AN UPDATE ON BRUGADA SYNDROME

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Brugada syndrome

- Channelopathy (mainly SCN5A gene mutations) characterized by coved-type ST-segment elevation in right precordial lead
- No structural heart disease (?)
- Males
- VT/VF (sudden death, arrhythmic syncope): highly lethal syndrome
- 30% of SCDs with negative autopsy
- High rate of atrial arrhythmias / SND
- Aborted SCD, syncope and spontaneous type 1 are well-known risk factors for future events
- ICD is the only proven therapy in symptomatic patients
The Brugada ECG pattern
Definitions of the Brugada ECG pattern

- According to the Second Consensus Conference on BrS, three types of ECG repolarization patterns in right precordial leads (V1-V3) have been recognized. Type 1 is diagnostic of BrS and is characterized by a coved ST-segment elevation ≥ 2 mm followed by a negative T wave in more than one right precordial leads (Antzelevitch et al. Circulation 2005;111:659-670).

- In a recent Consensus report, only 2 ECG types are considered: type 1 which is identical to the classic type 1 ECG pattern of the other Consensus (coved pattern) and type 2 that joins ECG patterns 2 and 3 of previous Consensus (saddleback pattern). (Bayés de Luna et al. J Electrocardiol 2012;45:433-42).

- Based on the HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes, the BS phenotype is definitively diagnosed when a type 1 ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocking agent in at least one right precordial lead (V1 and V2), which are placed in a standard or a superior position (up to the 2nd intercostal space) (Priori et al. Europace 2013;15:1389-406).

Prevalence of Brugada ECG pattern on the world map
Management of patients with Brugada syndrome

- ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who are survivors of an aborted cardiac arrest and/or have documented spontaneous sustained VT (class I, LOE C).
- ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope (class IIa, LOE C).
- Quinidine or isoproterenol should be considered in patients with Brugada syndrome to treat electrical storms (class IIa LOE C).
- Quinidine should be considered in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias (class IIa LOE C).
- ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during PVS with two or three extrastimuli at two sites (Class IIb, LOE C).
- Catheter ablation in ES (Class IIb, LOE C).

ESC 2105
The Brugada Syndrome is highly lethal: Can We Predict the Risk?
Based on the Second Expert Consensus Conference on BS, 68% of this population would have been categorized as low risk.

The “low-risk” asymptomatic Brugada group comprises the majority of SCD in this cohort.

Current risk stratification would appear to be inadequate, and new markers of risk are vital.
Clinical characteristics of patients with events at follow-up: data from the PRELUDE registry

<table>
<thead>
<tr>
<th>Patient ID #</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Family History of SCD</th>
<th>Spontaneous Type 1 ECG</th>
<th>History of Syncope</th>
<th>Inducibility</th>
<th>VRP &lt;200 ms</th>
<th>QRS-f</th>
<th>SCNS5A Mutation</th>
<th>Event Type</th>
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<td>M</td>
<td>43</td>
<td>-</td>
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<td>-</td>
<td>+</td>
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<td>ICD shock</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>M</td>
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<td>+</td>
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<td>+</td>
<td>-</td>
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<td>+</td>
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<td>+</td>
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<td>132</td>
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<td>+</td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>ICD shock</td>
</tr>
</tbody>
</table>

- 7 patients asymptomatic
- 4/7 without inducible arrhythmias at EPS
Clinical characteristics of non-inducible patients presenting arrhythmic events during the follow-up: data from the updated Brugada registry published in 2015

