The Heart in Sarcoidosis
“Electrophysiology”

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Background on Sarcoidosis

• Granulomatous disease of unknown etiology:
  – Immunological response to an unidentified antigenic trigger likely

• Prevalence: 5-64/100’000 inhabitants:
  – Highest prevalence in northern European and African American, particularly in women
  – USA: 11 in whites to 36 / 100’000 in Afro-American

• 70% occur in pts aged 25-45 yo:
  – Europe and Japan: 2nd peak in women > 50 yo
Background on Cardiac Sarcoidosis (CS)
MRI increases % of asymptomatic cardiac lesions

- Symptomatic cardiac involvement in 5% of pulmonary/systemic Sarcoidosis
- Asymptomatic cardiac involvement by imaging studies in 4-55% with extracardiac Sarcoidosis:
  - Table shows that adding LE-MRI ↑ % of asymptomatic CS

<table>
<thead>
<tr>
<th>Study Year</th>
<th>N</th>
<th>% of patients with asymptomatic CS</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>155</td>
<td>25.5</td>
<td>LGE-CMR</td>
</tr>
<tr>
<td>2011</td>
<td>152</td>
<td>19</td>
<td>LGE-CMR</td>
</tr>
<tr>
<td>2009</td>
<td>81</td>
<td>25.9</td>
<td>LGE-CMR</td>
</tr>
<tr>
<td>2008</td>
<td>62</td>
<td>38.7</td>
<td>PET/LGE-CMR</td>
</tr>
<tr>
<td>2005</td>
<td>82</td>
<td>3.7</td>
<td>Mostly CMR, but only a few with LGE-CMR</td>
</tr>
<tr>
<td>2003</td>
<td>50</td>
<td>14.0</td>
<td>Various</td>
</tr>
<tr>
<td>2002</td>
<td>31</td>
<td>54.9</td>
<td>CMR</td>
</tr>
</tbody>
</table>

Birnie D. HRS expert consensus statement on cardiac sarcoidosis. *Heart Rhythm* 2014
What Sarcoidosis does to the heart?
Transseptal LV biopsies at CHUV

• Disruption of cardiac architecture:
  – Inhomogeneous conduction \(\implies\) reentry and fibrillation
  – Conduction block
Clinical presentation of Cardiac Sarcoidosis

• Affects cardiac function:
  – Asymptomatic LV and RV dysfunction
  – Heart failure

• Affects cardiac electrophysiology:
  – 1° to 3° degree atrioventricular (AV) block and bundle branch block
  – Ventricular tachyarrhythmias: VT and VF
  – Atrial tachyarrhythmias: Atrial fibrillation/flutter/tachycardia
2° and 3° degree atrioventricular (AV) block
Screening for CS in pts with 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV block (AVB)

- Unexplained 2/3° AVB in <60 yo ⇒ Work-up
- Finland: 72 pts with new onset unexplained AVB ⇒ 23% CS, 4% giant cell myocarditis\textsuperscript{1}
- Canada: similar set-up in pts with no previous Sarcoidosis ⇒ 34% of CS \textsuperscript{2}

Birnie D. HRS expert consensus statement on cardiac sarcoidosis. Heart Rhythm 2014
Recommendations on screening for CS in pts with 2nd or 3rd degree AV block

• Screening for CS becomes a class IIa indication in pts with unexplained 2° (Mobitz II) or 3° AV block !!

• ICD may be useful in pts with CS and an indication for permanent PM implantation:
  • Both recent PM studies (Finland and Canada) reported a poorer prognosis in AVB due to CS vs idiopathic AVB ⇒ Sudden death and ventricular tachyarrhythmias
  ⇒ AV block suggests extensive septal lesions, hosting the substrate for potential reentrant VT/VF
Cardiac Sarcoidosis and risk of Ventricular Tachyarrhythmias
ICD for I and II prevention of VT in CS
Recommendations for ICD implantation: Consensus

Section 6: ICD Implantation and Follow-Up
Expert Consensus Recommendations for ICD Implantation in Patients With CS

Class I
ICD implantation is recommended in patients with CS and one or more of the following:
1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest61
2. LVEF ≤ 35%, despite optimal medical therapy61 and a period of immunosuppression (if there is active inflammation).

