3D-Electroanatomic mapping-guided endomyocardial biopsy findings in patients with Brugada syndrome

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Conflict of interest and funding

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Background

PRIMARY CARDIOMYOPATHIES
(predominantly involving the heart)

Genetic

Mixed*

Acquired

An AL
Clin
Qual
Trans

HCM
ARVC/D
LVNC

PRKAG2
Danon
Glycogen storage
Conduction Defects
Mitochondrial myopathies

Ion Channel Disorders
LQTS  Brugada  SQTS  CVPT  Asian SUNDS

DCM
Restrictive (non-hypertrophied and non-dilated)

Inflammatory (myocarditis)
Stress-provoked (“tako-tsubo”)
Peripartum
Tachycardia-induced
Infants of insulin-dependent diabetic mothers

Council on Clinical Cardiology and Council on Quality of Care and Outcomes Research
Background

- It remains unclear whether:
  - Structural myocardial changes are the substrate of corresponding electrophysiological abnormalities
  - Structural myocardial changes involve the RVOT considered the origin of ECG abnormalities and ventricular arrhythmias
Background

“Endomyocardial biopsies were performed in the septal-apical region………….”
Background

- 3D-EAM guided endomyocardial biopsy has been recently introduced as a valuable technique to investigate the histologic substrate of low-voltage areas in:
  - Clinically suspected ARVC*
  - Myocarditis in RV ventricular arrhythmias **
  - Concealed cardiomyopathies in athletes***

***DelloRusso, Pieroni et al, Heart Rhythm 2011
RV 3D-EAM-guided EMB
RV 3D-EAM
In the present study we aimed:

- To identify the presence and prevalence of RV low voltage areas at 3D-EAM in BrS
- To investigate the myocardial substrate of these areas and to compare these findings with clinical and genetic features
Methods

- 13 consecutive patients (11M, 49±8 year-old) with BrS according to current criteria
- Spontaneous (n=9) or after flecainide challenge (n=4) type I ECG pattern in all patients
- Clinical presentation included sustained polymorphic ventricular tachycardia in 7 patients, syncope in 3, while 3 patients were asymptomatic
Methods

- All patients were submitted to:
  - 3D-EAM
  - 3D-EAM-guided endomyocardial biopsy*
  - Programmed electrical stimulation
  - Endomyocardial biopsy were processed for histology and immunohistochemistry

* In patients with normal 3D-EAM, biopsies were drawn from both septal-apical region and right ventricular outflow tract (RVOT).
3D-EAM

- RV 3D-EAM were obtained by the CARTO system using a 7F 4-mm tip Navistar catheter
- We generated an accurate 3D-EAM, reflecting the shape evidenced by RV angiography sampling at least 150 points in each patient
- Electroanatomic scar definition: ≥3 adjacent points with bipolar signal amplitude <0.5 mV
  - Electroanatomic scar tissue=amplitude <0.5 mV
  - Electroanatomic normal tissue=amplitude ≥1.5 mV
The anatomical distribution of the pathological areas was evaluated dividing the RV voltage map into five segments:

- RV outflow tract (RVOT)
- Free (anterolateral) wall
- Inferior and postero-basal segment
- Apex
- Interventricular septum
Pathology

**Myocarditis:** T-lymphocyte infiltration (>14/mm²) in the presence of cytotoxic (CD8+) and/or activated (CD45RO+) lymphocytes

**ARVC:** Extensive fibrofatty myocardial atrophy with >3% of fat; >40% fibrous tissue; residual myocytes <45% of the specimen at morphometric analysis*

**Cardiomyopathic changes:** Hypertrophy, diffuse vacuolization, cytoplasm degeneration of myocytes

* Basso et al Eur Heart J 2008
Results 3D-EAM

- Abnormal RV 3D-EAM in 11 pts (84%)
  - 4 RVOT + free wall
  - 2 RVOT + posterobasal and inferior wall
  - 2 isolated RVOT
  - 2 free wall
  - 1 posterobasal wall
- Normal RV 3D-EAM in 2 pts
Results EMB

- Pathologic findings in 9 patients with abnormal EAM (81%)
  - **Fibrofatty replacement** in 2 patients with RVOT low-voltage areas
  - **Myocarditis** in 5 patients with low-voltages in the free wall (in 3 cases with RVOT involvement)
  - **Cardiomyopathic changes** in 2 patients with septal RVOT and posterobasal segment low-voltage areas
- **Normal myocardial tissue** was observed in biopsies from 2 patients with normal 3D-EAM, and in 2 patients with RVOT abnormal voltage areas
<table>
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<th>N</th>
<th>Clinical Present</th>
<th>ECG TYPE</th>
<th>CARTO Abnormal Areas</th>
<th>Abnormal Area %</th>
<th>Mapped points</th>
<th>PES</th>
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Patient N 9 M, 59 ys old
Syncope at rest

Residual myocytes 50%
Patient N. 7
F, 36 ys old
Asymptomatic
Results

- No significant correlation was observed between clinical and ECG features and neither 3D-EAM nor histologic findings
- Programmed electrical stimulation was positive in 5 patients (38%) inducing VF in 3 patients and sPVT in 2 patients
- Among these 5 pts, 2 had normal histology, 2 had myocarditis and 1 cardiomyopathic changes
Current limitations of the study

- Small population
- Genetic analysis still ongoing
Patient N. 3 F, 55 yrs old Pre-syncopal sPVT

CACNA1C mutation Exon 46 T1918M
Conclusions

- We found a high prevalence of abnormal 3D-EAM among BrS patients, with RVOT being the most frequently involved segment.
- Abnormalities of 3D-EAM reflected an underlying myocardial disorder in 81% of patients, thus reinforcing the notion that BrS is not a pure electrical disorder.
Conclusions

- Our findings further support the notion that RVOT harbors the arrhythmogenic substrate in BrS
- Our findings support the so-called “depolarization disorder” or “conduction delay” hypothesis on the genesis of ECG pattern and arrhythmic substrate
Conclusions

- The identification of abnormal voltage areas and the corresponding myocardial substrate may influence both prognosis and treatment, including ablation strategies.
- Future studies on BrS should better characterize patients through a comprehensive imaging, electrophysiologic, genetic and structural evaluation.
“The Chimera of Arezzo”
Structural Abnormalities

Electrophysiological Mechanisms

Genetic Defects

“The Chimera of Arezzo”
In future studies we should adopt a different approach: we should stop looking for a single common causal mechanism but rather focus on distinctive rather than common features of BrS patients.
A different approach