Myocarditis: The Role of Endomyocardial Biopsy
Disclosure Statement of Financial Interest

none whatsoever…
Myocarditis: General Considerations

- Inflammatory disease of the heart: viral infections and/or post-viral immune-mediated responses
- Important cause of dilated cardiomyopathy worldwide
- Diagnosis is presumed on clinical presentation and noninvasive diagnostic methods i.e. CMR
- *Endomyocardial biopsy* remains the gold standard for in vivo diagnosis of myocarditis

Kindermann I. et al. 
Update on myocarditis. 
J Am Coll Cardiol. 2012 Feb 28;59(9):779-92
Myocarditis: Definition of a Disease

- inflammatory disease of the heart muscle, diagnosed by:
  - Histological Criteria
  - Immunological Criteria
  - Immunohistochemical Criteria

Inflammatory Cardiomyopathy:
- Idiopathic
- Autoimmune
- Infectious

The Fate Of Acute Myocarditis: Spontaneous Improvement or Evolution to DCM

Asymptomatic

Chest pain
Arrhythmias
Heart failure
Fulminant

Recovery                DCM                Recovery               Sudden cardiac death               DCM               Death

D'Ambrosio A. et al.  
The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review.  
Heart. 2001 May;85(5):499-504
Myocarditis: a precursor of dilated cardiomyopathy (DCM)
Post-mortem data: myocarditis in 8.6% -12% of cases of SCD in young adults
Myocarditis: Causative Agents

Enterovirus Myocarditis

Nonenterovirus Myocarditis

Schultz JCC., Hilliard AA., Cooper LT. Jr, Rihal CS.
Diagnosis and treatment of viral myocarditis.
Myocarditis: Pathophysiology

Kindermann I. et al.
Update on myocarditis.
J Am Coll Cardiol. 2012 Feb 28;59(9):779-92
Time Course of Viral Myocarditis In 3 Phases

Acute Phase

Days after viral infection

Infectious virus

Viral antibodies

Cellular infiltration

Subacute Phase

Chronic Phase

Kawai C.

From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future.

Circulation. 1999 Mar 2;99(8):1091-100
Biopsy: The End Justifies the Means

- Weiberg M. (1958): first non surgical technique
- Stanford Caves –Schultz bioptome (1973)

Cooper LT. et al.
The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology.

J Am Coll Cardiol. 2007 Nov 6;50(19):1914-31

A minimum of 4 - 5 samples of 1 - 2 mm³ in size
Dallas Criteria: The Gold Standard

- **Acute myocarditis**: inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event at the same microscopic section.

- **Borderline myocarditis**: less intense inflammatory cell infiltrate and no light microscopy evidence of myocyte destruction.

Dallas Criteria Expanded

- **First Biopsy**
  - **Active Myocarditis**: infiltrate/edema/ and necrosis (attenuation or degeneration)
  - **Borderline Myocarditis**: infiltrate/ no necrosis

- **Subsequent Biopsies**
  - **Persistent Myocarditis**: criteria as in active/ borderline
  - **Resolving Myocarditis**: criteria as in active/ borderline but findings sparser
  - **Healed Myocarditis**: resolution after positive first biopsy

Maisch B. et al.
Definition of inflammatory cardiomyopathy (myocarditis): on the way to consensus. A status report.
Herz. 2000 May;25(3):200-9
Anatomopathology: Lymphocytic Myocarditis

- infiltration of myocardium by activated T lymphocytes/± signs of myocyte injury
- findings diffuse or focal (IHC)
Anatomopathology: Giant Cell Myocarditis

- extensive myocyte necrosis
- intensive infiltrate: lymphocytes, plasma cells, eosinophils
- giant multinucleated cells in the borders of necrotic areas
- CD8+ T-lymphocytes
- unknown cause
- particularly aggressive
- high mortality
Anatomopathology: Other Types of Myocarditis

- **Sarcoidosis**: non caseificating granulomas (histiocytes, giant cells, lymphocytes, plasma cells)
- **Hypersensitivity myocarditis**: chronic perivascular infiltrates with lymphocytes, macrophages and plasma cells, with a prominence of eosinophils
- **Eosinophilic myocarditis**: myocyte necrosis/ presence of intracavitary thrombi containing eosinophils

http://emedicine.medscape.com/article/1612533-overview#a7
Low Sensitivity: The Death of the Dallas Criteria?

Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis.

Chow LH, et al.
Sampling Error
CMR Guided Biopsy: A Compass to Destination?

Mahrholdt H. et al.
Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology.
Circulation. 2004 Mar 16;109(10):1250-8
New Emerging Technologies: 3Dimensional ElectroAnatomical Mapping Guided EMB

Pieroni M. et al.

High prevalence of myocarditis mimicking arrhythmogenic right ventricular cardiomyopathy differential diagnosis by electroanatomic mapping-guided endomyocardial biopsy.