Class IIa
ICD implantation can be useful in patients with CS, independent of ventricular function, and one or more of the following:
1. An indication for permanent pacemaker implantation;
2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology;
3. Inducible sustained ventricular arrhythmias (>30 seconds of monomorphic VT or polymorphic VT) or clinically relevant VF.

Class IIb
ICD implantation may be considered in patients with LVEF in the range of 36%–49% and/or an RV ejection fraction <40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).

Class III
ICD implantation is not recommended in patients with no history of syncope, normal LVEF/RV ejection fraction, no LGE on CMR, a negative EP study, and no indication for permanent pacing. However, these patients should be closely followed for deterioration in ventricular function.
ICD implantation is not recommended in patients with one or more of the following:
1. Incessant ventricular arrhythmias;
2. Severe New York Heart Association class IV heart failure.

*VF with triple premature beats of <220 ms is considered a nonspecific response

Birnie D. HRS expert consensus statement on cardiac sarcoidosis. Heart Rhythm 2014
ICD for I and II prevention of VT in CS

Work flow for ICD implantation: Consensus

- An EPS may be considered for further risk stratification
- Period of optimal Tx (including immunosupp.) before remeasuring LV/RVEF

Birnie D. HRS expert consensus statement on cardiac sarcoidosis. Heart Rhythm 2014
Open questions in Cardiac Sarcoidosis

1. **CS with preserved LV and RV ejection fraction:**
   Are they at risk?

2. **What is the prognostic value of persistent cardiac inflammation despite immunosuppressive treatment?**

3. **[Could it be something else?]**
   Arrhythmogenic cardiomyopathy: anything must be done to diagnose CS in pts fulfilling ARC criteria
Prognosis of myocardial damage in sarcoidosis with preserved LVEF

- 205 pts with Sarcoidosis: 20% (41) with +LGE at MRI:
  - No signif difference with 80% (164/305) –LGE group
  - Preserved LVEF of 61±6%
- 6% (12 cases) of event during 3y-FU among the 205 pts:
  - 4% of death, 2% VT ⇒ 10/12 belonged to +LGE group
  - Event rate in +LGE: 20x> -LGE (10/41 vs 2/164)
  - Annualized event rate: 5%/y in +LGE vs 0.23% in –LGE subgroup
  - All cause mortality in +LGE = 15% (6/41) = MADIT 2/DEFINITE

Murtagh G. Circ Cardiov Imag 2016; DOI: 10.1161
MRI as predictor of adverse events in Cardiac Sarcoidosis

• Events and event-free survival in 59 CS:
  – Mean FU time: 26 months
  – 39% (23/59) pts experienced an event:
    • 22/23 VTA and/or SCD = 96% of events
    • 1/23 underwent HTx

• Univariate predictors of adverse events:
  – LGE extent (panel A)
  – Septal thinning (panel B)
  – RVEF (Panel C)

• Panel A: even with LGE <14% of LV mass, adverse event rate was 20% at 5y!

Ekstrom K. JAHA 2016; DOI: 10.1161(JAHA.115.003040)
MRI as predictor of adverse events in Cardiac Sarcoidosis

• Multivariate analysis:
  – LGE tertiles (tertile 1 = <14%, tert 2: 14-22%, tert 3: >22%): ↑ 2.3x per Tertile
  – VTA as presenting clinical manifestation: x10 !!
  – NT-proBNP

