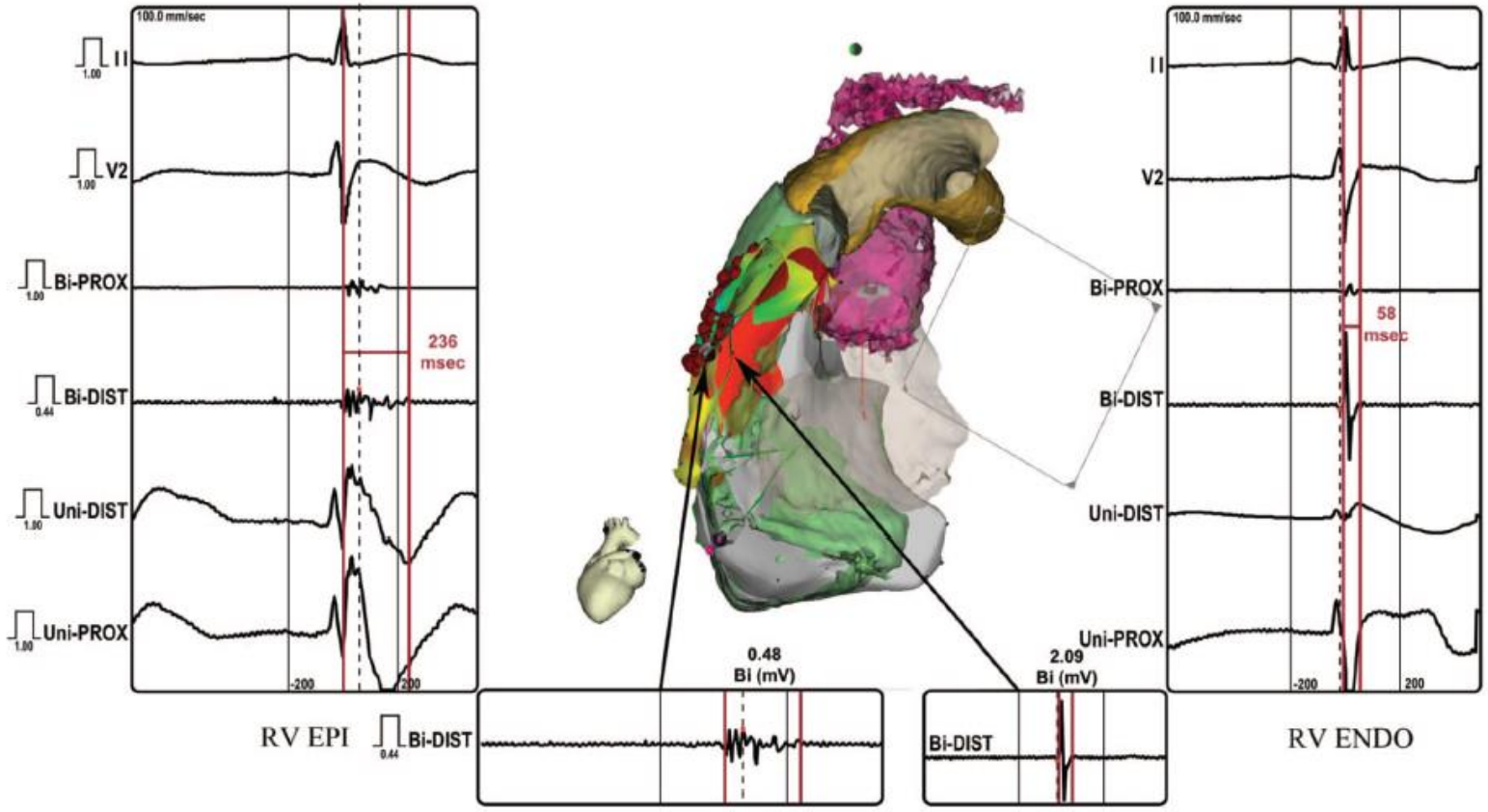

Figure 4. Left lateral view of the right ventricular outflow tract (RVOT) displays the difference in ventricular electrograms between the endocardial (ENDO) and epicardial (EPI) site of the anterior RVOT of the same patient (patient 4) as Figure 2. The left and right insets display bipolar and unipolar electrograms recorded from the epicardium and endocardium from the same site of the RVOT, respectively. Bi-DIST indicates bipolar distal; Bi-PROX, bipolar proximal; Uni-DIST, unipolar distal; and Uni-PROX, unipolar proximal.

