The Future of Risk Stratification in Channelopathy

Minoru Horie
Cardiovascular Medicine, Shiga University of Medical Science
COI:
The Future of Risk Stratification in Channelopathy

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None to declare in regard to this presentation
Q1: As to symptoms, which patient presents more cardiac arrest (CA)?

Brugada or long QT syndrome?

Brugada syndrome: Data for 1217 patients
Paul: *Eur Heart J* 2007

Long QT syndrome: Data for 3015 patients
Goldenberg: *Circulation* 2008

60% syncope
40% CA

12% CA
88% syncope
Q2: How many percent of pts experienced CA without warning syncope?

Most recently published Shanghai Scoring System for BrS diagnosis is also valid for Risk Stratification.

Shanghai Score for Diagnosis of Brugada Syndrome


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  2
   challenge
*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 o30 years without alternative  0.5
   etiology
*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.

IV. Genetic Test Result
A. Probable pathogenic mutation in BrS susceptibility gene 0.5

Score (requires at least 1 ECG finding)
\[ \geq 3.5 \text{ points: Probable/definite BrS} \]
\[ 2-3 \text{ points: Possible BrS} \]
\[ < 2 \text{ points: Nondiagnostic} \]
Shanghai scoring system is useful for risk stratification.


393 consecutive Jpn Brugada pts at a single hospital. Mean f/u 97.2 months

**FIGURE 2** Cumulative Event-Free Survival as a Function of Score

<table>
<thead>
<tr>
<th>Score Range</th>
<th>Numbers at Risk</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Score ≤3.0 points</td>
<td>45, 42, 36, 17, 6, 2, -</td>
<td>0, 50, 100, 150, 200, 250, 300</td>
</tr>
<tr>
<td>B: Score =3.5 points</td>
<td>186, 131, 78, 36, 12, 3, -</td>
<td></td>
</tr>
<tr>
<td>C: Score =4.0-5.0 points</td>
<td>81, 60, 43, 16, 4, -</td>
<td></td>
</tr>
<tr>
<td>D: Score ≥5.5 points</td>
<td>81, 53, 34, 15, 6, 2, -</td>
<td></td>
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Probable/definite BrS
Three major categories in Shanghai score system for risk stratification:

- **ECG features**
  - type 1 Brugada pattern: most powerful
  - only this? ER? QRS fragmentation…….

- **Clinical history**
  - Unexplained CA or documented VF/pVT

- **Genetic background**
  - family history and genetic test results
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Variability of the Diagnostic ECG Pattern in an ICD Patient Population with Brugada Syndrome

In patients with spontaneous coved-type ECG, only every third ECG is **diagnostic** and every third ECG **normal**.

**You should record at least 3 ECG in a single patient.**

Richter, *JCE* 2009
Other ECG features as Risk Predictors

- aVR sign (Babai et al, 2007)
- fragmented QRS in the right precordial leads (Morita et al, 2008; Priori et al, 2012)
- prolonged r-J interval in lead V₂ and QRS duration in lead V₆ (Takagi et al, 2007)
- Early repolarization patterns in other leads.
- precordial ST elevation during recovery of exercise test (Makimoto et al, 2010)
- amplitude (depth) of negative T wave in lead V₁ (Miyamoto et al, 2014)
- wide and/or deep S wave in lead I (Calo et al. 2016)
- minimum amplitude of late R’ plus S < 0.8 mV (Nagase et al, 2018)
✓ **aVR sign** (Babai et al, 2007)
✓ **fragmented QRS in the right precordial leads** (Morita et al, 2008; Priori et al, 2012)
✓ **prolonged r-J interval in lead V₂ and QRS duration in lead V₆** (Takagi et al, 2007)
✓ **Early repolarization patterns in other leads.**
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✓ **minimum amplitude of late R’ plus S < 0.8 mV** (Nagase et al, 2018)
fragmented QRS in the right precordial leads

Morita, *Circulation* 2008

Priori, *JACC* 2012
IN 81 IVF patients implanted with ICD (CS Seong ... YK On, PlosONE 2018)

f-QRS = fragmented QRS complexes
Hypothesis: Epicardial mapping revealed low-voltage areas on the right ventricular outflow tract in Brugada syndrome. This may influence the amplitude of type 1 ECGs. If any, it is associated with clinical severity of the syndrome (can be a risk factor).

In 209 Brugada patients with type 1 ECG pattern, they measured: S depth and R' height.

**Figure 2.** Measurements of ECG parameters in leads showing type 1. Among the 9 right precordial leads, the amplitudes of late R', S, and late R' plus S were evaluated in each ECG lead showing type 1.
Late R’ plus S = 0.78 mV was optimized cutoff point to predict VF episodes.

