Brugada Syndrome: An Update

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Brugada Syndrome

Updates

Mechanism and Genetics
Risk stratification
Treatment
Brugada syndrome

Brugada syndrome causes 4–12% of all SCDs, and up to 20% of SCDs without identifiable structural abnormalities

Very rare
5-50/10000
Leading cause of natural death in young men


Types of BS

The diagnostic is type 1 (either spontaneous or provoked)

Brugada syndrome and sudden unexpected nocturnal death

Brugada ECG sign is dynamic, typically manifest at night and SCD occurs during sleep (peak at 12 AM-6 AM)

Da cho
Batibat, Bangungot (Philippine)
Lai Tai (Thailand)

BS is included among a group of electric disorders sharing common mechanisms of arrhythmogenicity
### BS: Variant of Early repolarization syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Leads affected</th>
<th>Gene mutation</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERS type 1</td>
<td>Lateral leads</td>
<td>CACNA1C, CACNB2B</td>
<td>Rare</td>
</tr>
<tr>
<td>ERS type 2</td>
<td>Inferior or inferolateral</td>
<td>KCNJ8, CACNA1C, CACNB2B</td>
<td>Yes</td>
</tr>
<tr>
<td>ERS type 3</td>
<td>Global + Rt precordial leads</td>
<td>CACNA1C</td>
<td>Yes, electric storms</td>
</tr>
</tbody>
</table>

ERS type 4 → Brugada syndrome


### Genetics and pathophysiology of BS

- **SCN5A (BrS1):** Only in 20% of cases
- **GPD1L (BrS2)**
- **CACNA1C (BrS3)**
- **CACNB2 (BrS4)**
- **SCN1B (BrS5)**
- **KCNE3 (BrS6)**
- **SCN3B (BrS7)**
- **KCNJ8 (BrS8)**
- **CACNA2D (BrS9)**
- **KCND3 (BrS10)**
- **MOG1 (BrS11)**
- **SLMAP (BrS12)**
- **SCN2B (BrS13)**
- **Other candidate genes:** (KCNH2, KCNE5 (KCNE1L), HCN4)

No data regarding genotype-phenotype relationship (unlike LQTS)

Journal of Arrhythmia, Volume 29, Issue 2, April 2013, Pages 71–76
The action potential notch

(\(I_{to}\): Phase 1 of AP)

- Transient outward K current (\(I_{to}\))
- ATP-sensitive K channel
- AC-sensitive K channel
- Delayed rectifier K channel
- Inwardly rectifier K channel

Normally, AP notch is more prominent in the epicardium than the endocardium, in the RV than the LV, and in males than females.
Normal ECG

Increased AP notch affecting the RV epicardium will generate transmural gradient manifested as J point and ST elevation.
J wave syndromes

(> 1 mm elevation of J point ± ST elevation)

Duration and magnitude of endo to epicardial gradient determines the J point/ST segment elevation

Epicardium

Endocardium

ECG

Osborn

Early repolarization

STEMI

Brugada

Hypothermia

Precipitating factors

Epicardium

Endocardium
Increased AP notch results into failure of L-Ca^{++} channel activation $\rightarrow$ regional loss of AP dome

Propagation of the dome $\rightarrow$ phase 2 reentry
Genetic aspects and ion channel dynamics

Magnitude of Na⁺ current

 Normally

Cell memb

Na⁺ channels L- Ca²⁺ channels

Early closure of Na channels

Slow activation of L-Ca channels \(\rightarrow\) prominent notch

SCN5A Mutation
(BrS1, 20%)
NaCBs

Failed activation of L-Ca channels \(\rightarrow\) loss of AP dome

Cell memb

Na⁺ channels L- Ca²⁺ channels
**Genetic aspects and ion channel dynamics**

**No (or slow) L-Ca\(^{++}\) channel activation**

*CACNA1C (BrS3), CACNB2 (BrS4), CACNA2D (BrS9) gene mutation*

![Diagram showing Na\(^+\) channels and L-Ca\(^{++}\) channels with an arrow indicating CCBs and a decrease in L-Ca\(^{++}\) channel activation.]

**Increased transient outward K\(^+\) current (I\(_{to}\))**

- **I\(_{to}\) gain of function mutation**
  - KCNE3 (BrS6), KCND3 (BrS10)
  - Vagal stimulation

- **Increased ATP sensitive K\(^+\) current (I\(_{ATP}\))**
  - KCNJ8 (BrS8)


Factors contributing to SCD in Brugada patients

Vagal stimulation/bradycardia/pauses

Factors contributing to SCD in Brugada patients

Heavy meals at bed time


Factors contributing to SCD in Brugada patients

Hypokalemia

K channel openers (Nicorandil)

Rice cake

Spike and dome

Loss of dome

Circ J. 2003;67:93–96

Factors contributing to SCD in Brugada patients

The mutant gene is more functioning in high temperature in vitro

Febrile illness

Sleeping in hot weather

Factors contributing to SCD Brugada patients

Antihistaminics, class IA&IC, TCA, BBs, CCBs, nitrates, nicorandil, SSRIs, tramadol

Diagnostic considerations

- Provocative testing (only 36% of BS have spontaneous type 1 ECG signs). Ajmaline, role of exercise testing (Brugada sign on recovery)
- High suspicion (young men, short coupled PVCs not responding to BBs, CCBs or amiodarone, febrile dizzy spells, agonal breathing or nightmares during sleep)
- Recording V1 and V2 at higher intercostal spaces

