Understanding the Risks and Management of Brugada Syndrome

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Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, (HRS Chairperson)¹, Arthur A. Wilde, (EHRA Chairperson)², Minoru Horie, (APHRS Chairperson)³, Yongkeun Cho, (APHRS Chairperson)⁴, Elijah R. Behr⁵, Charles Berul⁶, Nico Blom⁷*, Josep Brugada⁸, Chern-En Chiang⁹, Heikki Huikuri¹⁰, Prince Kannankeril¹¹‡, Andrew Krahn¹², Antoine Leenhardt¹³, Arthur Moss¹⁴, Peter J. Schwartz¹⁵, Wataru Shimizu¹⁶, Gordon Tomaselli¹⁷‡, Cynthia Tracy¹⁸
Brugada Syndrome

- Primary electrical disorder
- ECG diagnosis
- Characteristic ECG
  - Persistent
  - Transient
  - Provoked
- Prevalence:
  - 1 in 2000 West
  - 1 in 500 SE Asia
Sudden Cardiac Death due to Brugada Syndrome

50-100,000 p.a.

4% Brugada

2-4,000 p.a. ?

SCD in the UK

Est. Incidence: 5-66/100,000 p.a.

1/1,000 p.a. Laos
Brugada syndrome: Spontaneous Type 1 ECG Pattern
The Brugada ECG

Type 1

Type 2

Type 3

Normal finding
The Ajmaline Test

Baseline    2 mins    3 mins
High RV leads and RVOT
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Brugada syndrome

1. BrS *is diagnosed* in patients with ST segment elevation with type 1 morphology $\geq 2$ mm in $\geq 1$ lead among the right precordial leads V1, V2 positioned in the $2^{nd}$, $3^{rd}$ or $4^{th}$ intercostal space occurring either spontaneously *or* after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

2. BrS *is diagnosed* in patients with type 2 or type 3 ST segment elevation in $\geq 1$ lead among the right precordial leads V1, V2 positioned in the $2^{nd}$, $3^{rd}$ or $4^{th}$ intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type 1 ECG morphology
J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge

Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), and the Latin American Society of Cardiac Pacing and Electrophysiology (Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología [SOLAECE])
Drug-induced Type 1 ECG

PLUS at least one of

- Documented VF or polymorphic VT
- Arrhythmic syncope
- A family history of:
  - SCD at <45 years old with negative autopsy
  - Coved-type ECGs
- Nocturnal agonal respiration
- Inducibility of VT/VF with 1 or 2 extrasystole
**Shanghai score**

**Score (requires at least 1 ECG finding)**

- ≥3.5 points: Probable/definite BrS
- 2–3 points: Possible BrS
- <2 points: Nondiagnostic

I. ECG (12-Lead/Ambulatory)

A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads  
   3.5

B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads  
   3

C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge  
   2

*Only award points once for highest score within this category. One item from this category must apply.*
II. Clinical History*

A. Unexplained cardiac arrest or documented VF/ polymorphic VT 3
B. Nocturnal agonal respirations 2
C. Suspected arrhythmic syncope 2
D. Syncope of unclear mechanism/unclear etiology 1
E. Atrial flutter/fibrillation in patients <30 years without alternative etiology 0.5

*Only award points once for highest score within this category.

III. Family History

A. First- or second-degree relative with definite BrS 2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative 1
C. Unexplained SCD <45 years in first- or second-degree relative with negative autopsy 0.5

*Only award points once for highest score within this category.
Brugada Syndrome

Prognosis

BS patients with typical ECG
Cardiac arrest

20% within 1 year

SUCD

40% in 4 years

Asymptomatic = Symptomatic

ICD = fully protective

Drugs = ineffective

Brugada et al, Circulation 1998
Population Follow-up Studies

Atarashi et al JACC 2001
Japanese factory population (~10,000):
- Prevalence 0.16%
- 90% male
- 3 year follow-up
- 1.5% cardiac event rate

Miyasaki et al JACC 2001
Japanese urban health screen (~14,000):
- Prevalence 0.12%
- 81% male
- 2.6 years follow-up
- 1.0% mortality rate
UK General Population Annual Mortality Rates 2009

>1% p.a. SCD risk for ICD
FINGER study: Symptoms

Asymptomatic

Syncope

SCD

Free from events (%) vs. Follow-up in months

0.5% p.a.

