Brugada Syndrome and Sudden Cardiac Death

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Yonsei University College of Medicine, Seoul, Korea
43-year-old Male School teacher

Two episodes of agonal breathing while asleep 1 week apart

ECG at ER

1998-8-30
<table>
<thead>
<tr>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bireated at BR</td>
</tr>
<tr>
<td>C.o.o: Nausea</td>
</tr>
<tr>
<td>Verified to be normal</td>
</tr>
<tr>
<td>Early CP was taken away</td>
</tr>
<tr>
<td>Late CP was taken away</td>
</tr>
<tr>
<td>CES: 153.5</td>
</tr>
<tr>
<td>E.S.E: 69.7</td>
</tr>
<tr>
<td>R.B.S: 250.8</td>
</tr>
<tr>
<td>C.R.B.S: 250.8</td>
</tr>
<tr>
<td>Trompetin:</td>
</tr>
<tr>
<td>Vomoses</td>
</tr>
</tbody>
</table>

**WNL**

**Negative**
ECG after Cardioversion
Dynamic ST segment changes

V1
98.8.30

V2
98.8.30

V3
98.8.30

99.10.28

99.11.8
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 V₁ to V₂–V₃, not explainable by electrolyte disturbances, ischemia or structural heart disease. No histologic abnormalities were found in the four patients in whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic ventricular tachycardia initiating after a short coupled ventricular extrasystole. A similar arrhythmia was initiated by two to three ventricular extrastimuli in four of the seven patients studied by programmed electrical stimulation. Four patients had a prolonged HV interval during sinus rhythm. One patient receiving amiodarone died suddenly during implantation of a demand ventricular pacemaker. The arrhythmia of two patients was controlled with a beta-adrenergic blocking agent. Four patients received an implantable defibrillator that was subsequently used by one of them, and all four are alive. The remaining patient received a demand ventricular pacemaker and his arrhythmia is controlled with amiodarone and diphenylhydantoin.

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

(J Am Coll Cardiol 1992;20:1391–6)
Additional features associated Brugada Syndrome

1. Male predominance
2. Familial incidence
   - Autosomal dominant inheritance
3. Molecular defect:
   - Mutation in cardiac Na channel gene (SCN 5A)
4. Characteristic response to pharmacologic testing with
   - Class IA or IC (procainamide, flecainide, ajmalin)
5. Induction of VF during PES
Sudden Unexplained Death Syndrome (SUDS) in Southeast Asia

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

- Philippine: “ban gun gut” (moaning during sleep)
- Japan: “Pokkuri” (sudden unexpected death)
- Thailand: “lai tai” (sleep death)
- Annual prevalence
  - 1/2,500 in Thailand
  - 1/1,000 in Laos
# Arrhythmogenic Marker for the Sudden Unexplained Death Syndrome in Thai Men

- Characteristics of 27 patients -

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

(Follow-up 11.8 ± 8 mos)

*Nademanee K et al. Circulation 1997;96:2595*
RBBB and ST-Segment Elevation in Leads V1 Through V3

Recurrence of first VT or Sudden death

asymptomatic   6/22 (27%)
symptomatic  14/41 (34%)

Log Rank test = 0.604

Arrhythmia events during follow-up of 34±32mos

RBBB and ST-Segment Elevation in Leads V1 Through V3

Survival according to treatment

Survival

Time in months

% survival

ICD

Drugs

No treatment

Logrank = 0.0005

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

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

- Fujimori K et al. Circulation 2000;102(suppl II)–676:3268
  0.48% (140 / 34,520)

- Atarashi H et al. JACC 2001;37:1916
  0.16% (16 / 10,000)

- Miyasaka Y et al. JACC 2001;38:771
  0.7% (98 / 13,929)
Prevalence and Mortality of the Brugada-Type ECG in One City in Japan

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

Miyasaka Y et al. JACC 2001;771
Three-year Prospective Follow-Up of Patients With RBBB and ST Segment Elevation in the Right Precordial Leads

Arrhythmia event during 3 years follow-up
- Symptomatic: 25.7%
- Asymptomatic: 1.5%

Log-rank test $p=0.0004$

Patients without Events (%)
- Asymptomatic n=67
- Symptomatic n=38

Atarashi H et al. JACC 2001;37:1916
Clinical and Genetic Heterogeneity of RBBB and ST-Segment Elevation Syndrome - A Prospective Evaluation of 52 Families -

60 patients with typical Brugada ECG pattern
(45 males, mean age 40±15 yrs)

- VF recurrence during 33±38 mos follow-up
  Symptomatic patients  5/30 (16%)
  Asymptomatic patients  0/30 (  0%)

- EPS :  Positive predictive value  : 50%
  Negative predictive value : 46%

- Drug test positive predictive value : 35%

Genetic Analysis in 52 Probands

52 proband (phenotype)

Genetic screening in 44 family members (ECG – NL, asymptomatic)

44

20 (45%) SCN5A mutation
Silent carrier (genotype)