<table>
<thead>
<tr>
<th>Predictors</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGE extent, per tertiles</td>
<td>2.27 (1.08–4.77)</td>
<td>0.031</td>
</tr>
<tr>
<td>VT/VF as the main presenting clinical manifestation</td>
<td>9.63 (3.01–30.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP, per +200 pg/mL difference</td>
<td>1.09 (1.02–1.16)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Ekstrom K. JAHA 2016; DOI: 10.1161(JAHA.115.003040)
Prognosis of myocardial damage in sarcoidosis with preserved LVEF

• Predictors of adverse outcome:
  – In +LGE, 8% increase in risk of death/VT for each 1% increase in LGE burden
  – LGE = best predictor
  – Cutoff value of 5.7% of the LV mass best discriminates between +LGE pts with vs w/o adverse outcome
Do we need to turn off the hypermetabolic activity within the heart in Cardiac Sarcoidosis?
Prognostic significance of PET-CT imaging in CS
Survival free of death or VT

Predictors of death or VT at mutivariable analysis:
- Abnormal PET imaging (left), with the worst outcome for pts with both abnormal perfusion and FDG
- RV uptake in addition to LV uptake (right)

Reduction in FDG uptake correlates with improved LVEF under immunosuppressive Tx

- Comparison of LVEF in pts with no change/↑ in SUV (non-Resp.) vs Resp. (↓ SUV) during Tx:
  - ↓LVEF in non-resp. vs ↑LVEF in resp.
- No diff in LVEF improvement between pts with and w/o perfusion defect, but trends for ↓ response for pts with >3 abnormal segments

*Osborne MT. J Nucl Cardiol 2014;21:166-74*
Conclusions

• Unexplained 2°/3° AV block in patients <60 yo warrants a systematic search for Cardiac sarcoidosis/inflammation:
  – Multimodality imaging (MRI, PET and Biopsies) mandatory because of the difficulty to establish Dx

• Cardiac lesions must be systematically sought in systemic sarcoidosis:
  – Prognostic value of the presence and extent of scars/LGE at MRI

• Cases with cardiac involvement must undergo a “metabolic” investigation with 18-FDG PET scan:
  – Prognostic value of active lesions on outcome and on the risk of heart failure
Conclusions

• LGE extent at MRI outperforms LVEF as key prognostic factor:
  – High event rate (VTA/death) in CS with normal LV function reported in recent series
  – Need for quantitative measure of LGE at MRI (cut-off value of 6% of LV mass)

• Despite immunosuppressive Tx, >90% of the events are attributable to fatal or lifethreatening VTA:
  – Terminal HF became very rare thanks to efficient contemporary heart failure management

• RV dysfct/dilatation also plays a significant predictive role

• Electrophysiological study and implantable defibrillators:
  – Standard of care in cardiac sarcoidosis independently of LVEF

**EP**

- CS may show some overlap with ARVD/C criteria \(^1\)

1. 1’140 pts from the John Hopkins ARVD/C registry:
   - 15 subsequently Dx with CS. All met 2010 ARVD/C criteria.
   - 42 ARVD/C with desmosomal mutation served asCtrls

- Older age*, ↑CHF* and no family history of disease in CS vs ARVD*

* = our patient

Distinguishing features between ARVD/C and Cardiac Sarcoidosis. **Electrocardiographic criteria** *(Philips B. CircAE. 2014;7:230-6)*

- Similar % of T-wave inversion, Epsilon wave and +SAECG
- 1°, 2°, 3° AVB only in CS:
  - Sensitivity 67%, specificity 100% for CS of any AVB
- Similar % of RBBB
- NIVD only seen in CS (larger QRS interval)