1.9% p.a.

7.7% p.a.
Lifestyle

Class I

1. The following lifestyle changes are recommended in all patients with diagnosis of BrS:

a) Avoidance of drugs that may induce or aggravate ST segment elevation in right precordial leads (Brugadadrugs.org),
b) Avoidance of excessive alcohol intake,
c) Immediate treatment of fever with antipyretic drugs.
<table>
<thead>
<tr>
<th>Class</th>
<th>ICD Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>ICD implantation <strong>is recommended</strong> in patients with a diagnosis of BrS who:</td>
</tr>
<tr>
<td></td>
<td>• Are survivors of a cardiac arrest, and/or</td>
</tr>
<tr>
<td></td>
<td>• Have documented spontaneous sustained VT with or without syncope.</td>
</tr>
<tr>
<td>Class IIa</td>
<td>ICD implantation <strong>can be useful</strong> in patients with a spontaneous diagnostic Type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.</td>
</tr>
</tbody>
</table>
FINGER Study: ECG appearance

Asymptomatic: 0.55% p.a.

Drug induced type 1: 1.7% p.a.

Spontaneous type 1: 2.3% p.a.
The majority of sudden deaths in familial Brugada syndrome would not be predicted by current accepted markers.

FINGER Study

- Median follow-up 31.9 (14 to 54.4) months
- 51 arrhythmic events
  - Appropriate ICD shocks 44 patients
  - SCD 7 patients

Only 10 in the asymptomatic group

SURVIVOR BIAS?

Raju et al JACC 2011
Primary Prevention: 2002/5 Consensus Recommendations

Class Ila:

Inducibility of sustained VT/VF at EP study *can be useful* as an indication for ICD implantation.
Primary Prevention: EP studies to Risk Stratify?

Viskin et al. Europace 2007

- Poor positive predictive value
- Good negative predictive value
- Low event rate
- Short follow-up

EPS positive vs. EPS negative
- Brugada series: 66% vs. 1%
- Other studies: 74% vs. 2%
PRELUDE study: Death Knell for EPS?

A

Up to 3 extras

Number at risk

Not inducible 182 172 153 111 71 37
Inducible 126 116 100 77 46 25

Arrhythmia-free survival (%)

Follow up (months)

p = 0.67
VTs/VF Inducible (n = 126)
VTs/VF Not inducible (n = 182)

B

1 or 2 extras

Number at risk

Not inducible 245 232 205 149 98 52
Inducible 63 56 48 37 19 9

Arrhythmia-free survival (%)

Follow up (months)

p = 0.89
VTs/VF Inducible (n = 63)
VTs/VF Not inducible (n = 245)

Priori et al JACC 2011
BUT Parametric Score?

Risk factors:
- Syncope
- FH of SD
- EPS positive
- EP studies
- NPV = 100%

Delise et al EHJ 2011
And…..

363 asymptomatic patients
11.3% spontaneous Type 1 pattern
88.4% underwent EPS
10% inducible

Follow-up 73.2±58.9 months
9 arrhythmic events
Annual incidence rate of 0.5%

Univariate analysis:
Inducibility HR 11.4 [CI 2.7–41.8, p<0.01]
Spontaneous type 1 HR 4.0 [1.1–14.9, p=0.04]
Sinus node disease HR 8.0 [1.0–63.9, p=0.049]

Multivariate only inducibility significant HR 9.1, p<0.01

BUT Positive predictive value was 18.2%
and negative predictive value 98.3%
Why differences?

Pacing sites:
- RV apex
- RV outflow tract

Extra-stimuli:
- Two vs Three
- Minimum coupling intervals (200ms)
Alternative Risk Markers?

