State of the Art: Brugada Syndrome
Novel diagnostic approaches and risk stratification

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I have nothing to disclose.
Asymptomatic Brugada syndrome: a cardiac ticking time-bomb?

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Tel Aviv 64239, Israel

*Online publish-ahead-of-print 22 August 2007
Prevalence-Estimations

„Brugada-ECG“ oder „Brugada-Sign“

- Asian: 1:1000 (Denjoy et al, 2007)
- Caucasian: 5:1000 (Napolitano et al, 2006)

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>3.2 million</td>
</tr>
<tr>
<td>Germany</td>
<td>425,000</td>
</tr>
<tr>
<td>Japan</td>
<td>1,820,000</td>
</tr>
</tbody>
</table>
Low Prevalence of Risk Markers in Cases of Sudden Death Due to Brugada Syndrome

Relevance to Risk Stratification in Brugada Syndrome

Hariharan Raju, MBChB,* Michael Papadakis, MBBS,* Malini Govindan, B Med,* Rachel Bastiaenen, MBBS,* Navin Chandra, MBBS,* Ann O'Sullivan, BSc;† Georgina Baines, BSc;‡ Sanjay Sharma, MBChB, MD,* Elijah R. Behr, MBBS, MD* London and Oxford, United Kingdom

<table>
<thead>
<tr>
<th>Clinical Characteristics of SADS Probands With Familial Diagnosis of BrS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Presentation</td>
</tr>
<tr>
<td>No. of probands</td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Age, yrs</td>
</tr>
<tr>
<td>Type 1 BrS pattern/no. of ECGs available</td>
</tr>
<tr>
<td>Family history of prior SCD</td>
</tr>
<tr>
<td>Died in sleep or rest</td>
</tr>
<tr>
<td>Definite mutation/SCN5A analysis</td>
</tr>
</tbody>
</table>

Results

A total of 49 consecutive families with a confirmed SADS death and a diagnosis of BrS were evaluated, comprising assessment of 202 family members in total. One family had 2 members with SADS, resulting in a total of 50 probands included. Mean age of death of probands was 29.1 ± 10.6 years, with 41 males (82%) (p < 0.05). Antemortem ECGs were available for 5 SADS probands, 1 of which demonstrated a spontaneous type 1 pattern. In 45 probands, symptoms before death were reported reliably by family members. Of these, 9 (20%) had experienced at least 1 syncopal episode before the fatal event. Importantly, 68% of probands would not have fulfilled any current criteria for consideration of implantable cardioverter-defibrillator.

Conclusions

The “low-risk” asymptomatic BrS group comprises the majority of SCD in this cohort. Current risk stratification would appear to be inadequate, and new markers of risk are vital. (J Am Coll Cardiol 2011;57:2340–5)
Brugada Syndrome

Autonomic imbalance (Increased vagal tone)
Febrile (Body temperature)
Bradycardia
Myocardial ischemia
Glucose-induced insulin
Meal ingestion
Higher leads placement

Na⁺ channel blocker
β-blocker, α-stimulater
Muscarinic stimulater (Acetylcholine, Edrophorium)
Ca²⁺ channel blocker
Tricyclic or Tetracyclic antidepressarites
Antihistamine (Dimenhydrinate)

V₁ Saddleback type
V₂ Type 2 ST elevation

V₁ Coved type
V₂ Type 1 ST elevation

Nishizaki et al., Circulation Journal 2010
Correlation between diagnostic criteria and results of genetic screening in Brugada Syndrome

the appearance of a BrS pattern in the higher intercostals spaces or in only one precordial lead should be considered diagnostic in order to increase sensitivity without losing specificity.

