Cardiac sarcoidosis: a rare cause of heart block

Dr Antoine NOEL
A 37-year-old business manager

- Avid marathon runner

- Presented with a 4-week history of decreased exercise tolerance and syncope at rest

- No prior cardiovascular disease

- No medication
Physical examination

• Blood pressure 120 / 65 mmHg

• Heart rate 38 b.p.m.

• No audible murmur

• No evidence of erythema nodosum or tick bites

• No peripheral adenopathy
Unexplained Mobitz II or 3rd degree AV block in adults aged < 60 years

High resolution CT chest
Advanced cardiac Imaging (CMR or FDG-PET)

1. CT scan suggestive of pulmonary sarcoidosis
2. CMR or FDG-PET suggestive of CS

One or more of 1-2

Positive – High probability of CS

Biopsy
Extra-cardiac if feasible, otherwise Guided EMB* to confirm diagnosis

Negative – Consider further biopsy and/or interval repeat imaging (especially if cardiac deterioration in follow-up)

Neither of 1-2

Negative – Low probability
Consider alternative diagnosis

*EBMB: Endobronchial ultrasound guided mediastinal biopsy
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HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis
David H. Brinton, MD (Chair).1 William H. Sears, MD, FHRS, CCCS (Chair). Frank Bogan, MD,1 Joshua H. Cooper, MD, FHRS,1 Daniel A. Cutsforth, MD,1,2 Colton S. Quinones, MD,1,2 Marc A. Judson, MD,1,2 Joceline Kerei, MD,1,2 Gawande Mathew, MD, PhD, FHRS,1,2 Jens Casida Roberts, MD,1,2 Andre R. Fadel, MD,1,2 Tohru Ohe, MD, FHRS,1,2 Petru Razumok, MD,1,2 Igino Scognamo, MD3

*EMB - endomyocardial biopsy
Unexplained Mobitz II or 3rd degree AV block in adults aged < 60 years

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HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis

David H. Brinio, MD (Chair), 1 William H. Sauer, MD, FHRS, CCS (Chair), 2 Frank Bujak, MD, 3 Joshua M. Cooper, MD, FHRS, 4 Daniel A. Colvin, DO, 4, 5 Claire S. Overhage, MD, 6, 10 Marc A. Judson, MD, 1 1 Jordan Krow, MD, 7 Davaendry Mohita, MD, PhD, FHRS 5, 8 Jens Covaci, MD, 9, 10 Andy R. Patel, MD, 9, 11 Takahiro Oh, MD, FHRS, 5, 12 Felicia Rastikian, MD, 13, 14 Kyoko Surimoto, MD 14

*EBM: Endomyocardial biopsy
Endomyocardial biopsy

• Low sensitivity

• Due to the focal nature of the disease

• Revealing granulomas in < 25% of patients with CS
<table>
<thead>
<tr>
<th>BIOCHIMIE - Biochimie générale</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ECA - Enzyme de Conversion de l'Angiotensine</td>
<td>68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BIOCHIMIE - Thyroïde</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH Ultrasensible</td>
<td>4</td>
</tr>
</tbody>
</table>

**Anticorps anti Borrelia burgdorferi (confirmation)**

Western Blot IgM  Négatif
Sarcoidosis

- Multi-system granulomatous disease

- Non-caseating granulomas in involved organs

- Pulmonary involvement but may also involve the heart, liver, peripheral lymph node, spleen, skin, eyes, phalangeal bones, parotid gland or other organs and tissues.
Sarcoidosis

- A prevalence of about 4.7 – 64 in 100,000

- Most disease (70%) occurs in patients aged 25 – 45 years, with a second peak in women older than 50 years

- Rare in people younger than 15 or older than 70 years
Cardiac sarcoidosis

- Rare (5% of the patients with pulmonary / systemic sarcoidosis)
- But a significant cause of mortality (85%)
- Often asymptomatic and underdiagnosed
- Heart blocks, ventricular arrhythmia, congestive heart failure, valvular regurgitation and pericarditis
- Sudden cardiac death can be the first presentation
Cardiac sarcoidosis

- Cardiac involvement: poor outcome
- Sudden cardiac death and heart failure
- LV dysfunction: most important predictor of survival
Heart block in cardiac sarcoidosis

• Involvement of the **basal septum** by:
  ✓ scar tissue
  ✓ granulomas
  ✓ the nodal artery causing ischemia in the conduction system

• Mechanism of AVB:
  ✓ atrio-hisian block is observed in the inflammation stage
  ✓ infra-hisian block in the fibrotic stage
Heart block in cardiac sarcoidosis (management)

- **Pacemaker implantation** can be useful in patients with CS with an indication for pacing even if the AV block reverses transiently.