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event</th>
<th>Gender</th>
<th>Age*</th>
<th>Proband</th>
<th>Family History of SCD</th>
<th>Spontaneous type I</th>
<th>Symptoms at presentation</th>
<th>f-QRS</th>
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<tbody>
<tr>
<td>1</td>
<td>ICD shock</td>
<td>Male</td>
<td>52.8</td>
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<td>No</td>
<td>No</td>
<td>SCD</td>
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<td>2</td>
<td>Aborted SCD</td>
<td>Male</td>
<td>53.8</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Asymptomatic</td>
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<tr>
<td>3</td>
<td>ICD shock</td>
<td>Male</td>
<td>8.3</td>
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<td>No</td>
<td>No</td>
<td>Syncope</td>
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<tr>
<td>4</td>
<td>ICD shock</td>
<td>Male</td>
<td>15.1</td>
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<tr>
<td>5</td>
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<td>Male</td>
<td>36.7</td>
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<td>6</td>
<td>ICD shock</td>
<td>Female</td>
<td>43.0</td>
<td>Yes</td>
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<td>Female</td>
<td>60.3</td>
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<td>SCD</td>
<td>No</td>
</tr>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Asymptomatic</td>
<td>No</td>
</tr>
</tbody>
</table>
Implantable Cardioverter-Defibrillator Therapy in Brugada Syndrome: A 20-Year Single-Center Experience

Do we really have risk stratification tools?
The prognosis and risk stratification of asymptomatic individuals still remain the most controversial issues in Brugada syndrome.

Several clinical, ECG and electrophysiological markers have been proposed for risk stratification of subjects with BS phenotype, but the majority of them have not been tested in a prospective manner in asymptomatic individuals!
Long-term prognosis of asymptomatic individuals with spontaneous or drug-induced type 1 electrocardiographic phenotype of Brugada syndrome

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Panagiotis Korantzopoulos, MD, c Klaus Astheimer, MD, b Charalampos Charalampous, MD, a
Spyros Tsikrikas, MD, a Nikolaos Fragakis, MD, FESC, d Dietrich Kalusche, MD, b
Antonios Sideris, MD, a Thomas Arentz, MD b

**Background:** Risk stratification of asymptomatic individuals with type 1 electrocardiogram (ECG) phenotype of Brugada syndrome (BS) still remains controversial. This study investigated the long-term prognosis of asymptomatic subjects with spontaneous or drug-induced type 1 ECG pattern of BS.

**Methods and results:** Data from 33 apparently healthy individuals (30 males; age, 43.6 ± 13.4 years) with spontaneous (n = 12) or drug-induced (n = 21) type 1 ECG pattern of BS were retrospectively analyzed. Thirteen subjects (39.4%) displayed a positive family history of BS and/or sudden cardiac death. Electrophysiologic study was performed in 16 subjects, and programmed right ventricular stimulation induced polymorphic ventricular tachycardia in 9 (56.3%) of them. A cardioverter defibrillator was implanted in 6 cases. During a mean follow-up period of 5.3 ± 2.8 years, all subjects remained asymptomatic. None of them had syncope or cardioverter defibrillator discharges due to ventricular arrhythmias.

**Conclusions:** Asymptomatic individuals with spontaneous or drug-induced type 1 ECG phenotype of BS display a benign clinical course during long-term follow-up.
Arrhythmic events in asymptomatic individuals with spontaneous type 1 pattern
Arrhythmic events in asymptomatic individuals with drug-induced type 1 pattern

Circ Arrhythm Electrophysiol. 2012;5:606-616
Asymptomatic Brugada Syndrome: Clinical Characterization and Long Term Prognosis

- 363 consecutive asymptomatic patients (200 males, 55.1%; mean age: 40.9±17.2 years, 41 (11.3%) with spontaneous type I ECG) were included.

- After a mean follow-up time of 73.2±58.9 months, 9 arrhythmic events occurred, accounting for an annual incidence rate of 0.5%.

- Arrhythmic event free survival in patients in whom an ICD was implanted was 94.8% at 1 year and 89.5% at 5 years and 86.7% at 10 and 15 years.

- Event free survival in patients without an ICD was 100% at 1 year and 97.9% at 5 years and beyond.

Sieira et al. CIRCEP 2015
Spontaneous type 1 ECG !!!!