As the minimum amplitude of late R’ plus S wave was smaller, the risk for VF recurrence during f/u increased.
ECG features
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Clinical history
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Risk of cardiac arrest in Brugada patients presenting with syncope

Risk of cardiac arrest in Brugada patients presenting with syncope:
- Aborted cardiac arrest
- Arrhythmic syncope
- Non-arrhythmic syncope

Olde-Nordkamp, HeartRhythm 2015
Long term follow-up of 166 patients with asymptomatic Brugada who underwent ICD implantation (because of inducible VF in 84%)

Event free survival rate

Spontaneous VF in asymptomatic Brugada syndrome

Mean follow-up: 7 ± 3 years:

Appropriate ICD therapy: 7% (1% per year)

8.7% for patients with spontaneous type I

5.4% for patients with drug-induced type I

Sacher, Haissaguerre et al. *Circulation* 2013
### Value of VF inducibility in asymptomatic Brugada syndrome

Data for 703 patients who had EP studies.

<table>
<thead>
<tr>
<th></th>
<th>Japanese study</th>
<th>FINGER</th>
<th>PRELUDE</th>
</tr>
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<tbody>
<tr>
<td>Inducible VF</td>
<td>52 ➞ 1 VF</td>
<td>137 ➞ 4 VF</td>
<td>97 ➞ 3 VF</td>
</tr>
<tr>
<td>Negative EPS</td>
<td>39 ➞ 2 VF</td>
<td>232 ➞ 3 VF</td>
<td>146 ➞ 4 VF</td>
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Spontaneous VF if INDUCIBLE 8 of 286 = 2.7%

Spontaneous VF if EPS negative 9 of 417 = 2.1%
108 consecutive patients with Brugada syndrome (VF=26, syncope=40, asymptomatic=42). EPS: One cycle length (500 msec) and up to 3 VES (first RVA and then RVOT); Coupling interval > 180 msec.

Makimoto et al. Heart Rhythm 2011
PRELUDE: 308 patients with no history of cardiac arrest (56% with type I ECG)

Inducible VF: Single 2%, double 19%, triple 26%. Total 41%

Priori et al, JACC 2012
The prognostic impact of single extra-stimulus on programmed ventricular stimulation in Brugada patients without previous cardiac arrest: multi-centre study in Japan.

Aims:
The prognostic value of programmed electrical stimulation (PES) in Brugada syndrome (BrS) remains controversial. One of the reasons for discrepant results may be due to the selection of stimulation protocol. We evaluated the prognostic value of a positive PES result (PES+) according to the inducible pacing sites and the number of extra-stimuli in BrS patients without previous cardiac arrest (CA).

Methods and results:
We enrolled 224 consecutive BrS patients without previous CA (mean age 51 ± 14 years, 209 males), who underwent PES with the identical protocol. Clinical outcomes of development of CA were explored in the patients with and without PES+ according to sites and number of extra-stimuli. During a mean follow-up period of 76 months, 12 cardiac events (CE: sudden cardiac death or documented VF) occurred (8 with and 4 without PES+). The incidence of CE was not different in patients with and without PES+, those with PES+ from RVA (n = 72) or RVOT (n = 60), and those with and without PES+ by up to 2 extra-stimuli (n = 58). However, in patients that were PES+ by a single extra-stimulus (n = 8) the incidence of CE was significantly higher than in those without PES+ (8.8 vs. 0.6%/year, P < 0.0001). On univariate analysis, syncope, spontaneous type 1 ECG, and PES+ by a single extra-stimulus were associated with CE.
The prognostic impact of single extra-stimulus on programmed ventricular stimulation in Brugada patients without previous cardiac arrest: multi-centre study in Japan

(Takagi et al, Europace 2018)
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Prof. Ohno will talk about this in detail.
Shanghai scoring system is useful for risk stratification. Kawada et al. JACC, 2018. 393 Brugada pts at a single hospital.

**Figure 2** Cumulative Event-Free Survival as a Function of Score

- *A:* Score ≤ 3.0 points
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Log Rank Test P < 0.001
Patient Management of JWS including BrS

1. Secondary prevention
   - ER resuscitated from VF

2. Primary prevention
   - Asymptomatic individuals with ER
   - ER with unexplained syncope

Risk stratification

- High risk ECG?
- Family history of sudden death?
- VF inducibility?
- Gene mutations?

ICD (Class I indication)
- Quinidine (adjuvant therapy)
- ISP (VF storm)
As the first symptom can be cardiac arrest in Brugada syndrome, the risk stratification of asymptomatic pts is of paramount importance.

Risk can be assessed based on 3 major categories of Shanghai scoring system: ECG, clinical history, and genetic background.
As to the future measure, several ECG criteria would be included to the scoring system, as well as positive VF inducibility by a single extra-stimulus.

Pathogenic SCN5A variants are currently underscored (personal opinion).
Thank YOU for your ATTENTION!

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