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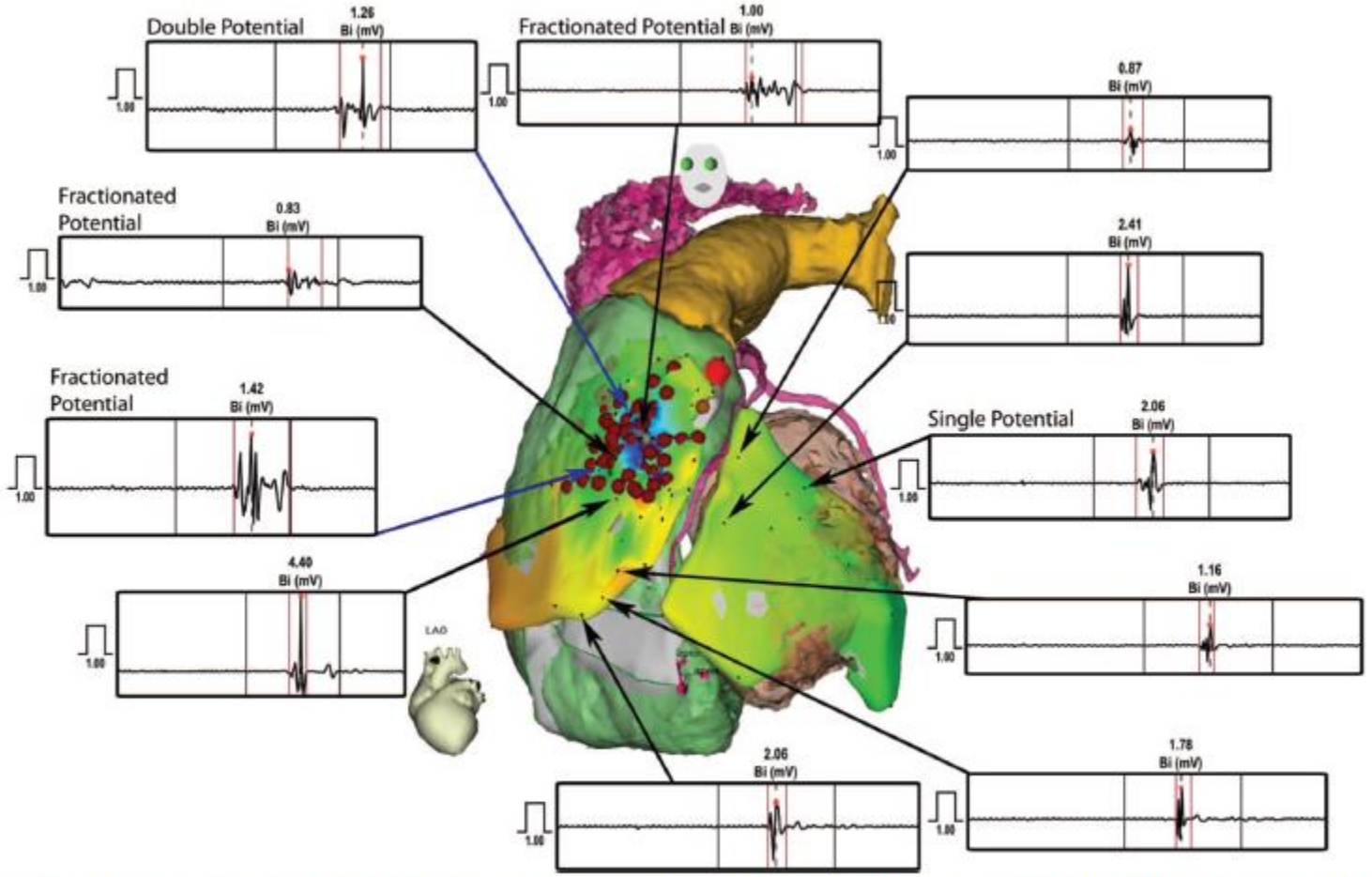
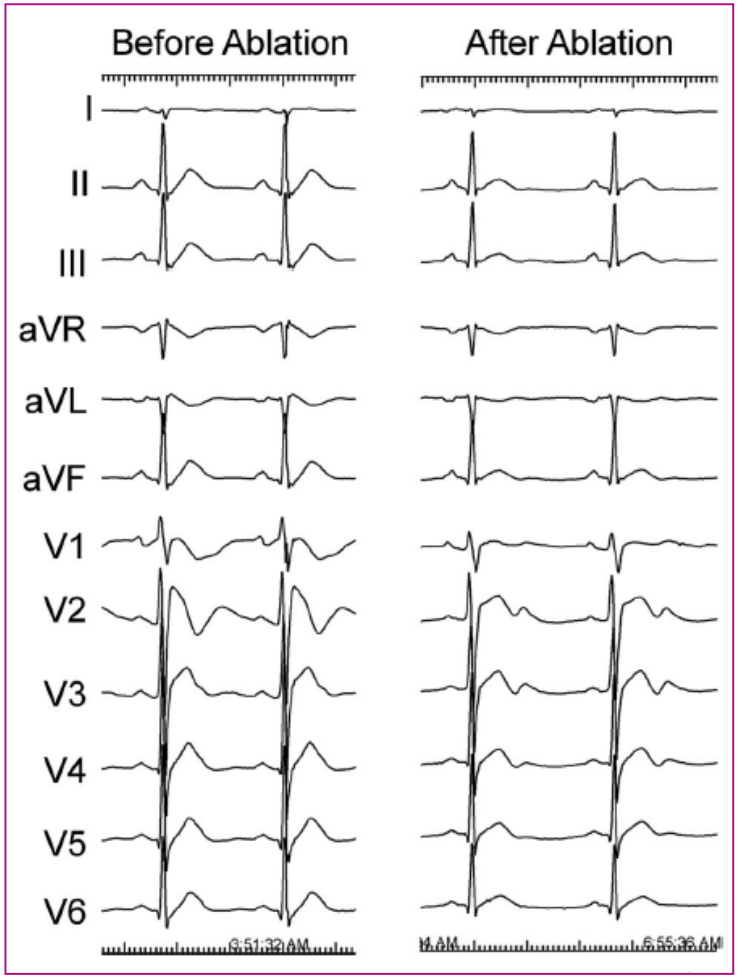