FINGER REGISTRY

PRELUDE REGISTRY

Circulation. 2010;121:635-643

J Am Coll Cardiol 2012;59:37–45
Asymptomatic subjects with spontaneous type 1 ECG pattern of BS exhibit an increased risk of future arrhythmic events (odds ratio [3.56, 95% confidence interval 1.70 to 7.47, Z [3.37, p [0.0008])

Fragmented QRS complex in patients with Brugada syndrome

Morita et al. Circulation 2008;118:1697-1704
Missense Mutations in Plakophilin-2 Cause Sodium Current Deficit and Associate with a Brugada Syndrome Phenotype

Epsilon-like waves and ventricular conduction abnormalities in subjects with type 1 ECG pattern of Brugada syndrome

Konstantinos P. Letsas, MD, FESC,*† Michael Efremidis, MD,* Reinhold Weber, MD,† Panagiotis Korantzopoulos, MD, PhD,‡ Nikos Protonotarios, MD,§ Efstathia Prappa, MD,* Stavros P. Kounas, MD,* Eleni N. Evagelidou, MD,¶ Sotirios Xydonas, MD,* Dietrich Kalusche, MD,† Antonios Sideris, MD,* Thomas Arentz, MD†
Epsilon-like waves and ventricular conduction abnormalities in subjects with type 1 ECG pattern of Brugada syndrome

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Post-QRS deflections: new ECG markers ???

f-QRS as a ECG marker for future arrhythmic events

58% with f-QRS displayed an arrhythmic event vs. 5% without f-QRS

Morita et al. Circulation 2008;118:1697-1704
QRS-fragmentation: Data from the PRELUDE registry

Priori et al. J Am Coll Cardiol 2012;59:37–45
Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities.

Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome

Konstantinos P. Letsas, MD, Frédéric Sacher, MD, Vincent Probst, MD, PhD, Reinhold Weber, MD, Sébastien Knecht, MD, Dietrich Kalusche, MD, Michel Haïssaguerre, MD, Thomas Arentz, MD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 290)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>48.3 ± 14.2</td>
</tr>
<tr>
<td>Males</td>
<td>223 (79)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>88 (30)</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>83 (29)</td>
</tr>
<tr>
<td>Spontaneous type 1 ECG pattern of BS</td>
<td>131 (45)</td>
</tr>
<tr>
<td>SCN5A gene mutation</td>
<td>42/146 (28)</td>
</tr>
<tr>
<td>ER pattern</td>
<td>35 (12)</td>
</tr>
<tr>
<td>PR interval in lead II, ms</td>
<td>178.5 ± 29.3</td>
</tr>
<tr>
<td>QTc in lead II, ms</td>
<td>407.9 ± 37.8</td>
</tr>
<tr>
<td>QRS duration in lead II, ms</td>
<td>105.7 ± 18.7</td>
</tr>
<tr>
<td>EPS</td>
<td>216 (74)</td>
</tr>
<tr>
<td>AH, ms</td>
<td>101.1 ± 32.1</td>
</tr>
<tr>
<td>HV, ms</td>
<td>52.9 ± 12.1</td>
</tr>
<tr>
<td>Inducible ventricular tachycardia at EPS</td>
<td>93/216 (43)</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>132 (45)</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>44.9 ± 27.5</td>
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<tr>
<td>Arrhythmic event during follow-up</td>
<td>22 (8)</td>
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</tbody>
</table>

Heart Rhythm, Vol 5, No 12, December 2008
Coexistence of Brugada ECG is a key predictor of poor outcome in patients with ER
Inferolateral ER and Brugada syndrome

- Approximately 30% of the patients with ER and VF who had been diagnosed with the previous criteria showed BS-ECG only in higher intercostal space.
- VF mostly recurred in patients showing BS-ECG in any precordial lead including higher intercostal space; these comprised 50% of the ERS cohort.
- These results indicate the importance of a systematic search for BS-ECG with high intercostal ECG recording for the risk stratification of patients with ERS.