Variations in Interpretation: Beauty is in the Eye of the Beholder

Interobserver variability in the pathologic interpretation of endomyocardial biopsy results.
Circulation. 1987 Feb;75(2):401-5

Shanes JG. et al.
Biopsy-proven Myocarditis: Prognostic Relevance

Angelini A. et al.
Active versus borderline myocarditis: clinicopathological correlates and prognostic implications.
Heart. 2002 Mar;87(3):210-5
<table>
<thead>
<tr>
<th>Diagnostic Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>Electrocardiographic changes (AV block; Q wave, ST changes)</td>
<td>47</td>
<td>?</td>
</tr>
<tr>
<td>Troponin (lower threshold of &gt;0.1 ng/mL)</td>
<td>34-53</td>
<td>89-94</td>
</tr>
<tr>
<td>Creatine kinase MB isoform</td>
<td>6</td>
<td>?</td>
</tr>
<tr>
<td>Antibodies to virus or myosin</td>
<td>25-32</td>
<td>40</td>
</tr>
<tr>
<td>Indium 111 antimyosin scintigraphy</td>
<td>85-91</td>
<td>34-53</td>
</tr>
<tr>
<td>Echocardiography (ventricular dysfunction)</td>
<td>69</td>
<td>?</td>
</tr>
<tr>
<td>Cardiac magnetic resonance</td>
<td>86</td>
<td>95</td>
</tr>
<tr>
<td>Myocardial biopsy (Dallas criteria of pathology)</td>
<td>35-50</td>
<td>78-89</td>
</tr>
<tr>
<td>Myocardial biopsy (viral genome by PCR)</td>
<td>38-65</td>
<td>80-100</td>
</tr>
</tbody>
</table>
Air: Just Because You Can't See It …

Doesn’t Mean It’s Not There.!!!
In 26 of 38 myocardial samples (68%), viral genome was detected by PCR whereas all control myocardial samples and blood samples were negative.
Frustaci A. et al.

Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders.

*Circulation. 2003 Feb 18;107(6):857-63*
Immunohistology: Amplifying Sensitivity

Alternative pathological classification based on cell-specific immunoperoxidase stains for surface antigen: anti-CD3, anti-CD4, anti-CD20, anti-CD68, anti-HLA

### Endomyocardial Biopsy: When?

**Maisch B. et al.**  
Management of patients with suspected (peri-)myocarditis and inflammatory dilated cardiomyopathy. Herz. 2006 Dec;31(9):881-90

<table>
<thead>
<tr>
<th>Indications</th>
<th>Marburg</th>
<th>Category</th>
<th>Mayo</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute heart failure symptoms refractory to current medical management CAD excluded</td>
<td>Yes</td>
<td>C I</td>
<td>Yes</td>
<td>Consensus</td>
</tr>
<tr>
<td>Rapidly decreasing EF without established etiology</td>
<td>Yes</td>
<td>C I</td>
<td>Yes</td>
<td>Consensus</td>
</tr>
<tr>
<td>Heart failure with acutely worsening rhythm disturbances</td>
<td>Yes</td>
<td>C I</td>
<td>Yes</td>
<td>Consensus</td>
</tr>
<tr>
<td>New heart failure with conduction disturbances, particularly nodal block</td>
<td>Yes</td>
<td>C I</td>
<td>Yes</td>
<td>Consensus</td>
</tr>
<tr>
<td>Heart failure in the setting of peripheral eosinophilia, rash, and fever</td>
<td>Yes</td>
<td>C I</td>
<td></td>
<td>Consensus</td>
</tr>
<tr>
<td>Heart failure in the setting of clinical history and/or features or secondary causes where EMB may change or modify therapy</td>
<td>Yes</td>
<td>C I</td>
<td>Yes</td>
<td>Consensus</td>
</tr>
<tr>
<td>Collagen vascular diseases (SLE, scleroderma, polyarteritis nodosa, dermatomyositis)</td>
<td>Yes</td>
<td>C I</td>
<td>Yes</td>
<td>Rarely carried out, except if differential diagnosis of viral myocarditis is suspected</td>
</tr>
<tr>
<td>Suspected giant cell myocarditis</td>
<td>Yes</td>
<td>C I</td>
<td>?</td>
<td>Consensus</td>
</tr>
<tr>
<td>Suspected fulminant myocarditis</td>
<td>Yes</td>
<td>C I</td>
<td>?</td>
<td>Indispensable in the DD to giant cell myocarditis</td>
</tr>
<tr>
<td>Suspected cardiac sarcoidosis</td>
<td>Yes</td>
<td>C I</td>
<td>?</td>
<td>Indispensable in the DD to giant cell myocarditis</td>
</tr>
<tr>
<td>Suspected tuberculous peri(myocarditis)</td>
<td>Yes</td>
<td>C I</td>
<td>?</td>
<td>Rare indication</td>
</tr>
<tr>
<td>Dilated nonfamilial cardiomyopathy of unknown origin with the suspicion of myocarditis</td>
<td>Yes</td>
<td>B Iia</td>
<td>?</td>
<td>Most frequent clinical situation</td>
</tr>
<tr>
<td>Symptomatic pericarditis with myocardial involvement (dilatation, reduced EF)</td>
<td>Yes</td>
<td>B Iia</td>
<td>?</td>
<td>To identify the causative agent of perimyocarditis</td>
</tr>
<tr>
<td>Familial cardiomyopathy but no monogenetic disorder and suspected myocarditis</td>
<td>Yes</td>
<td>C Iia</td>
<td>?</td>
<td>Suspected genetic predisposition to infection needs biopsy confirmation of inflammation for treatment</td>
</tr>
<tr>
<td>MRI positive for edema and/or inflammation (CAD or infarction excluded)</td>
<td>Yes</td>
<td>B Iia</td>
<td>?</td>
<td>To identify the causative agent of perimyocarditis</td>
</tr>
<tr>
<td>Echocardiography with pericardial effusion, LV dilatation (&gt; 60 mm) and reduced EF (&gt; 50%)</td>
<td>Yes</td>
<td>C Iia</td>
<td>?</td>
<td>To identify the causative agent of perimyocarditis</td>
</tr>
</tbody>
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The Role of Endomyocardial Biopsy in 14 Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario Number</th>
<th>Clinical Scenario</th>
<th>Class of Recommendation (I, IIa, IIb, III)</th>
<th>Level of Evidence (A, B, C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New-onset heart failure of &lt;2 weeks’ duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure of &gt;3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure associated with suspected anthracycline cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>Suspected cardiac tumors</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>Unexplained cardiomyopathy in children</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Heart failure of &gt;3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>Heart failure associated with unexplained HCM</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>12</td>
<td>Suspected ARVD/C</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>13</td>
<td>Unexplained ventricular arrhythmias</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
| 14              | Unexplained atrial fibrillation                                                    | III                                         | C                           