Journal of Arrhythmia, Volume 29, Issue 2, April 2013, Pages 88–95
Provocation of type 1 BS by ajmaline

Diagnostic considerations

- Provocative testing (only 36% of BS have spontaneous ECG signs). Ajmaline, role of exercise testing (Brugada sign on recovery).
- Cardiac MRI to exclude ARVD (overlap, variant?).
- Asymptomatic pts with spontaneous type 1 BS are at moderate risk.
- High suspicion (short coupled PVCs not responding to BBs, CCBs or amiodarone, febrile dizzy spells, syncope after a hot bath, agonal breathing or nightmares during sleep).
How Brugada syndrome is missed:
Diagnostic pitfalls

<table>
<thead>
<tr>
<th>Brugada Syndrome</th>
<th>Misdiagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope in hot weather or after a hot bath</td>
<td>Neurocardiogenic syncope</td>
</tr>
<tr>
<td>Fainting+fits during febrile episodes</td>
<td>Febrile convulsions</td>
</tr>
<tr>
<td>Agonal breathing during sleep</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>ST elevation in V1-3 that resolves</td>
<td>Anteroseptal MI</td>
</tr>
</tbody>
</table>

The recordings of V1 and V2 leads at higher intercostal spaces increase the sensitivity and the specificity of the ECG diagnosis for detecting the Brugada phenotype

According to a recent study of 460 patients with BS, the presence of a J wave in multiple leads and horizontal ST-segment morphology after J wave are associated with a higher incidence of cardiac events.

Takagi et al. The prognostic value of early repolarization (J wave) and ST-segment morphology after J wave in Brugada syndrome: Multicenter study in Japan. Heart Rhythm. Dec 27 2012

Type 1 ST elevation in one or more limb leads can be seen in 10% of the patients with BS and is an independent predictor for a malignant arrhythmic event (odds ratio 4.58; 95% CI 1.7–12.32; \( P = .0025 \)).

Heart Rhythm, Volume 10, Issue 7, July 2013, Pages 1012–1018
Patient with idiopathic VF (the bottom ECG was taken during sleep)

**Day**

**Night**

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**Structural abnormalities are found in BS**

Late RV epicardial activation contribute to ST elevation

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Circulation.2005; 112: 3680-3687
Circulation: Arrhythmia and Electrophysiology.2010; 3: 283-290
Late RV epicardial activation contribute to ST elevation

Conduction delay is associated with fragmented QRS

Areas of structural abnormalities

Fragmented Br. ECG
“Notched ST ?”

Circulation: Arrhythmia and Electrophysiology. 2010; 3: 283-290
**Newly indentified High risk criteria in BS**

**Fragmented QRS in V1,2**

F-QRS in V1,2 was associated with higher risk of VF related syncope

Journal of Arrhythmia, Volume 29, Issue 2, April 2013, Pages 77–82

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**Newly indentified High risk criteria in BS**

**Concomitant dysautonomia**

Disturbance in ANS is present in >11-13% that is responsible for the high incidence of vasospastic angina (VSA) and neurally mediated syncope in BS

Special concern regarding VSA (CCBs) and NMS (mineralocorticoid induced hypokalemia)

Journal of Arrhythmia, Volume 29, Issue 2, April 2013, Pages 83–87
Newly indentified
High risk criteria in BS

Role of EP study

Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry.

VT/VF inducibility is unable to identify high-risk patients, whereas ventricular ERP<200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic ICD.


Short coupled PVCs characterizing BS and ERS

Coupling interval that induces VF is longer in BS than ERS

Journal of Arrhythmia, Volume 29, Issue 2, April 2013, Pages 126–133
**Pharmacotherapy of BS**

**Isoprenaline infusion during electric storms**

![Diagram showing the effect of Isoprenaline on AP dome](image)

**Quinidine is the only effective drug to prevent arrhythmia**

![Diagram showing the effect of Quinidine on AP dome](image)

**Non-pharmacologic ttt of BS**

**Pacing**

Eliminate pauses → Reduce AP notch

**ICD**

For high risk patients

2012 ACCF/AHA/HRS guidelines recommends ICD implantation in BS patients who have survived cardiac arrest (Class I) or have a history of syncope (class IIa), and documented ventricular arrhythmia (Class IIa).
Non-pharmacotherapy for BS

Role of catheter ablation

In one study, RVOT ablation targeting late activation zone could normalize ECG and suppress VT storm.

In another study, epicardial ablation of the anterior RVOT targeting late fractionated potentials could normalize ECG and suppress VT storm.

J Cardiovasc Electrophysiol. 2012 Nov;23 Suppl 1:1540-8167

Management of BS

Future perspectives

- Selective *Ito* blockers
- Selective ATP and AC sensitive K channel blockers for individual cases
- Tedisamil, Dimethyl lithospermate B (slows inh. of phase 0) *
- Phosphodiesterase inhibitors
- *Gene therapy*

* Circulation. 2006; 113: 1393-1400
**Home message**

- BS is one of J wave syndromes, in which arrhythmogenesis is due to regional loss of AP dome (phase 2 reentry).
- 13 genotypes are currently known.
- It is the most underdiagnosed channelopathy. Majority of patients have unremarkable ECG.
- Symptoms, concomitant dysautonomia, spontaneous type 1 ECG, extent of J wave, fragmented QRS, and short V. ERP (but not VT inducibility) contribute to risk stratification.
- Asymptomatic pts with type 1 BS are at moderate risk → ICD ??
- In addition to Isoprenaline and Quinidine, catheter ablation may be a therapeutic option.