Figure 5. Comparison of ventricular electrograms recorded from different sites in both the left ventricle (LV) and right ventricle (RV) of the same patient as Figures 3 and 4 (patient 4).



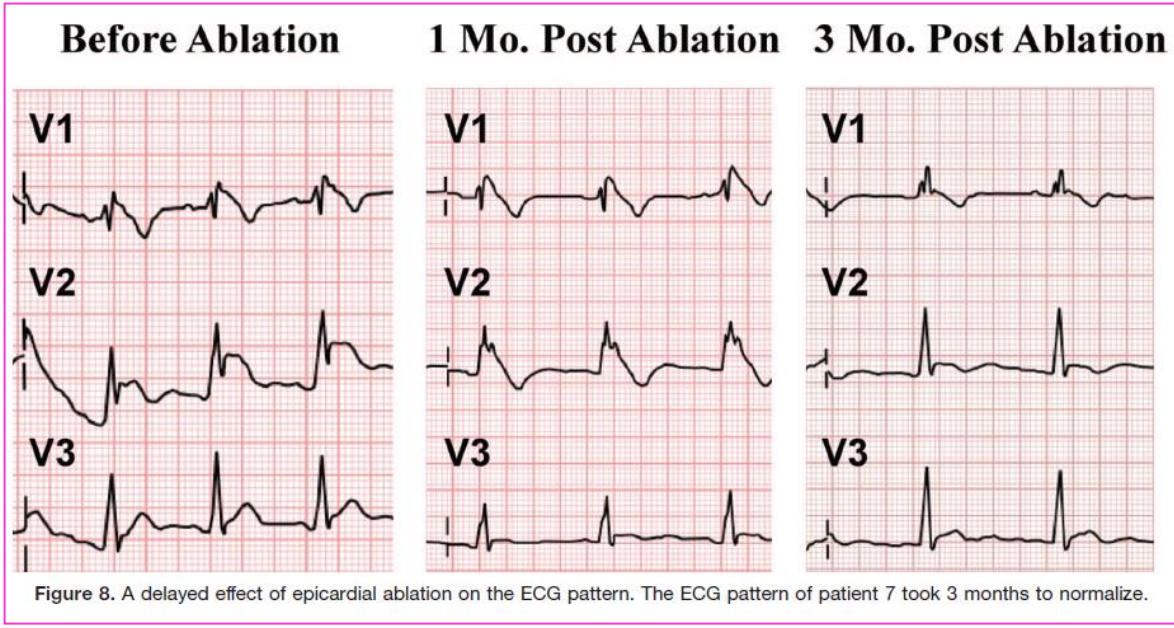


Figure 8. A delayed effect of epicardial ablation on the ECG pattern. The ECG pattern of patient 7 took 3 months to normalize.

Nademanee Circulation 2011

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Brugada sendromu-AF

- Genel populasyondan daha sık görülür (%20 ye karşın %2.3) Muggenthaler,M.Europace 2011

- AF'nu olan BrS hastalarında
  - Senkop (%60 vs %22)
  - VF daha sık (%40 vs %14) Kusano KF, JACC 2008
  - Uygunsuz ICD şokları
  - Ritm kontrolünde kullanılan pek çok ilaç kontraendike

Europace (2014) **16**, 528–532
doi:10.1093/europace/eut309

Pulmonary vein isolation in patients with Brugada syndrome and atrial fibrillation: a 2-year follow-up

Giulio Conte*, Gian-Battista Chierchia, Kristel Wauters, Carlo De Asmundis, Andrea Sarkozy, Moises Levinstein, Juan Sieira, Giannis Baltogiannis, Giacomo Di Giovanni, Giuseppe Ciconte, Ruben Casado-Arroyo, Yukio Saitoh, and Pedro Brugada

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Received 16 July 2013; accepted after revision 9 September 2013; online publish-ahead-of-print 9 October 2013

Aims Pharmacological treatment of atrial fibrillation (AF) in the setting of Brugada syndrome (BS) might be challenging as many antiarrhythmic drugs (AADs) with sodium channel blocking properties might expose the patients to the development of ventricular arrhythmias. Moreover, patients with BS and implantable cardioverter-defibrillator (ICD) might experience inappropriate shocks because of AF with rapid ventricular response. The role of pulmonary vein isolation (PVI) in patients with BS and recurrent episodes of AF has not been established yet. In this study, we analysed the outcome of PVI using radiofrequency energy or cryoballoon (CB) ablation at 2 years follow-up.

Methods and results Consecutive patients with BS having undergone PVI for drug-resistant paroxysmal AF were eligible for this study. Nine patients (three males; mean age: 52 ± 26 years) were included. Six patients (67%) had an ICD implanted of whom three had inappropriate shocks because of rapid AF. At a mean 22.1 ± 6.4 months follow-up, six patients (67%) were free of AF without AADs. None of the three patients who had experienced inappropriate ICD interventions for AF had further ICD shocks after ablation.

Conclusion In our study PVI can be an effective and safe procedure to treat patients with BS and recurrent episodes of paroxysmal AF.

Europace (2014) **16**, 528–532
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Pulmonary vein isolation in patients with Brugada syndrome and atrial fibrillation: a 2-year follow-up

Table 1 Clinical characteristics of study population ($n = 9$)

Age (years)	52 ± 26
Male (*n*)	3 (33%)
Family history of SCD (*n*)	2 (22%)
Previous SCA	1 (11%)
History of syncope	4 (44%)
Spontaneous type 1 pattern ECG	3 (33%)
Previous ICD implantation	6 (67%)
Inappropriate ICD interventions	3 (33%)
LVEF (%)	58 ± 7
LA diameter (mm)	40 ± 5
Previous ineffective AADs	1.2 ± 0.7

Among the study population, four patients (44%) underwent a procedure using RF energy, the remaining patients received a CB ablation. No ST-segment elevation was observed during PVI in any of the patients.

