Interventional therapies to “Cure” Brugada Syndrome

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• Cambodia
Discussion Outlines

- Underlying Electrophysiologic mechanisms
  - Evidence of depolarization abnormality
- Brugada Syndrome substrates
  - Characteristics and Pathology of the Substrates.
  - Ablation of the substrates.
- Combined BrS and ER syndrome
- A World-Wide Brugada Ablation of VF Substrate Ongoing Multicenter (BRAVO) Registry

Brugada Syndrome: Underlying Electrophysiologic Mechanisms

- Repolarization disorder.
- Depolarization Disorder,
Intrinsic Heterogeneity

Accentuate Notch & Cause Loss of APD Dome in Epicardium

Dispersion of Repolarization

Transmural

Epicardial QT interval

Phase 2 reentry

ST Segment (Vulnerable Window)

Extrasystole

VT/VF (Reentry)

Transmural Dispersion of Repolarization Phase 2 Reentry

Brugada Syndrome

I Na, I Ca, I to, I Kr, I Ks, I K-

ATP, I Cl(Ca)

Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011; 123: 1270-1279.

Summary

- Abnormal delayed depolarization
  - Identified exclusively over anterior RVOT epicardium.
  - Characterized by abnormal prolonged fractionated late potentials.
- Catheter ablation over this area of abnormal potentials.
  - Normalization of the Brugada ECG pattern
  - Preventing VT/VF episodes, both spontaneously occurring or induced via PES.
Summary

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Fractionated electrogram de Bakker J M, and Wittkampf F H Circ Arrhythm Electrophysiol. 2010;3:204-213

Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome
Koonlawee Nademanee, MD,* Harsharan Ralu, PhD; Sofia C. De Naurois, PhD; Michael Papadakis, MD; Laurence Robinson, MBBS; Stephen Rothney, BSc; Noor ana Makita, MD; Shinya Kowase, MD; Nakorn Boonmee, MD; Anirup Sripatsakhun, MD; Samrerng Ratanarapee, MD; Sanjay Sharma, MD; Alard C. Van der Wal, MD; ** Michael Christiansen, MD; Hanno L. Tan, MD; ** Arthur A. Wilde, MD; ** Akihiko Nogami, MD; Mary N. Sheppard MD, Gunpanrat Veeakul, MD; Elijah R. Behr, MD

Reduced Cx43 Expression

Control VS BrS

Epicardial Ablation

Open Heart Epicardial Ablation

Epicardial Fibrosis

** Biopsy site
Interstitial, Epicardial and Focal Replacement Fibrosis

**Epicardial Biopsy**

**ECG Changes**
Overlapping Cardiomyopathy & Arrhythmia Phenotype

- Is BrS a subclinical cardiomyopathic disease or ionchannelopathy or both?
- A generalized disease of:
  - Myocardial architecture
  - Myocyte electrical coupling
  - Predilection for severity in RVOT

Conduction hypothesis

Mechanism of conduction abnormalities?

- Zigzag conduction (increased distance)
- Reduced electrical coupling
- Reduced excitability
- Current-to-load mismatch
A 52 year old Thai male who had out of hospital cardiac arrests. ICD was implanted with sporadic ICD discharged for occasional VF episodes. 10 Years after index events, he experienced an ICD storm due to recurrent VF episodes.

**Arrhythmias in conduction hypothesis**

- Normal excitability
- Re-entry after INa reduction
CardioInsight: Workflow

WORKFLOW STEPS AND PRACTICAL CONSIDERATIONS

- Place the sensor vest on patient
- CT Scan to define heart-torso geometry
- Manual heart and vest segmentation
- Record VF data in EP lab
- Induce VF & record using CIT system
- Create and display 3D electroanatomical maps

**CIT personnel will place vest and operate system**
- Entire workflow (including CT) must be done on same day
- CT scan (attached)
  - Field of view (FOV) includes the entire patient torso
  - Requires saving DICOM images to CD or USB stick
  - Navigation patches underneath vest could decrease mapping resolution

<table>
<thead>
<tr>
<th>Step</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place sensor vest</td>
<td>15 min</td>
</tr>
<tr>
<td>CT Scan</td>
<td>15 min</td>
</tr>
<tr>
<td>Manual segmentation</td>
<td>30 min</td>
</tr>
<tr>
<td>Record VF data in EP</td>
<td>5-30 min</td>
</tr>
<tr>
<td>Induce VF &amp; record</td>
<td></td>
</tr>
<tr>
<td>Create and display</td>
<td>2 min per single beat</td>
</tr>
</tbody>
</table>