Signal averaged ECG
Full stomach test
rJ interval in lead V1
QRS duration (lead V6)
Dynamic ST elevation
Heart rate variability (?)
S-wave in lead I
Severity of SCN5A mutation

Higher risk: SE Asian
Spontaneous type 1 and syncope

Sens 42.9% (19–69)
Spec 90.5% (89–92)

Priori et al. JACC 2011
# QRS-f and ERP

<table>
<thead>
<tr>
<th>Male/female</th>
<th>236/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>47.6 ± 13.6</td>
</tr>
<tr>
<td>Mean f-up period, mo</td>
<td>45.1 ± 44.3</td>
</tr>
<tr>
<td>History of syncope</td>
<td>40 (16.3)</td>
</tr>
<tr>
<td>History of VF episodes</td>
<td>13 (5.3)</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>69 (28.0)</td>
</tr>
<tr>
<td>PAF</td>
<td>44 (17.9)</td>
</tr>
<tr>
<td>Spontaneous type 1 ECG</td>
<td>156 (63.4)</td>
</tr>
<tr>
<td>ER pattern</td>
<td>25 (10.2)</td>
</tr>
<tr>
<td>f-QRS</td>
<td>78 (31.7)</td>
</tr>
<tr>
<td>Positive LP</td>
<td>166/235 (70.6)</td>
</tr>
<tr>
<td>SCN5A gene mutation</td>
<td>17/123 (13.8)</td>
</tr>
<tr>
<td>VF induction during EP study</td>
<td>71/155 (45.8)</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>63 (25.6)</td>
</tr>
<tr>
<td>VF or SCD event during f-up</td>
<td>24 (9.8)</td>
</tr>
</tbody>
</table>

Tokioka et al., JACC 2014
Management

Type 1 Brugada pattern

- Avoid drugs that may induce or aggravate ST segment elevation in right precordial leads (www.Brugadadrugs.org)
- Avoid cocaine and excessive alcohol intake
- Immediately treat fever with antipyretic drugs. (Class I)

Asymptomatic

Spontaneous and fever-induced type 1 Brugada pattern

Based on patient and ECG characteristics (Age, Gender, Jp amplitude, QRS fragmentation, ...)

Inducible VT/VF with up to 2 ES

- Close follow-up

+ Quinidine

- ICD

+ ICD (Class IIb)

Quinidine, if ICD indicated but refused or contraindicated (Class IIa)
ICD complications in Brugada Syndrome

176 patients

Mean follow-up 83.8 ± 57.3 months

33 (18.7%) had inappropriate shocks

8 (15.9%) experienced device-related complications

Complications consisted of:

- lead fracture 14
- lead dislocation 7
- generator migration 2
- device infections 5

Sarkozy et al. Eur Heart J 2007

Conte et al. JACC 2015
Epicardial mapping and ablation

Nademanee et al Circ 2011
Summary: Risk Stratification

Cardiac Arrest and Syncope = **High Risk**

Asymptomatic drug-induced ECG = **Low risk**

**BUT** Largest group

May harbour many SCDs: How do we stratify?

Asymptomatic + Spontaneous Type 1 ECG = **Risk intermediate**
Conclusions

Risk stratification is still imperfect

Asymptomatic need better markers

EPS remain albeit class IIb: spontaneous type 1

New ECG/EP measures for risk: ECG/EP/Genomic risk score

Less and better ICD implantation!! S-ICD

Replace with substrate ablation?
? QUESTIONS
Management

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Management

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Symptomatic

- Electrical storm
- Prior cardiac arrest sustained VT
- Syncope seizure NAR

Isoproterenol +/- quinidine (Class IIa)

Presumably arrhythmic origin

ICD (Class I)

ICD (Class IIa)

Close follow-up with/without ILR

Repeated appropriate shocks

Quinidine (Class IIa)
RVOT ablation (Class IIb)
cilostazol

Quinidine, if ICD indicated but refused or contraindicated (Class IIa)