University of Pavia, Division of Cardiology, Pavia
Brugada Syndrome
Report of the Second Consensus Conference
Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association

Symptomatic
- Aborted SCD
  - Syncope
    - NAR
      - Evaluate for clear extracardiac cause
      - (-)
        - ICD (Class I)
      - (+)
        - ICD (Class I)
        - Close follow-up (Class II a)

Asymptomatic
- Family History of SCD suspected to be due to BS
  - Family History (-)
    - EPS justified (Class II a)
      - (+)
        - ICD (Class II a)
      - (-)
        - Close follow-up (Class II b)
    - EPS justified (Class II a)
      - (+)
        - ICD
      - (-)
        - Close follow-up

Antzelevitch et al., Circulation 2005; 111: 659-70
Brugada Syndrome
Report of the Second Consensus Conference

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Symptomatic

- Aborted SCD
  - ICD (Class I)
- Syncope
  - Seizure
  - NAR
  - Evaluate for clear extracardiac cause
    - (-)
      - ICD (Class I)
    - (+)
      - Close follow-up

Asymptomatic

- Family History of SCD suspected to be due to BS
  - EPS justified (Class II a)
    - (+)
      - ICD (Class II a)
    - (-)
      - Close follow-up (Class II b)
  - Family History (-)
    - EPS justified (Class II a)
      - (+)
        - ICD
      - (-)
        - Close follow-up

Antzelevitch et al., Circulation 2005; 111: 659-70
Scientific publications on Brugada Syndrome

Brugada Syndrome
Report of the Second Consensus Conference
Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association

It is time for a new consensus paper!

n= 553

modified from Brugada et al., Hellenic J Cardiol 2009
Widespread use of prophylactic ICD is associated with intolerably high rates of complications

Much longer survival of BS pts as compared to ICD pts with structural heart disease

Sacher et al., Circ 2006
Rosso et al., Isr Med Assoc J 2008

J Cardiovasc Electrophysiol 2011
Asymptomatic individuals with an arrhythmic event during follow-up in different publications

Paul et al., Eur Heart J 2007; 28: 2126-33
Asymptomatic individuals with an arrhythmic event during follow-up in different publications

Paul et al., Eur Heart J 2007; 28: 2126-33
Asymptomatic individuals with an arrhythmic event during follow-up in different publications
Determinants of Sudden Cardiac Death in Individuals With the Electrocardiographic Pattern of Brugada Syndrome and No Previous Cardiac Arrest

Josep Brugada, MD, PhD; Ramon Brugada, MD; Pedro Brugada, MD, PhD

Symptoms

Inducibility at EPS

<table>
<thead>
<tr>
<th>Multivariable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>2.51</td>
<td>1.2-5.3</td>
<td>0.017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducibility of VF</td>
<td>5.88</td>
<td>2.0-16.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Brugada et al., Circulation 2003
Long-Term Prognosis of Individuals With Right Precordial ST-Segment–Elevation Brugada Syndrome

Lars Eckardt, MD*; Vincent Probst, MD*; Jeroen P.P. Smits, MD*; Eric Schulze Bahr, MD; Christian Wolpert, MD; Rainer Schimpf, MD; Thomas Wichter, MD, FESC; Pierre Boisseau, PhD; Achim Heinecke, PhD; Günter Breithardt, MD, FESC; Martin Borggreve, MD; Herve LeMarec, MD, PhD; Dirk Böcker, MD; Arthur A.M. Wilde, MD, FESC

Mean follow-up: $40\pm50$ months: $n=9$ VT/VF events

!! VT/VF inducibility without predictive value !!!

Eckardt et al., Circulation 2005
n=9 VT/VF events during follow-up EP in all 9 pts
- n=5 inducible (2 with one; 3 with 2 extra beats)
- n=3 with a coupling interval < 200ms

<table>
<thead>
<tr>
<th></th>
<th>PVS</th>
<th>Extras</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

sensitivity (95%) | 55.6 |
specificity (95%) | 50.3 |
positive predictive value (95%) | 5.4 |
negative predictive value (95%) | 95.7 |

Eckardt et al., Circulation 2005
It can be concluded from these data that:

- the risk for spontaneous VF at 4 to 5 years follow-up is likely between 1 and 6% for asymptomatic individuals and inducible VF and

- between 1% and 4% for asympt. pts and negative EPS

- long term risk??