- 15 min
- 30 min
- 5-30 min
- 2 min per single beat map

INTRODUCTION: CardioInsight | Confidential
Figure-of-eight at RVOT

Propagation movie

Baseline

Post Ablation

11 K31

11 K31
Conclusions

• In vivo evidence in BrS

**Strongest data yet to support depolarization hypothesis**
Epicardial conduction delay
Correlation with, interstitial and focal fibrosis
Ablation abolishes type 1 pattern and VF

BrS Substrates are Expansive

• Abnormal low-voltage late potential fractionated signals:
  – Not exclusively over anterior RVOT epicardium but also commonly present in the RV body and inferolateral aspect of the RV epicardium

How & When
To Ablate Brugada Substrate
When to Ablate BrS Substrates:
HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndrome

Class IIb

- Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type 1 ECG.
- Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.

How to Ablate BrS Substrates

1. Detail Epicardial and Endocardial mapping.
2. Use of Sodium Channel blockade to enhance the BrS substrates.
   - Ajmaline, Procainamide, Flecainide, pilsicainide.
   - Warm saline

New Ablation End Points

Primary End Point:
- Elimination of all abnormal late-fractionated electrograms.

Secondary End Point:
- Non-inducible VT/VF.
- Normalization of the BrS ECG pattern.

How to Ablate BrS Substrates

1. Detail Epicardial and Endocardial mapping.
2. Use of Sodium Channel blockade to enhance the BrS substrates.
   - Ajmaline, Procainamide, Flecainide, pilsicainide.
   - Warm saline
3. Use of saline-irrigated tip catheter, preferably with contact sensor
Brugada J, Papone C Cir Arrhyth Electrophysiology 2015

BrS Treatment Options

- ICD.
- Quinidine.
- Ablation

Increase in Ablation Treatment For BrS

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age/ Male (%)</th>
<th>Spont-BrS ECG (%)</th>
<th>History of VT/VF episodes (%)</th>
<th>SCN5A (%)</th>
<th>ICD (%)</th>
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</thead>
<tbody>
<tr>
<td>Nademanee</td>
<td>60</td>
<td>34 (100%)</td>
<td>(75%)</td>
<td>100%</td>
<td>10%</td>
<td>100%</td>
</tr>
<tr>
<td>Papone et al</td>
<td>135</td>
<td>39 (78%)</td>
<td>(23%)</td>
<td>47%</td>
<td>24%</td>
<td>100%</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>11</td>
<td>48 (100%)</td>
<td>82%</td>
<td>100%</td>
<td>40%</td>
<td>73%</td>
</tr>
<tr>
<td>Chung et al</td>
<td>15</td>
<td>41 (100%)</td>
<td>53%</td>
<td>100%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Combined Several Case reports</td>
<td>12</td>
<td>30-40</td>
<td>100%</td>
<td>100%</td>
<td>NA</td>
<td>100%</td>
</tr>
</tbody>
</table>
A 33 years old male with a history of aborted sudden cardiac death with multiple ICD discharges: (BH 7)

Co-Localizing of VF Drivers and abnormal Fractionated EGM
Co-Localizing of VF Drivers and abnormal Fractionated EGM

Distribution of VF Substrates

A World-Wide Brugada Ablation of VF Substrate Ongoing Multicenter (BRAVO) Registry

- 106 BrS with ICD (median age =38; 1 Female)
  - 90 cardiac arrest survivors
  - 16 Syncope

- 98 Percutaneous epicardial ablations.

- 8 Open thoracotomy ablation
**Conclusion**

Patients with a pure Brugada syndrome without concomitant Early repolarization syndrome who has normal EKG after catheter ablation of the BrS substrates, especially after sodium channel blockade could possibly be treated without ICD.

**Curing Brugada Syndrome?**

Key Questions

- Do we understand the substrates and underlying electrophysiologic mechanisms?
  - Substrate change over a period of time?

- Effects of Ablation?
  - How does one know that durable and permanent lesions have been achieved?
  - No residual substrates left behind?
  - Can ablation cause another arrhythmogenic site?
Ultimate Questions

If the Brugada ECG pattern in BrS patients is completely eliminated by ablations, do they then have no more risk of VF occurrence or sudden cardiac death and do not need ICD?

BRAVE STUDY DESIGN

Symptomatic BrS with ICD

Ablation

Control

no BrS marker

BrS ECG; one more Abl

follow-up every 3 months