Cardiomyopathy Classifications

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Disclosures

• S. Emani:
  – Abbott (formerly St. Jude Medical) – consultant, grant funding, steering committee member
  – Medtronic – consultant
  – Boston Scientific – travel reimbursement for unpaid advisory board
  – CareDx – advisory board
  – EvaHeart – adjudication committee
Cardiomyopathy Definition

- **Historical definition**
  - First used by W Brigden in 1972 to describe myocardial disease in the absence of CAD

- **AHA Definition**
  - Heterogeneous group of diseases of the myocardium
  - Exhibit inappropriate ventricular hypertrophy or dilatation
  - From a variety of causes


Modern (but slightly inaccurate) Use

Cardiomyopathy is used to refer to any process that abnormally affects the myocardium
- Ischemic Cardiomyopathy
- Non-ischemic Cardiomyopathy
Epidemiology

• Estimated prevalence of 40 cases per 100,000
• Annual incidence of 7 cases per 100,000
• Higher prevalence & incidence in children
• Genetic causes estimated in 35% of cases


Etiology of Heart Failure

Fuster V, et al. Hurst's The Heart, 12th Ed.
# Classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Disease processes predominately within the heart</td>
</tr>
<tr>
<td>Secondary</td>
<td>Systemic disorders with cardiac involvement</td>
</tr>
</tbody>
</table>

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## Primary Cardiomyopathies

- **Genetic**
  - HCM
  - ARVC/D
  - LVNC
  - Mitochondrial myopathies
  - etc
- **Acquired**
  - Myocarditis
  - Tako-tsubo
  - Peripartum
  - Tachycardia-induced
- **Mixed**
  - Probably unidentified genetic causes

Secondary Cardiomyopathy Examples

- Infiltrative
  - Amyloidosis
- Toxicity
  - Chemotherapy agents
- Inflammatory
  - Sarcoidosis
- Autoimmune
  - Lupus, scleroderma


Hypertrophic Cardiomyopathy (HCM)

- Refers to abnormal hypertrophy of left ventricle due to genetic abnormalities
- Can be present with or without outflow obstruction
- Common cause of sudden cardiac death in young people
- Prevalence of 1 in 500
- Generally manifests during adolescence

Maron BJ and Maron MS, Lancet 2013;381: 242-55
www.medlineplus.gov
Genetic Basis for HCM

• More than 1400 mutations in 11+ genes
• Autosomal dominant
• Most mutations occur in 2 genes
  – Myosin heavy chain
  – Myosin binding protein C

Maron BJ and Maron MS, Lancet 2013;381: 242-55

Myocarditis

• “Inflammation of the myocardium”
• Can vary from non-specific systemic presentation to fulminant cardiogenic shock
• Possible etiology of 9% of idiopathic DCM

openi.nlm.nih.gov
**Myocarditis**

- Viral is the most common
  - Coxackievirus in the 80s
  - Adenovirus in the 90s
  - Parvovirus B19 in the last 5 years (USA and Germany)
  - Hepatitis C and Herpes virus-6 in Japan
- Co-infection with more than 1 virus >25%
- HIV direct infection of myocytes is rare, most likely co-infection

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**Myocarditis Pathogenesis**

- Viral Infection
- Myocardial Injury
  - Immune Response
  - Viral Clearance
  - Viral Persistence
- Resolution
- Autoimmune Myocarditis
- DCM

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Kühl U & Schultheiss HP, Dtsch Arztebl Int 2012;109:361-368
## Giant Cell Myocarditis

- Previous viral infection may trigger response
- Associated autoimmune disorders are noted in up to 20% of patients
- Rare, aggressive, resistant to treatment and usually fatal
- Sudden onset fever, chest pain, rapidly progressive heart failure
- Arrhythmias (VT poorly responsive to medical therapy)
- Female = Male, but testosterone levels may be part of the pathogenesis

Blauwet LA & Cooper LT, Heart Fail Rev 2013;18(6):733-746

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## Giant Cell Myocarditis

- Diagnosis is confirmed by biopsy
- Myocyte necrosis, mixed inflammatory infiltrate including eosinophils, multinucleated giant cells without granuloma formation, Langhans type (fusion of macrophages), histiocytes and T-lymphocytes

Blauwet LA & Cooper LT, Heart Fail Rev 2013;18(6):733-746
**Giant Cell Myocarditis**

- Survival without immunosuppressant therapy is very poor, <3 months

- Steroid alone has little benefit

- Combining Azathiaprine, OKT3, and Cyclosporine improve survival to 1 year.

- Can reoccur in transplanted heart in <25%, treated with intensification of immunosuppressive therapy.