- **Immunosuppression** can be useful in patients with CS presenting with Mobitz II or third-degree heart block.

- **ICD implantation** can be useful in patients with CS and an indication for permanent pacemaker implantation.
Role of immunosuppression

- Recovery of AV nodal conduction can occur, and treatment with corticosteroids seems to help

<table>
<thead>
<tr>
<th>Study</th>
<th>Steroids No. of patients</th>
<th>AV recovery n (%)</th>
<th>No steroids No. of patients</th>
<th>AV recovery n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto et al</td>
<td>3</td>
<td>3 (100)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Kato et al</td>
<td>7</td>
<td>4 (57.1)</td>
<td>13</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chapelon-Abric</td>
<td>9</td>
<td>7 (75)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Banba et al</td>
<td>9</td>
<td>5 (56.6)</td>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Yodogawa et al</td>
<td>12</td>
<td>4 (33.3)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Kandolin et al</td>
<td>17</td>
<td>4 (23.5)</td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>57</td>
<td>27 (47.4)</td>
<td>16</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Modified with permission from Sadek et al. [59]
Role of immunosuppression

• Clinical characteristics of non-recovery:
  ✓ Complete atrioventricular block
  ✓ Impaired LVEF
  ✓ Thinning of interventricular septum
  ✓ Late initiation of steroid

block [10]. Our findings suggest that steroid therapy before device implantation is a possible therapeutic strategy for some selected patients. In clinical settings, the strategy may be allowed in patients with preserved LVEF and a stable heart rhythm. Even after recovery of AV block, close follow-up should be taken when patients are followed without pacemaker because there is potential risk of recurrence of AV block.
Role of immunosuppression

- But ... reversibility is unpredictable

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Type of AV block</th>
<th>LVEF (%)</th>
<th>IVST (mm)</th>
<th>BNP (pg/ml)</th>
<th>ACE (U/L)</th>
<th>Ga uptake (heart)</th>
<th>Time to recovery of AV block</th>
<th>Other organ involvement</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>F</td>
<td>Advanced</td>
<td>78</td>
<td>12</td>
<td>141.0</td>
<td>10.6</td>
<td>(+)</td>
<td>3 days</td>
<td>Lung, skin</td>
<td>PM</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>F</td>
<td>Advanced</td>
<td>68</td>
<td>8</td>
<td>21.7</td>
<td>30.0</td>
<td>(+)</td>
<td>7 days</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>F</td>
<td>Complete</td>
<td>80</td>
<td>9</td>
<td>78.1</td>
<td>19.9</td>
<td>(+)</td>
<td>6 days</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>F</td>
<td>Advanced</td>
<td>53</td>
<td>9</td>
<td>124.0</td>
<td>19.4</td>
<td>(-)</td>
<td>1 day</td>
<td>Eye, lung</td>
<td>ICD</td>
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<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>Advanced</td>
<td>72</td>
<td>9</td>
<td>48.9</td>
<td>9.7</td>
<td>(-)</td>
<td>3 weeks</td>
<td>Skin</td>
<td>PM</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>F</td>
<td>Advanced</td>
<td>69</td>
<td>7</td>
<td>212.8</td>
<td>32.0</td>
<td>(-)</td>
<td>6 months</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>Complete</td>
<td>69</td>
<td>7</td>
<td>54.3</td>
<td>25.6</td>
<td>(-)</td>
<td>14 months</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>F</td>
<td>Complete</td>
<td>56</td>
<td>7</td>
<td>643.0</td>
<td>20.2</td>
<td>(-)</td>
<td>–</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>F</td>
<td>Complete</td>
<td>72</td>
<td>5</td>
<td>149.8</td>
<td>13.2</td>
<td>(-)</td>
<td>–</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>F</td>
<td>Complete</td>
<td>19</td>
<td>6</td>
<td>244.4</td>
<td>14.8</td>
<td>(-)</td>
<td>–</td>
<td>Lung</td>
<td>PM</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>F</td>
<td>Advanced</td>
<td>34</td>
<td>5</td>
<td>834.8</td>
<td>10.9</td>
<td>(-)</td>
<td>–</td>
<td>Lung</td>
<td>ICD</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>F</td>
<td>Complete</td>
<td>32</td>
<td>5</td>
<td>75.6</td>
<td>16.2</td>
<td>(-)</td>
<td>–</td>
<td>Skin</td>
<td>PM</td>
</tr>
<tr>
<td>13</td>
<td>46</td>
<td>M</td>
<td>Complete</td>
<td>40</td>
<td>10</td>
<td>162.0</td>
<td>11.5</td>
<td>(-)</td>
<td>–</td>
<td>Eye, lung, skin</td>
<td>PM</td>
</tr>
<tr>
<td>14</td>
<td>57</td>
<td>M</td>
<td>Complete</td>
<td>69</td>
<td>10</td>
<td>74.1</td>
<td>31.4</td>
<td>(-)</td>
<td>–</td>
<td>Skin</td>
<td>PM</td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>F</td>
<td>Complete</td>
<td>31</td>
<td>9</td>
<td>208.2</td>
<td>21.0</td>
<td>(-)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Original article: Recovery of atrioventricular block following steroid therapy in patients with cardiac sarcoidosis
Koji Yodogawa (MD)1, Yoshikazu Seno (MD, FJCC)2, Reiko Shiomura (MD)3, Kenji Tazimazumi (MD)4, Lipci Tsuboi (MD)4, Shutsuke Ikata (MD)4, Hiroshi Hayashi (MD)5, Tsunio Horie (MD)5, Yuji Ishizaki (MD)5, Masashi Hayashi (MD)5, Yasushi Miyaschi (MD)5, Watanabe Shizuku (MD, FJCC)6