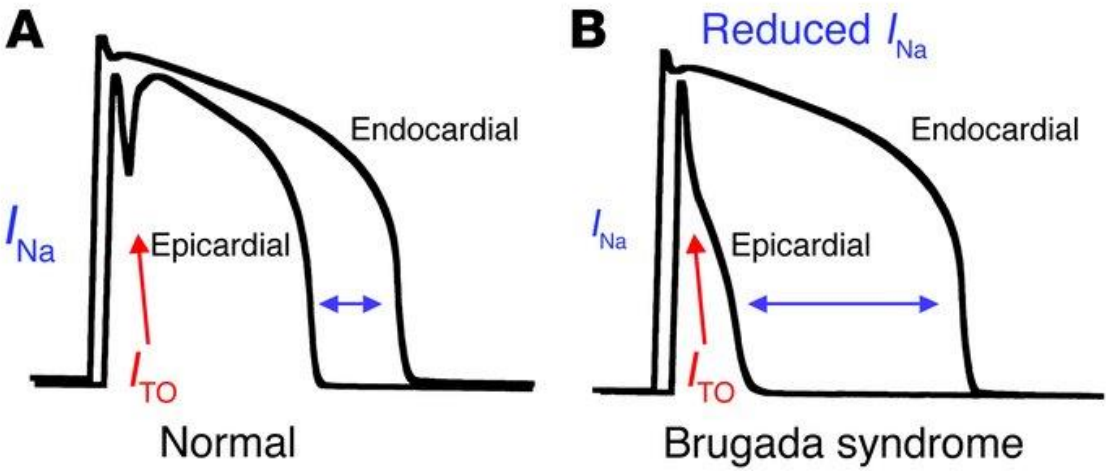
Yeni gelişmeler

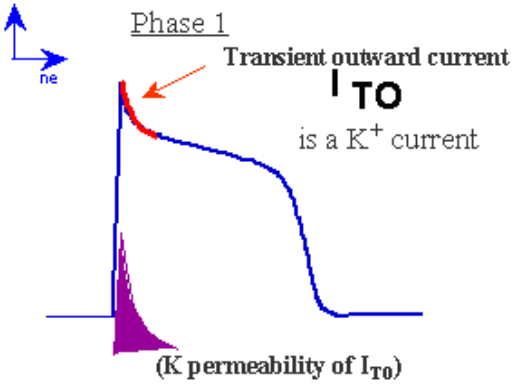
- Ablasyon
  - Endokardiyal
  - Epikardiyal
  - Pulmoner ven izolasyonu
- İlaç
  - Kinidin, Isoproterenol: VF fırtınası
  - Posfodiesteraz inhibitörleri: cAMP ↑ ICa ↑ (Isoproterenol'e benzer)
    - Cilostazol
    - Milrinone
  - Bepridil

Cilostazol

- Brugada sendromunda ⇩ INa, ICa ⇧ K (Ito)

- PDE III inh, antiplatelet, vazodilatör
- ⇧ Ca, ⇩ Ito, Epikardiyal AP düzeliyor, VT suprese





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JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY, Volume 13, No. 7, July 2002

Prevention of Ventricular Fibrillation by Cilostazol, an Oral Phosphodiesterase Inhibitor, in a Patient with Brugada Syndrome

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Cilostazol and Brugada Syndrome. We report the case of 67-year-old man with Brugada syndrome, in whom daily episodes of ventricular fibrillation (VF) occurred every early morning for 4 days. The episodes of VF were completely prevented by an oral administration of cilostazol, a phosphodiesterase inhibitor. This effect was confirmed by the on-and-off challenge test, in which discontinuation of the drug resulted in recurrence of VF and resumption of the drug again prevented VF. This effect may be related to the suppression of I_{to} secondary to the increase in heart rate and/or to an increase in Ca^{2+} current (I_{Ca}) due to an elevation of intracellular cyclic AMP concentration via inhibition of phosphodiesterase activity. This drug might have an anti-VF potential in patients with Brugada syndrome. *(J Cardiovasc Electrophysiol, Vol. 13, pp. 698-701, July 2002)*

Conversion of Brugada type I to type III and successful control of recurrent ventricular arrhythmia with cilostazol