Cooper LT. et al.

The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation. 2007 Nov 6;116(19):2216-33
Suspected Fulminant Myocarditis

Clinical presentation: rapid and severe deterioration of hemodynamics
• Noninvasive cardiac imaging (nonobligatory but helpful):
  • Echocardiography: severe global left ventricular dysfunction with or without ventricular dilatation
  • Cardiac MRI: myocardial edema, late enhancement after application of contrast media
  • Coronary angiography: exclusion of CAD or functional disturbance not explained by CAD

Endomyocardial biopsy

Fulminant inflammation with giant cells, no virus
  Giant cell myocarditis

Fulminant inflammation without giant cells and no virus
  Cardiac sarcoidosis
  Heart failure treatment if deteriorated

Fulminant inflammation without giant cells, but with virus
  Heart failure treatment if deteriorated
  Antiviral treatment and assist device

Karatolios K., Pankuweit S., Maisch B.
Diagnosis and treatment of myocarditis: the role of endomyocardial biopsy.
Curr Treat Options Cardiovasc Med. 2007 Dec;9(6):473-81
Symptomatology: precordial discomfort, dyspnea, rhythm disturbance (VT, Vfib, VES)

- Noninvasive cardiac imaging:
  - Echocardiography: disturbed global or segmental contraction and relaxation, pericarditis (Horowitz classification B to D)
  - Cardiac MRI: myocardial edema, late enhancement after application of contrast media
  - Obligatory coronary angiography: exclusion of CAD or functional disturbance not explained by CAD

Endomyocardial biopsy

- Inflammation (biopsy) > 14 cells/mm²
  - PCR for cardiotropic agents positive = viral myocarditis
  - PCR for cardiotropic agents negative = autoreactive myocarditis
  - Agent-specific antiviral therapy

- Inflammation (biopsy) > 14 cells/mm²
  - PCR for cardiotropic agents negative = autoreactive myocarditis
  - Immunosuppressive or immunomodulatory therapy

- Inflammation (biopsy) < 14 cells/mm²
  - PCR for cardiotropic agents positive = viral cardiomyopathy
  - Agent-specific antiviral therapy

- Inflammation (biopsy) < 14 cells/mm²
  - PCR for cardiotropic agents negative = no myocarditis
  - Heart failure and antiarrhythmic therapy

Karatolios K., Pankuweit S., Maisch B.
Diagnosis and treatment of myocarditis: the role of endomyocardial biopsy.
Curr Treat Options Cardiovasc Med. 2007 Dec;9(6):473-81
Ergo…

- gold standard for the definite diagnosis
- ultimate tool in clinical investigation
- vital if the pathogenesis of human myocarditis is to be unravelled
- ICH and PCR establish a causa causatum relation with further implications in treatment and prognosis

A disease is much more than a tissue sample: a number of people (clinicians, pathologists, immunologists, and molecular cardiologists) must coordinate to interpret a multitude of information which should include clinical presentation, histopathology, immunohistochemistry, viral PCR, cardiac antibody assessment, and imaging results.