1 Division of Cardiology, Department of Internal Medicine, Nagoya Medical School, Showa, 161, Showa, Nagoya City, Japan
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4 Division of Cardiology, Department of Internal Medicine, Showa Medical School, Showa, 161, Showa, Nagoya City, Japan
5 Division of Cardiology, Department of Internal Medicine, Showa Medical School, Showa, 161, Showa, Nagoya City, Japan
6 Division of Cardiology, Department of Internal Medicine, Showa Medical School, Showa, 161, Showa, Nagoya City, Japan
Pacing vs. defibrillation?
1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest AND/OR
2. The LVEF is ≤35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)

→ Yes →
ICD recommended

→ No →
1. An indication for permanent pacemaker implantation AND/OR
2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology AND/OR
3. Inducible ventricular arrhythmias (>30 seconds of monomorphic VT, or clinically relevant polymorphic VT/ventricular fibrillation)

→ Yes →
ICD can be useful

→ No →
LVEF 36-49% and/or RV ejection fraction <40%, despite optimal medical therapy and a period of immunosuppression, if appropriate. (CMR +/- an electrophysiological study may be considered to help with risk stratification of these patients)

→ Yes →
ICD may be considered

→ No →
CMR may be considered

→ No Late Gadolinium Enhancement →
ICD Not recommended
Patient should be followed for deterioration in ventricular function

→ Late Gadolinium Enhancement →
An electrophysiological study may be considered

→ Negative →

→ Positive →
ICD can be useful
### Table 5: Studies evaluating the role of the ICD in the prevention of sudden death in patients with CS

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting/design</th>
<th>N</th>
<th>Follow-up period (y)</th>
<th>Primary Prevention</th>
<th>Annualized appropriate therapy rate (shock + ATP)</th>
<th>Adverse events</th>
<th>Associations with appropriate ICD therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kron et al\textsuperscript{74}</td>
<td>United States, Canada, India/multicenter academic retrospective</td>
<td>235</td>
<td>4.2 ± 4.0</td>
<td>62.6%</td>
<td>8.6%</td>
<td>17.4%</td>
<td>Male, syncope, lower LVEF, secondary prevention ICD, ventricular pacing on electrocardiogram</td>
<td>99 patients were included in the other two series\textsuperscript{69,70}</td>
</tr>
<tr>
<td>Betensky et al\textsuperscript{73}</td>
<td>United States/single-center academic retrospective</td>
<td>45</td>
<td>2.6 ± 2.7</td>
<td>64.4%</td>
<td>14.5%</td>
<td>15.6%</td>
<td>Lower LVEF, complete heart block</td>
<td>23 (51.5%) patients were VT/VF-free, mean LVEF was 50.5% ± 16.6% in this group</td>
</tr>
<tr>
<td>Schuller et al\textsuperscript{72}</td>
<td>United States/three-center academic retrospective</td>
<td>112</td>
<td>2.8</td>
<td>74.1%</td>
<td>13.2%</td>
<td></td>
<td>LVEF &lt;55%, right ventricular dysfunction, symptomatic heart failure</td>
<td>In the primary prevention cohort, no patient with normal right and left ventricular function received an appropriate therapy</td>
</tr>
</tbody>
</table>

ATP = Antitachycardic pacing; CS = cardiac sarcoidosis; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.
ICD complications with CS and ICD

• Adverse events occurred in 15.6% and 17.4% of the patients:
  ✓ lead dislodgement (15%)
  ✓ lead fracture (17%)
  ✓ inappropriate ICD shock (24%)