Évolution d'un syndrome de Brugada de type I à un type III et succ traitement des arythmies ventriculaires récurrentes avec le cilostazol

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Received 14 May 2012; received in revised form 9 June 2012; accepted 18 June 2012
Available online 16 January 2013

Combination therapy of cilostazol and bepridil suppresses recurrent ventricular fibrillation related to J-wave syndromes

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BACKGROUND Brugada syndrome and idiopathic ventricular fibrillation (VF) associated with inferolateral early repolarization patterns are termed "J-wave syndromes." In such patients, an implantable cardioverter-defibrillator (ICD) is first-line therapy for prevention of sudden cardiac death. However, frequent ICD shocks due to recurrent VF remain serious problems.

OBJECTIVE The purpose of this study was to ascertain if combination therapy of cilostazol and bepridil could suppress recurrent VF.

METHODS We enrolled 7 patients with J-wave syndromes who experienced ICD shocks due to recurrent VF after ICD implantation. At first, cilostazol was instituted. In all subjects, palpitations due to sinus tachycardia caused by cilostazol were symptomatic. Addition of bepridil attenuated cilostazol-induced palpitations and maintained the suppressive effect of cilostazol against VF (87 ± 12 bpm to 66 ± 7 bpm, $P < .01$).

RESULTS Six patients remained free of VF. Three patients underwent replacement of the ICD generator 4–5 years after ICD placement. Cilostazol was discontinued 2 days before replacement because of its antiplatelet effects. In all 3 patients, temporary discontinuation of cilostazol led to the reappearance of J waves, culminating in VF and an appropriate ICD shock in 1 patient. J waves disappeared with reinstitution of cilostazol.

CONCLUSION These data suggest that combination therapy of cilostazol and bepridil may be effective and safe in suppressing VF recurrence in some cases of J-wave syndromes.

KEYWORDS J-wave syndrome; Bepridil; Cilostazol; Ventricular fibrillation

ABBREVIATIONS **BrS** = Brugada syndrome; **cAMP** = cyclic adenosine monophosphate; **ECG** = electrocardiography; **ERS** = early repolarization syndrome; **ICD** = implantable cardioverter-defibrillator; $\mathbf{I_{Ca}}$ = inward calcium current; $\mathbf{I_{to}}$ = transient outward current; **VF** = ventricular fibrillation

(Heart Rhythm 2014;11:1441–1445)

Combination therapy of cilostazol and bepridil suppresses recurrent ventricular fibrillation related to J-wave syndromes

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7 hasta alınmış; 5 hasta BrS

Rekürren VF nedeni ile ICD şokları

Cilostazol başlanmış (200 mg/gün, J dalgası devam ederse 300 mg/gün)

Tüm hastalarda semptomatik sinüs taşikardisi:

