Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death


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Department of Defense Cardiovascular Death Registry Group, Walter Reed Army Medical Center, Washington, DC

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<table>
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<tr>
<th>a. REPORT</th>
<th>b. ABSTRACT</th>
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Myocarditis

- Myocarditis as a cause of sudden death in the young population has widely variable incidence, ranging from 5 to 42%.
- Men may be more predisposed than women to develop myocarditis.
- Worse outcome in the younger population.
  - 162 subjects under the age 40 with myocarditis
  - Sudden death seen in 22% of those <30 years compared to only 11% in those between 30-40 years
### Etiologies

#### Infectious myocarditis

<table>
<thead>
<tr>
<th>Enterovirus</th>
<th>Herpes virus</th>
<th>Rickettsial</th>
<th>Bacterial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackie A and B</td>
<td>Mumps</td>
<td>Fungal</td>
<td>Legionella</td>
</tr>
<tr>
<td>ECHO</td>
<td>Rubella</td>
<td>Cryptococcus</td>
<td>Clostridium</td>
</tr>
<tr>
<td>Influenza</td>
<td>Rubenola</td>
<td>Protozoan</td>
<td>Salmonella/Shigella</td>
</tr>
<tr>
<td>Polio</td>
<td>Hepatitis B and C</td>
<td>Trypanosomiasis cruzi</td>
<td>Spirochetal</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>HIV</td>
<td>Toxplasmosis gondi</td>
<td>Borrelia burgdorferi</td>
</tr>
</tbody>
</table>

#### Noninfectious Myocarditis

<table>
<thead>
<tr>
<th>Cardiotoxic drugs</th>
<th>Hypersensitivity drug reactions</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>Antibiotics</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Tetracycline</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Systemic illness</td>
<td>Sulfisoxazole</td>
<td>Others</td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td>Other collagen disease</td>
<td></td>
<td>Indomethecin</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Classifications of Myocarditis

- Active viral infection
- Postviral or lymphocytic myocarditis
- Other infectious etiologies
- Hypersensitivity myocarditis
- Giant cell myocarditis
  - Multinucleated giant cells
  - High mortality
Clinical Presentation

- Fulminant myocarditis
  - Acute critical illness
  - Distinct viral prodrome
  - Multiple foci of active myocarditis by histology
  - Favorable prognosis
- Acute myocarditis
  - Less distinct onset
  - Hemodynamically stable
- Chronic Myocarditis
  - Manifest with heart failure secondary to dilated cardiomyopathy
Contributors to malignant cardiac arrhythmias in myocarditis

- Structural changes in the region of the injured myocardium, during both active myocarditis and healing (deleterious ventricular remodeling).
- Inflammatory process in the cardiac myocytes and interstitium can lead to fluctuations in the membrane potential.
- Activated neutrophils have been associated with generation of early after depolarization.
Fibrosis and scarring as substrate for both automaticity and reentry
Study Design

- Review of non-traumatic sudden death within the Department of Defense with an available clinical record or autopsy for adjudication as to the cause of death.
- Statistical measures
  - Categorical variables were compared using the $x^2$ test or the Fisher exact test and the Student’s $t$-test was used to compare normally distributed continuous variables.
  - Differences considered statistically significant if $p < 0.05$.
- Sponsored by the Air Force Medical Research Program (AF/SGRS).
Defining the Cohort

- 902 non-traumatic suspected cardiac deaths
  - 1998 to 2008
  - Records available for review in which adjudicated cause of death was of cardiac etiology
- Identified 30 subjects with death due to myocarditis. Used 187 subjects with structurally normal heart as control group.
## Results

<table>
<thead>
<tr>
<th></th>
<th>Myocarditis n=30</th>
<th>Idiopathic SCD n=187</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>32±10</td>
<td>32±11</td>
<td>0.940</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>26 (86.7%)</td>
<td>174 (93.1%)</td>
<td>0.265</td>
</tr>
<tr>
<td>Prodromal symptoms</td>
<td>16/23 (69.6%)</td>
<td>48/99 (48.5%)</td>
<td>0.104</td>
</tr>
<tr>
<td>Fever, headache, URI symptoms</td>
<td>13/23 (56.5%)</td>
<td>0/99 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Out of hospital death</td>
<td>5 (16.7%)</td>
<td>55 (29.4%)</td>
<td>0.219</td>
</tr>
</tbody>
</table>
Baseline Characteristics

Military specific findings for those with death due to myocarditis

Branch

- Navy 12 (40%)
- Air Force 6 (20%)
- Army 8 (27%)
- Marines 4 (13%)

Not shown is the 1 Warrant Officer
## Results

<table>
<thead>
<tr>
<th></th>
<th>Myocarditis n=30</th>
<th>Idiopathic SCD n=187</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac mass, gms</td>
<td>451±88</td>
<td>395±72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.6±0.4</td>
<td>1.5±0.3</td>
<td>0.033</td>
</tr>
<tr>
<td>LV thickness, cm</td>
<td>0.5±0.2</td>
<td>0.4±0.2</td>
<td>0.457</td>
</tr>
<tr>
<td>RV thickness, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valve circumference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV annulus, cm</td>
<td>13.7±2.0</td>
<td>12.7±1.7</td>
<td>0.158</td>
</tr>
<tr>
<td>PV annulus, cm</td>
<td>8.0±1.9</td>
<td>7.1±1.0</td>
<td>0.092</td>
</tr>
<tr>
<td>MV annulus, cm</td>
<td>11.1±1.0</td>
<td>10.7±1.1</td>
<td>0.385</td>
</tr>
<tr>
<td>AV annulus, cm</td>
<td>7.2±0.7</td>
<td>6.8±0.8</td>
<td>0.213</td>
</tr>
<tr>
<td><strong>Histologic findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>11 (36.7%)</td>
<td>34 (18.2%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Necrosis</td>
<td>13 (43.3%)</td>
<td>5 (2.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disarray</td>
<td>2 (6.7%)</td>
<td>5 (2.7%)</td>
<td>0.250</td>
</tr>
</tbody>
</table>
Ventricular specification

<table>
<thead>
<tr>
<th>Heart Region</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated Right Ventricle</td>
<td>31.3%</td>
</tr>
<tr>
<td>Isolated Left Ventricle</td>
<td>25.0%</td>
</tr>
<tr>
<td>Bi-ventricle</td>
<td>43.8%</td>
</tr>
</tbody>
</table>
Findings on gross examination to suggest myocarditis were noted in 85.7% of cases.
Conclusion
Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death


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Defining Myocarditis

Dallas Classification (1987)

- Myocarditis: Myocardial necrosis, degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrate with or without fibrosis.
- Borderline myocarditis: Inflammatory infiltrate too sparse or myocyte damage not apparent.
- No myocarditis:

WHO Marburg Criteria (1996)

- Acute (active) myocarditis: A clear-cut infiltrate (diffuse, focal or confluent) of \( >14 \) leukocytes/mm\(^2\) (preferably activated T-cells). The amount of the infiltrate should be quantitated by immunohistochemistry. Necrosis or degeneration are compulsory, fibrosis may be absent or present and should be graded.
- Chronic myocarditis: An infiltrate of \( >14 \) leukocytes/mm\(^2\) (diffuse, focal or confluent, preferably activated T-cells). Quantification should be made by immunohistochemistry. Necrosis or degeneration are usually not evident, fibrosis may be absent or present and should be graded.
- No myocarditis: No infiltrating cells or \( <14 \) leukocytes/mm\(^2\).