Kamakura et al., Circ EP 2009  Probst et al., Circ 2010
### Brugada Syndrome – risk stratification

<table>
<thead>
<tr>
<th>Feature</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of VF/VT or syncope</td>
<td>YES</td>
</tr>
<tr>
<td>Male Gender ?? (testosterone)</td>
<td>Perhaps</td>
</tr>
<tr>
<td>but 70% of asymp. are male (FINGER)</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>Probably not</td>
</tr>
<tr>
<td>Genetic testing/mutation</td>
<td>Probably not</td>
</tr>
<tr>
<td>Spontaneous type 1 (coved type) ECG</td>
<td>Probably</td>
</tr>
<tr>
<td>But high variability</td>
<td></td>
</tr>
<tr>
<td>But not found in large Japanese registry</td>
<td></td>
</tr>
<tr>
<td>Late potentials</td>
<td>Perhaps</td>
</tr>
<tr>
<td>Early repola. pattern inferolat. leads</td>
<td>Perhaps</td>
</tr>
<tr>
<td>ST elevation during recovery of exercise</td>
<td>Perhaps</td>
</tr>
<tr>
<td>But test failed to identify 68% of SCD</td>
<td></td>
</tr>
<tr>
<td>QRS fragmentation in V1-V3</td>
<td>Perhaps</td>
</tr>
</tbody>
</table>
Fragmented QRS as a Marker of Conduction Abnormality and a Predictor of Prognosis of Brugada Syndrome

Hiroshi Morita, MD; Kengo F. Kusano, MD; Daiji Miura, PhD; Satoshi Nagase, MD; Kazufumi Nakamura, MD; Shiho T. Morita, MD; Tohru Ohe, MD; Douglas P. Zipes, MD; Jiashin Wu, PhD

Morita et al., Circulation 2008
2. There is a close relation between RVOT anatomical location and ECG manifestation of Brugada Syndrome

3. Echo-guided right leads positioning may help to better identify diagnostic patterns.
Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

Nademanee et al., Circulation 2011
Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

Figure 8. A delayed effect of epicardial ablation on the ECG pattern. The ECG pattern of patient 7 took 3 months to normalize.
3D-Electroanatomic Mapping-guided Endomyocardial Biopsy findings in patients with Brugada syndrome

Maurizio Pieroni, MD, PhD

.....the identification of abnormal voltage areas and the corresponding myocardial substrate may influence both prognosis and treatment, including ablation strategies
Electro-anatomical mapping, biopsies ....
Case V
Electro-anatomical mapping, biopsies ....
Quinidine Depresses the Transmural Electrical Heterogeneity of Transient Outward Potassium Current of the Right Ventricular Outflow Tract Free Wall

Peng Zhou, M.D. & Ph.D.*,†, Xinchun Yang, M.D. & Ph.D.,* Cuiyan Li, Ph.D.,†, Ying Gao, M.D.,§, Dayi Hu, M.D.,‡

Effects of Low-Dose Quinidline on Ventricular Tachyarrhythmias in Patients With Brugada Syndrome
Low-Dose Quinidine Therapy as an Adjunctive Treatment

Yuka Mizusawa, MD,* Harunizu Sakurada, MD, PhD,* Mitsuhiko Nishizaki, MD, PhD,† and Masayasu Hiraoka, MD, PhD, FACC, FAHA, FESC,‡

Test Potential (mV)

-40 -30 -20 -10 0 10 20 30 40 50 60 70 80

-60mV -40mV -30mV -300mV

• Epi Cells
• M Cells
• Endo Cells

+70mV

Figure 4. I-V relationship of a typical example of 10 μM quinidine on the same typical Epi cell line
Risk vs Benefit of quinidine

- Quinidine often causes side effects (e.g. diarrhea)
- 1 of 3 discontinues drug
- ? Low dose quinidine
- Proarrhythmia (acquired LQTS) – close monitoring required!!

http://www.brugadasyndrome.info/
Subcutaneous-ICD

- 78,2 x 68,5 x 15,7 mm
- Volume: 70 cm³
- Weight: 145 g
- Duration: ~ 5 yrs
- Maximal energy: 80 J
- Post-shock pacing
- 1 or 2 zones
- 170 - 250 bpm
Primary ICD prophylaxis in Brugada syndrome

- Syncope in the presence of Brugada ECG (IIA)
- Asymptomatic pts with a Brugada-ECG have a relatively low arrhythmogenic risk
- The accidental finding of a „Brugada“-ECG alone does not justify ICD-implantation
- Programmed ventricular stimulation is of limited value for risk stratification (IIB)

ACC/AHA/ESC Practice Guidelines Prevention of SCD 2006
Thank YOU