Bepridil (KKB, Ito blokeri) eklenmiş

Takipte 6 hastada VF yok

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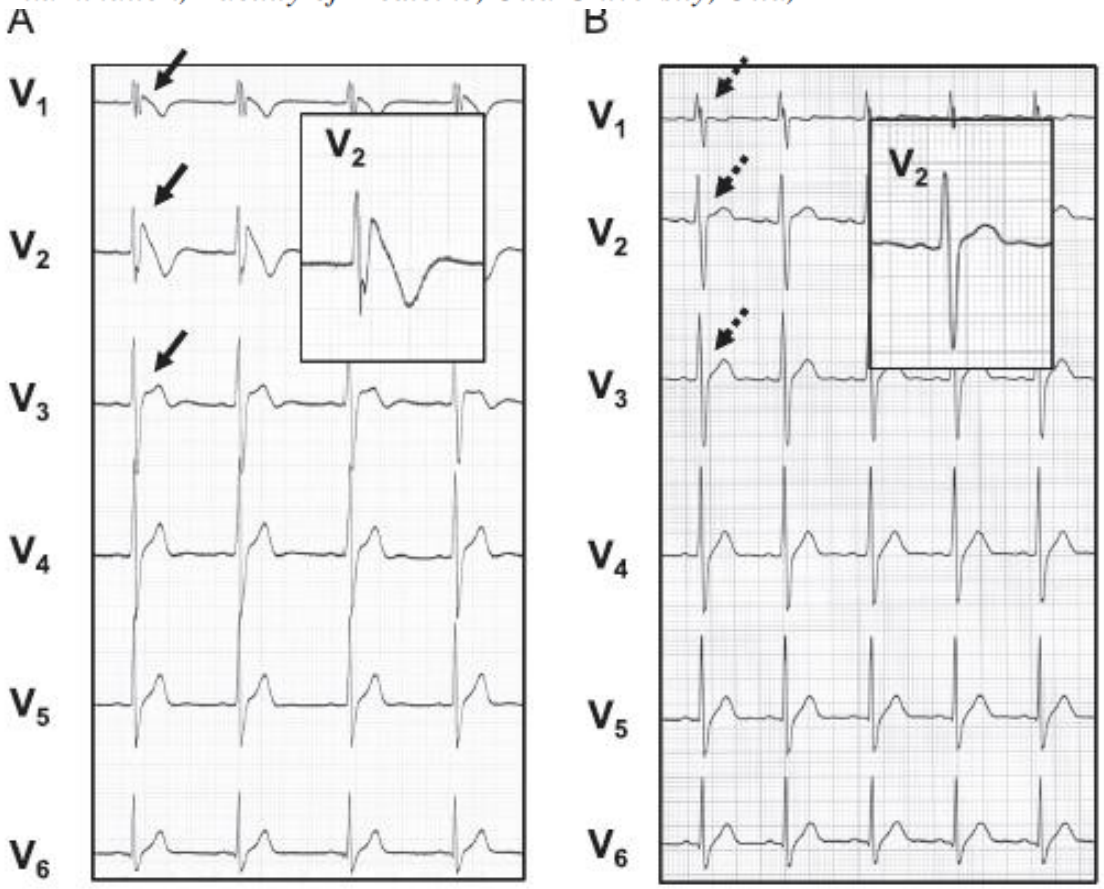
Table 1 Clinical characteristics of the study patients

Case	Age	Diagnosis	ICD generator replacement	VF app during
1	35	BrS	Y	N
2	35	BrS	Y	N
3	39	BrS	N	N
4	44	BrS	N	N
5	37	BrS	N	N
6	39	ERS	Y	Y
7	21	ERS	N	N

BrS = Brugada syndrome; CTCB = combination therapy of defibrillator; N = no; VF = ventricular fibrillation; Y = yes.



Efficacy and safety of bepridil for prevention of ICD shocks in patients with Brugada syndrome and idiopathic ventricular fibrillation

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Table 1
Clinical characteristics of the patients

Case	Age	Sex	Dx	ICD shocks before bepridil	ICD shocks after bepridil	Dose of bepridil	Follow-up period (year)
1	46	M	IVF	12	0	200 mg	1.3
2	57	M	IVF	1–2/year	2	200 mg	11.6
3	60	M	BrS	13	2 → 0‡	150 → 200 mg‡	8.4
4	76	F	BrS	1†	0	100 mg	2.2
5	39	M	BrS	5	0§	100 mg	0.5
6	55	M	BrS	1	0	100 mg	0.3