Blauwet LA & Cooper LT, Heart Fail Rev 2013;18(6):733-746

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**Cardiomyopathy Evaluation**

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Diagnostic Approach

- Clinical diagnosis
  - No single diagnostic test
  - Careful history and physical remain foundation of assessment
  - Eval should also include assessment of risk factors & potential etiologies of HF

Modified Framingham Criteria for Diagnosis of Heart Failure

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Dyspnea on ordinary exertion</td>
</tr>
<tr>
<td>Rales</td>
<td>Nocturnal cough</td>
</tr>
<tr>
<td>S3 gallop</td>
<td>Tachycardia &gt; 120 bpm</td>
</tr>
<tr>
<td>Radiographic cardiomegaly</td>
<td>Radiologic pleural effusion</td>
</tr>
<tr>
<td></td>
<td>Weight loss &gt; 4.5 kg in 5 days in response to diuretic treatment</td>
</tr>
</tbody>
</table>

Diagnosis of HF requires that 2 major or 1 major and 2 minor criteria cannot be attributed to another medical condition.

History

- Symptoms
  - Fluid accumulation: dyspnea, abdominal bloating, weight gain, LE edema
  - Reduced cardiac output: fatigue, hypotension, nausea

NYHA Functional Classification

<table>
<thead>
<tr>
<th>Class I</th>
<th>No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>
Cardiomyopathy: Clinical Parameters

<table>
<thead>
<tr>
<th></th>
<th>ADHERE (150,000 pts)</th>
<th>OPTIMIZE-HF (48,612 pts)</th>
<th>EURO HF (11,327 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Dyspnea</td>
<td>89</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Rest Dyspnea</td>
<td>34</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Rales</td>
<td>68</td>
<td>65</td>
<td>N/A</td>
</tr>
<tr>
<td>Pulm. edema</td>
<td>66</td>
<td>65</td>
<td>23</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>2</td>
<td>&lt;8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>90-140</td>
<td>48</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>&gt;140</td>
<td>50</td>
<td>48</td>
<td>29</td>
</tr>
</tbody>
</table>

Gheorghiade M. JAMA 2008
Cleland JGF. Eur Heart J 2003

History

- Clinical presentation can help identify etiology
  - Angina: ischemic heart disease
  - Recent flu like illness: viral myocarditis
  - Long standing hypertension: hypertensive
  - Heavy alcohol use: alcoholic cardiomyopathy
  - Low voltage ECG, LVH, proteinuria: Amyloidosis
  - Certain drugs may provoke or worsen: CCB, NSAIDS, antiarrhythmics (disopyramide, flecainide)
Physical Exam

• Provides evidence of extent of volume overload and cardiac output
  – Tachypnea
  – Tachycardia
  – Crackles or wheezing (“cardiac asthma”)
  – Extra cardiac sounds (S3 and/or S4)
  – Elevated jugular venous pressure (use central lines for CVP)
  – Edema
  – Abdominal bloating / poor appetite

By James Heilman, MD - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=11787530

Physical Exam

• Findings to suggest other causes of HF
  – Murmur: valvular disease
  – Periorbital purpura or peripheral neuropathy: amyloid
  – Triad of cirrhosis, DM, and skin pigmentation (“bronze diabetes”): hemochromatosis

Initial Testing

- EKG to identify underlying causes (LVH, ischemia, afib, heart block)
- CXR may reveal pulmonary vascular congestion, but normal chest x-ray does not exclude ADHF
- Initial blood tests
  - CBC to identify anemia or infection
  - Chemistries to evaluate for renal dysfunction, hyponatremia
  - LFTs, which may be affected by hepatic congestion
  - Cardiac biomarkers if ischemia is suspected
  - Fasting blood glucose and lipids to identify underlying DM and lipid disorders
  - TSH
  - BNP

Initial Testing – BNP

- BNP: natriuretic hormone released from heart in response to ↑ filling pressures
- BNP useful if diagnosis uncertain
  - > 400 pg/mL predictive of HF as cause of dyspnea
  - < 100 pg/mL very high negative predictive value for HF as a cause of dyspnea
- NT-proBNP
  - In pts with HF, NT-proBNP levels are ~ 4 times higher than BNP
  - Optimal value for distinguishing HF is age dependent:
    - < 50 yo: > 450 pg/mL
    - 50-75 yo: > 900 pg/mL
    - > 75 yo: > 1800

<table>
<thead>
<tr>
<th>Noncardiac Causes of Elevated Natriuretic Peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>OSA</td>
</tr>
<tr>
<td>PH</td>
</tr>
<tr>
<td>Critical illness</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
</tr>
<tr>
<td>Severe burns</td>
</tr>
<tr>
<td>Toxic metabolic insults</td>
</tr>
<tr>
<td>including chemotherapy</td>
</tr>
</tbody>
</table>
### Use of BNP in Diagnosing Heart Failure