Eur Heart J. 2015
Meta-Analysis on the prognostic significance of the ER pattern in Brugada syndrome

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ER Events</th>
<th>Total</th>
<th>no ER Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
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<td>Letsas 2008</td>
<td>4</td>
<td>35</td>
<td>18</td>
<td>255</td>
<td>17.7%</td>
<td>1.70 [0.54, 5.35]</td>
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<td>33</td>
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<td>4.43 [1.69, 11.67]</td>
<td>2009</td>
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<td>Takagi 2013</td>
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<td>53</td>
<td>166</td>
<td>407</td>
<td>27.2%</td>
<td>1.51 [0.85, 2.68]</td>
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<td>Kawata 2013</td>
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<td>31</td>
<td>8</td>
<td>18</td>
<td>14.4%</td>
<td>8.44 [2.08, 34.30]</td>
<td>2013</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<td></td>
<td><strong>1198</strong></td>
<td></td>
<td></td>
<td><strong>3.26 [1.61, 6.60]</strong></td>
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<td>225</td>
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</tbody>
</table>

Heterogeneity: Tau² = 0.39; Chi² = 10.78, df = 4 (P = 0.03); I² = 63%
Test for overall effect: Z = 3.27 (P = 0.001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ER Events</th>
<th>Total</th>
<th>no ER Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<td>33</td>
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<td>297</td>
<td>39.9%</td>
<td>4.43 [1.69, 11.67]</td>
<td>2009</td>
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<tr>
<td>Takagi 2013</td>
<td>9</td>
<td>12</td>
<td>166</td>
<td>407</td>
<td>21.4%</td>
<td>4.36 [1.16, 16.33]</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>70</strong></td>
<td></td>
<td><strong>925</strong></td>
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<td></td>
<td><strong>4.98 [2.70, 9.17]</strong></td>
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<tr>
<td>Total events</td>
<td>24</td>
<td></td>
<td>199</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.15 (P < 0.00001)
ST-segment elevation during the recovery phase from exercise

J Am Coll Cardiol 2010;56: 1576-84
Exercise test for Brugada syndrome
Signal-average ECG and future arrhythmic events
In univariate analysis, patients with inducible VT/VF at EPS had a shorter time to first arrhythmic event compared with those with a negative EPS (event rate per year, 1.1% vs. 0.4%; p: 0.05)
Prognostic Value of PES in Brugada Syndrome: 20 Years Experience

Event free survival

Positive predictive value was 21.6% and negative predictive value 97.7%

Circ Arrhythm Electrophysiol. 2015 Aug;8(4):777-84
Event free survival for the non-inducible group was 99.0% at 1 year and 96.8% at 5, 10 and 15 years.

Among the inducible patients it was 89.0% at 1 year, 78.4% at 5 years and 75.0% at 10 and 15 years.

Among asymptomatic patients, those without PES inducibility had an event free survival of 100.0% at 1 year, and 99.2% at 5, 10 and 15 years. Inducible subjects event free survival was 90.6% at 1 year and 79.5% at 5, 10 and 15 years. PES inducibility remained significative (p<0.01).

Sensitivity of PES for predicting arrhythmic events was 64.0% and specificity was 86.6%. Positive predictive value was 21.6% and negative predictive value 97.7%.

If restricted to asymptomatic patients these values increased to a sensitivity of 75.0% and a specificity of 91.3% and predictive values to 18.2% and 98.3% respectively.
Inducible sustained VT/VF during PES confers a 3.5-fold higher risk of future arrhythmic events in previously asymptomatic subjects

Ventricular ERP: Data from the PRELUDE registry

Priori et al. J Am Coll Cardiol 2012;59:37–45
Other non-invasive risk markers: NOT TESTED PROSPECTIVELY

- prolonged QTc interval $>460$ ms in lead V2, Tpeak-end interval, and Tpeak-end dispersion
- prolonged QRS duration in leads II, V2 and V6
- the “aVR sign” (R wave $>0.3$ mV or R/q $>0.75$ in lead aVR)
Risk stratification of asymptomatic individuals with type 1 ECG pattern of Brugada syndrome