• Programming longer tachycardia detection times may help avoid unnecessary delivery of ICD therapy for self-terminating arrhythmias.
### Table 1  Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cardiac sarcoidosis cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.5 ± 11.2</td>
</tr>
<tr>
<td>Sex: Women (%)</td>
<td>40</td>
</tr>
<tr>
<td>Status (number of patients)</td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td>40</td>
</tr>
<tr>
<td>Deceased</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac transplant</td>
<td>4</td>
</tr>
<tr>
<td>Follow-up from ICD insertion (y)</td>
<td>2.6 ± 2.7 (median 2.0)</td>
</tr>
<tr>
<td>VT zone (beats/min)</td>
<td>188 ± 17</td>
</tr>
<tr>
<td>VF zone (beats/min)</td>
<td>215 ± 21</td>
</tr>
<tr>
<td>Duration of extracardiac sarcoidosis (y)</td>
<td>6.3 ± 7.6 (median 2.3)</td>
</tr>
<tr>
<td>Diagnostic testing (% of patients who had test)</td>
<td></td>
</tr>
<tr>
<td>PET only</td>
<td>44</td>
</tr>
<tr>
<td>MRI only</td>
<td>9</td>
</tr>
<tr>
<td>Both PET and MRI</td>
<td>29</td>
</tr>
<tr>
<td>Heart biopsy/explant pathology</td>
<td>18</td>
</tr>
<tr>
<td>Myocardial scar detection (% of patients who underwent test with positive results)</td>
<td></td>
</tr>
<tr>
<td>Positive PET only</td>
<td>45</td>
</tr>
<tr>
<td>Positive MRI only</td>
<td>22</td>
</tr>
<tr>
<td>Positive PET and MRI</td>
<td>13</td>
</tr>
<tr>
<td>Positive biopsy/explant</td>
<td>18</td>
</tr>
</tbody>
</table>

![Image of bar chart](image.png)

**Figure 1** Temporal distribution of appropriate ICD therapies for VT/VF. ICD = implantable cardioverter-defibrillator; pts = patients; VF = ventricular fibrillation; VT = ventricular tachycardia.

### Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators

Brian P. Betensky, MD, Cory M. Tschabrunn, CEPS, Erica S. Zado, PA-C, FHRs, Lee R. Goldberg, MD, MPH, Francis E. Marchinski, MD, FHRs, Fermin C. Garcia, MD, Joshua M. Cooper, MD
Appropriate therapy with ICD for CS:

- longer follow-up from implantation date (4.5 ± 3.1 years vs 1.5 ± 1.5 years, \( p \) .001; median 3.7 vs 0.8 years)
- lower LVEF (35.5% ± 13.5% vs 50.9% ± 15.5%; \( p \) .002)
- higher prevalence of high degree heart block (47.1% vs 17.9%; \( p \) .048)
### Suivi

Classification de la tachycardie

<table>
<thead>
<tr>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nom</td>
</tr>
<tr>
<td>Dernier suivi</td>
</tr>
<tr>
<td>Implantation</td>
</tr>
</tbody>
</table>

### État de la prothèse

<table>
<thead>
<tr>
<th>Mode</th>
<th>DDD-ADI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fréq. base/max. [bpm]</td>
<td>50 / 160</td>
</tr>
<tr>
<td>Amplitude A/V [V]</td>
<td>3.5 / 1.9</td>
</tr>
<tr>
<td>Durée impulsion A/V [ms]</td>
<td>0.4 / 0.4</td>
</tr>
<tr>
<td>Durée dernière charge</td>
<td>9.3 s (40 J)</td>
</tr>
<tr>
<td>Tension de pile [V]</td>
<td>3.12</td>
</tr>
<tr>
<td>Capacité résiduelle pile [%]</td>
<td>100</td>
</tr>
<tr>
<td>Tension de la pile</td>
<td>BOS</td>
</tr>
<tr>
<td>N° programme</td>
<td>6</td>
</tr>
<tr>
<td>Téléécardiologie</td>
<td>ON</td>
</tr>
</tbody>
</table>
Follow-up

• Unrevevant after 1 year

• Vp : 9% then 0 %

• No ATP, no shock

• Complete recovery of exercise capacity

• Cardiac MRI : LVEF 40%
Take home messages

• Unexplained Mobitz II or CAVB in adults aged < 60 years

• Chest CT scan and cardiac MRI, consider PET → biopsy

• LV dysfunction : most important predictor of survival in CS

• Pacing vs. defibrillation ?
**Expert Consensus Recommendations for ICD Implantation in Patients With CS**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 arrest;  
2. LVEF ≤ 35%, despite optimal medical therapy 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.*

*Recommendations are summarized in Figure 7*