4

4/24 (16%) SCN5A penetrance

24 SCN5A mutation(-)

8/52 (15%) SCN5A mutation Prevalence

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

<table>
<thead>
<tr>
<th>Underlying Heart Disease</th>
<th>No of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugada Syndrome</td>
<td>10</td>
<td>29.4%</td>
</tr>
<tr>
<td>No Structural Heart Disease</td>
<td>8</td>
<td>23.5%</td>
</tr>
<tr>
<td>CAD</td>
<td>6</td>
<td>17.6%</td>
</tr>
<tr>
<td>HCMP</td>
<td>5</td>
<td>14.7%</td>
</tr>
<tr>
<td>DCMP</td>
<td>3</td>
<td>8.8%</td>
</tr>
<tr>
<td>Non Specified CMP</td>
<td>1</td>
<td>2.9%</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>1</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

- **No of Patients**: 34
- **Gender (M : F)**: 29 : 5
- **Age (yrs)**: 48 ± 16 (14-74)
Brugada Syndrome in YUMC (1997-2004)

N = 12
Sex : all male
Mean age = 44 ± 14 years (range 22 – 74)
Clinical manifestation
- 6 : Syncope
- 3 : Aborted SD with preceding syncope
- 1 : Aborted SD without preceding syncope
Brugada Syndrome in YUMC (1997-2004)

Activity at time of event: sleeping 5/10
Family Hx: 6/12
EPS: VF induced 10/10
Recurrence: 3/10 (within 1 year)
The Circardian Pattern of three Patients with ICD

![Graph showing the frequency of VF detections (%)]

- Time of day:
  - 0:00-6:00
  - 6:00-12:00
  - 12:00-18:00
  - 18:00-24:00

- Frequency of VF detections (%)
  - While awake
  - During sleeping

- Occurrences:
  - 0:00-6:00: 12
  - 6:00-12:00: 1 (while awake) + 3 (during sleeping)
  - 12:00-18:00: 2 (while awake)
  - 18:00-24:00: 2 (while awake) + 1 (during sleeping)
Genetic study

- SCN5A genetic abnormality was found in one out of 10 probands and three out of 14 family members.
- One brother, son, and daughter of this proband showed same SCN5A genetic abnormality among 8 family members who underwent genetic study.
Kim YH #3478762

I

Sudden death

II

49

52

57

ECG(+) ECG(+) ECG(+)

DNA no DNA NL DNA

III

ECG(-) ECG(-)

ECG(+) ECG(+) ECG(-)

V1 V2 V3 V1 V2 V1 HDF V2 HDF
**SCN5A (Human cardiac sodium channel α subunit gene)**

- Localization: 3p21
- 28 exons (2,016 amino acid, 6,048bp)
- Mutations in SCN5A have been linked to Brugada syndrome.
  
  *(Chen et al. Nature 1998;392:293)*

- More than 60 mutations

---

SCN5A: Human cardiac sodium channel α subunit gene

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---

**Extracellular**

**Intracellular**

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Yonsei Cardiovascular Center 2005
Mutation Detection (#3478762)
G1262S (G→A) at exon 21

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

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

- Aborted sudden cardiac death
- Unexplained syncope
- Positive family history for SCD

YES

ICD

+ ??

QUESTIONABLE

- EPS
- Pharmacological testing
- Genetic testing
- Family studies

NO

Clinical follow-up
Consider RV pathology, drug toxicity, electrolyte disturbance

Littmann L et al. Am Heart J 2003;145:768
### Long-Term Prognosis of individuals With Right Precordial ST Elevation Brugada Syndrome (n=212)

Follow-up duration: 40 ± 50 months

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

Previous syncope and a spontaneous type I ECG indicate a worse prognosis.

PES has a low positive predictive value but a high negative predictive value.

All asymptomatic, noninducible individuals remained asymptomatic.
Efficacy of Quinidine in High-Risk Patients With Brugada Syndrome (N=25/38)

15/15 symptomatic and 10/23 asymptomatic Brugada syndrome Inducible VF in all patients by PES (up to triple stimuli)

- Quinidine is highly effective for preventing VF induction in Brugada patients inducible VF. 22/25 (88% efficacy)
  16: quinidine (15 responder, 1 non-responder)
  6: ICD
  3: ICD + quinidine

- Quinidine appears to be effective in preventing spontaneous VF for 6 to 219 months. (11 symptomatic, 8 asymptomatic)

- 9 ICD
  2 quinidine non responder, 5 side effects, 1 syncope, 1 patient’s wish

Brugada Syndrome 2003
Report of the Second Consensus Conference

Conclusion

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

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

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

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

Brugada syndrome (SCD)

Brugada ECG Pattern and high risk
- Family history for SCD
- Unexplained syncope
- SE Asian ethnicity (?)

Brugada ECG Pattern provoked by
- RV pathology
- Sodium channel blockade: drugs, electrolyte disturbance

Brugada ECG Pattern without above features

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