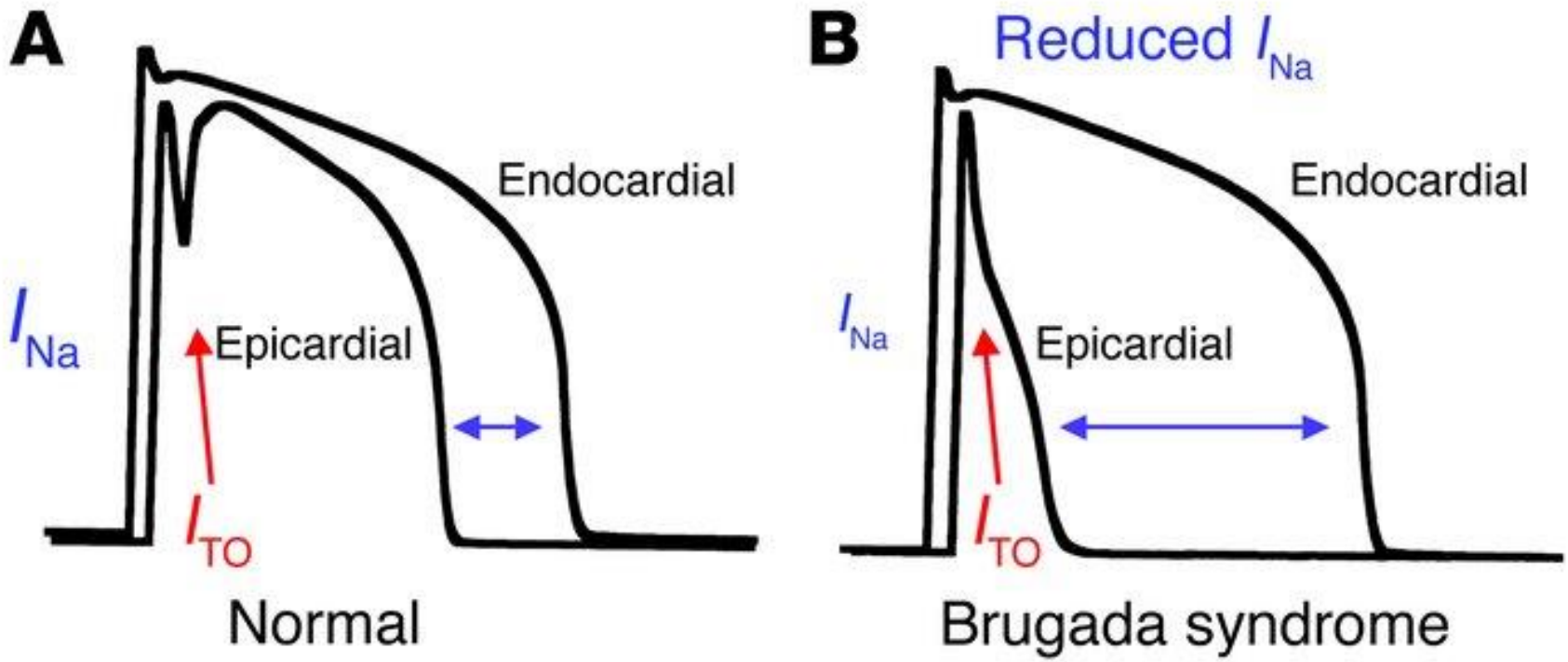
Teşekkürler

Table 2. Genes with mutations associated with the Brugada syndrome and their relative prevalence.

BrS type	Locus	Gene	Protein	Channel	% of probands
1	*3p21*	*SCN5A*	$Na_v1.5$	$\downarrow I_{Na}$	11–28
5	*19q13.1*	*SCN1B*	$Na_v\beta1$	$\downarrow I_{Na}$	<1
7	*11q23.3*	*SCN3B*	$Na_v\beta3$	$\downarrow I_{Na}$	<1
2	*3p24*	*GPD1L*	GPD1L	$\downarrow I_{Na}$	<1
11	*17p13.1*	*MOG1*	MOG1	$\downarrow I_{Na}$	<1
3	*12p13.3*	*CACNA1C*	$Ca_v1.2$	$\downarrow I_{Ca}$	8–12
4	*10p12.33*	*CACNB2B*	$Ca_v\beta2b$	$\downarrow I_{Ca}$	8–12
9	*7q21.11*	*CACNA2D1*	$Ca_v\alpha2\delta$	$\downarrow I_{Ca}$	8–12
6	*11q13-14*	*KCNE3*	MiRP2	$\uparrow I_{to}$	<1
10	*1p13.2*	*KCND3*	$K_v4.3$	$\uparrow I_{to}$	<1
8	*12p11.23*	*KCNJ8*	Kir6.1	$\uparrow I_{K\text{-}ATP}$	<1

BrS: Brugada syndrome.

- There are two theories to explain the electrocardiographic manifestations of BS: (1) delayed conduction in the free wall epicardium of the right ventricular outflow tract; (2) premature repolarization of the right ventricular epicardial action potential; or a combination of the two.


A
Endocardial
I_{Na}
Epicardial
I_{TO}
Normal
B
Reduced I_{Na}
Endocardial
I_{Na}
Epicardial
I_{TO}
Brugada syndrome

- Brugada sendromunda ⇩ INa, ICa ⇧ K (Ito)