* = our patient

<table>
<thead>
<tr>
<th>Table 2. Electrocardiographic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Variable</td>
</tr>
<tr>
<td>PR interval prolongation</td>
</tr>
<tr>
<td>Second degree AV block</td>
</tr>
<tr>
<td>Third degree AV block</td>
</tr>
<tr>
<td>Any AV block</td>
</tr>
<tr>
<td>Interventricular conduction delay</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>LBBB</td>
</tr>
<tr>
<td>RBBB</td>
</tr>
<tr>
<td>NIVCD</td>
</tr>
<tr>
<td>PR interval, ms</td>
</tr>
<tr>
<td>QRS interval, ms</td>
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<tr>
<td>TWI V1, V2, or V3 only</td>
</tr>
<tr>
<td>TWi&gt;V3 only</td>
</tr>
<tr>
<td>Epsilon wave</td>
</tr>
<tr>
<td>Atrial pacing</td>
</tr>
<tr>
<td>Ventricular pacing</td>
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<tr>
<td>Late potentials on SAECG</td>
</tr>
</tbody>
</table>
Distinguishing features between ARVD/C and Cardiac Sarcoidosis (CS)

**Imaging characteristics**


- Similar % of RV abnormalities and RVEF value
- Higher % of LV dysfunction in CS*
- Similar % of LE at MRI*
- But septal scar more frequent in CS*

* = our patient

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>ARVD/C (N=42)</th>
<th>Cardiac Sarcoidosis (N=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major RV structural abnormality</td>
<td>19 (45)</td>
<td>5 (33)</td>
<td>0.56</td>
</tr>
<tr>
<td>LV dysfunction (EF&lt;50%)</td>
<td>3 (7)</td>
<td>8 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVEF*</td>
<td>45 [30-45]</td>
<td>38 [28-45]</td>
<td>0.47</td>
</tr>
<tr>
<td>RVEDV, mL*</td>
<td>223 [150-278]</td>
<td>261 [177-277]</td>
<td>0.85</td>
</tr>
<tr>
<td>LVEF*</td>
<td>63 [55-65]</td>
<td>57 [35-60]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any scar*</td>
<td>18 (49)</td>
<td>7 (58)</td>
<td>0.18</td>
</tr>
<tr>
<td>RV scar*</td>
<td>10 (27)</td>
<td>3 (25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Septal scar*</td>
<td>4 (11)</td>
<td>5 (42)</td>
<td>0.004</td>
</tr>
<tr>
<td>LV free wall scar*</td>
<td>14 (38)</td>
<td>6 (50)</td>
<td>0.16</td>
</tr>
<tr>
<td>Intramyocardial fat*</td>
<td>28 (67)</td>
<td>1 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mediastinal lymphadenopathy*</td>
<td>0 (0)</td>
<td>4 (27)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Discrete data shown with percentages in parentheses. Values are median with first and third quartiles shown in brackets. ARVD/C indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; LV, left ventricle; LVEF, left ventricle ejection fraction; RV, right ventricle; RVEDV, right ventricle end-diastolic volume; and RVEF, right ventricle ejection fraction.

*Data obtained from 12 patients with cardiac sarcoidosis and 37 patients with ARVD/C who underwent cardiac MRI and adequate image quality.
Typical ECG of Cardiac Sarcoidosis showing RBBB and Epsilon wave in V1 (Philips B. CircAE. 2014;7:230-6). EP

- Representative 12-lead ECG obtained from a patient with cardiac sarcoidosis who was initially misdiagnosed with ARVD/C
- Characteristic T wave inversions associated with ARVD/C in leads V1 through V5!
- Note the PR interval prolongation, which is not present in patients with ARVD/C.
Hypermetabolic activity within the lateral wall and into the interventricular septum, but no extracardiac activity

⇒ Cardiac Sarcoidosis likely
Follow-up data. 2014

Immunosuppressive Tx. EP

- Clinical suspicion of Cardiac Sarcoidosis maintained
- Corticosteroid therapy (1 mg/kg during 6 weeks).
- Switched to Methotrexate 20 mg/week subcut.
- PET-SCAN 07.2014
Case presentation
M. P.F, 1949. FT

• 2007-2009: normal evolution, isolated palpitations due to isolated VPCs.
• 11-2009: Hospitalization at CHUV for recurrent palpitations under B-blockers due to ↑ incidence of VPCs:
  – Holter recording: non sustained VT