- Spontaneous type 1 ECG
  - EPS
    - Positive EPS
    - Negative EPS
      - ERP<200 ms
      - QRS fragmentation
      - ST-segment elevation at the recovery phase of an exercise test
      - Late potentials

- Drug-induced type 1 ECG

  - ICD implantation
  - Quinidine as an alternative

  - YES

  - NO
    - Follow-up every 6-12 months with 12-lead ECG Holter monitoring
Data from the Greek registry

- **81 subjects with Brugada phenotype** (60 males, 45.3 ± 14.01 years).
- 40 patients (49%) with spontaneous type 1 ECG.
- 12 patients with fever-induced type 1 ECG.
- 30 patients (37%) were symptomatic (27 with syncope and 3 aborted SD) and 10 displayed a family history of Brugada syndrome/SD (12.3%).
- Atrial arrhythmias were seen in 17 patients (21%).
- EPS was performed in 33 patients (18/33 with inducible VT/VF).
- A cardioverter defibrillator (ICD) has been implanted in 29 cases.
- **During a mean follow-up of 3.2 ± 2.8 years, 7 patients developed arrhythmic events (appropriate ICD shocks).**
Data from the Greek registry

- 6/7 males (p: 0.493)
- 5/7 with spontaneous type 1 ECG (p: 0.209)
- 6/7 symptomatic (p: 0.008)
- 5/7 inducible VT/VF at EPS (0.312)
- QRS duration in leads II, V2 and P wave duration in lead II were significantly associated with arrhythmic events.
- One patient developed pocket infection and two patients suffered inappropriate shocks.
Case presentation

- 35 years-old male
- asymptomatic
- family history of SCD
- spontaneous type 1 Brugada phenotype
- positive SAECG
- structural heart disease ruled out (plus MRI)
Spontaneous type 1 ECG pattern
Risk stratification

- Low risk
- High risk

LOW RISK BASED ON ESC 2015 GUIDELINES
PES: induction of VF
Multiparametric scores for risk stratification

- In subjects with the Brugada type 1 ECG, no single clinical risk factor, nor EPS alone, is able to identify subjects at highest risk;
- A multiparametric approach (including syncope, family history of SD, and positive EPS) helps to identify populations at highest risk;
- Subjects at highest risk are those with a spontaneous type 1 ECG and at least two risk factors;
- The remainder are at low risk

Risk stratification

- Low risk
- High risk

HIGH RISK BASED ON MULTIPARAMETRIC SCORES
Two years later: VF !!!!!!!!
The balance between benefits and complications after ICD implantation is particularly important when dealing with asymptomatic patients: Data from the Brugada registry in 2015

- Inappropriate shocks occurred in 18.7% of patients.
- 15.9% of patients experienced device-related complications. Twenty-one (75%) were younger than 40 years at the time of implantation.
- Complications consisted of fracture of the ventricular electrode, lead dislocation, device infections and pulse generator migration.
THANK YOU VERY MUCH FOR YOUR ATTENTION
Catheter ablation in Brugada syndrome

Circulation 2011;123;1270-1279
Drugs and fever may induce the diagnostic ECG and predispose to VT/VF

Drug-Induced Brugada Syndrome by Noncardiac Agents

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Drug-induced Brugada syndrome (BrS) represents a great challenge for the prescribing clinicians as well as for those involved in the development of novel pharmaceuticals and in the regulatory bodies responsible with monitoring drug safety. Apart from well-known cardiac agents (mainly Class I antiarrhythmics), an increasing number of noncardiac agents, including psychotropic and anesthetic drugs, have been shown to induce the characteristic Brugada electrocardiogram pattern predisposing to fatal ventricular arrhythmias. Up to now, both repolarization and depolarization abnormalities are thought to be related to the development of ventricular fibrillation in BrS patients. This review highlights the mechanisms and the noncardiac medical agents that unmask a genetic predisposition to BrS. (PACE 2013; 00:1–8)