- **Patient presenting with dyspnea**
  - Physical examination, chest X-ray, ECG, BNP level
  - **BNP < 100 pg/mL**
    - CHF very unlikely (2%)
  - **BNP 100–400 pg/mL**
    - Baseline LV dysfunction, underlying cor pulmonale or acute pulmonary embolism?
      - Yes
      - Possible exacerbation of CHF (25%)
      - No
      - CHF likely (75%)
  - **BNP > 400 pg/mL**
    - CHF very likely (95%)

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### Initial Testing - Echocardiography

- Use in all patients with new onset heart failure
- Provides info about ventricular size and function
- Other important potential findings:
  - Pericardial thickening suggests constrictive pericarditis
  - Valvular disease
  - Interatrial and interventricular shunts
  - LVH and “sparkling” pattern suggestive of amyloid
  - RV size and function
  - Pulmonary pressure
  - Diastolic function
Initial Testing – Ischemic Evaluation

- Ischemic evaluation
  - Almost all patients with unexplained HF should be evaluated for CAD
  - Noninvasive stress test is reasonable first step
  - Coronary angiography in any patient with angina or other risk factors
  - Coronary CTA may be reasonable alternative

- 67,161 patients between 2010 – 2013
- 17.5% underwent ischemic evaluation during index hospitalization
- 27.4% by 90 days
Additional Testing

• If no cause apparent after initial evaluation, other testing may be warranted
• Blood tests:
  – HIV
  – Iron studies (hemochromatosis)
  – ANA and other serologies for lupus / rheum disease
  – Thiamine, carnitine, and selenium levels
  – Viral serologies and antimyosin antibody if suspect myocarditis
  – Evaluation for pheochromocytoma

Additional Testing - Genetics

• Genetic evaluation
  – Family syndromes occur in 20-35% of patients with idiopathic DCM
  – 3 generation family history should be obtained in all patients
  – Referral to center with expertise in genetic cardiomyopathies may be helpful
  – Consider genetic testing and family screening in DCM patients and at-risk family members
  – Dilated Cardiomyopathy Research Project: https://dcmproject.com/

Hershberger RE, Siegfried JD. J Am Coll Cardiol 2011
Additional Testing - Genetics

- Clinical screening in asymptomatic 1st degree relative recommended (regardless of whether genetic cause identified)
  - H&P
  - ECG
  - Echo
  - Holter monitor in HCM and ARVC
  - Exercise testing in HCM
  - Cardiac MRI in ARVC
- Screen q 3-5 years


Additional Testing – Cardiac MRI

- High spatial resolution
- Accurate assessment of ventricular size and EF
- Can help differentiate btwn ischemic and nonischemic
  - LGE: reflects fibrosis/scar
  - ICM characterized by subendocardial or transmural LGE
  - NICM has isolated mid-wall or epicardial LGE

Butler J. J Card Fail 2007
Additional Testing – Cardiac MRI

- Additional info about perfusion, viability, fibrosis
- Particularly helpful for
  - Hypertrophic cardiomyopathy
  - ARVC
  - Noncompaction
  - Sarcoidosis
  - Amyloidosis
  - Myocarditis
  - Differentiating restrictive vs constrictive disease

Additional Testing

- Endomyocardial Biopsy
  - Can be useful if seeking specific diagnosis that would influence treatment
  - Rapidly progressive cardiomyopathy (giant cell, myocarditis)
  - Primary cardiac amyloid to determine specific chemotherapy
  - Routine use not recommended given limited diagnostic yield and procedural risk

### Additional Testing - RHC

- No established role for routine or periodic RHC
- Indications:
  - Clinically indeterminate volume status
  - Patients refractory to initial therapy
  - Clinically significant hypotension or worsening renal function during initial therapy
  - Patients being evaluated for transplant or LVAD


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### Additional Testing - RHC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate of</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP Edema</td>
<td>RAP</td>
<td>48</td>
<td>78</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>94</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Pulse Press</td>
<td>Cardiac Index</td>
<td>27</td>
<td>69</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>S3 Dyspnea</td>
<td>PCWP</td>
<td>36</td>
<td>81</td>
<td>69</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Rales</td>
<td>50</td>
<td>73</td>
<td>67</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>90</td>
<td>60</td>
<td>48</td>
</tr>
</tbody>
</table>
**Additional Testing**

- **Exercise testing**
  - Risk stratification / determine prognosis
  - Serial measurements can assess efficacy of treatment
- **Cardiopulmonary exercise testing (“VO2”)**
  - Combines standard exercise testing with measures of ventilatory gas exchange
  - Helps differentiate extent of cardiac versus pulmonary or other limitations
  - More precise quantification of functional impairment
  - Used to triage for advanced therapies

**Predictive Models**

- Variety of predictive models to estimate prognosis
- Enable patients and families to have realistic expectations
- Enable selection of therapies most likely to positively impact mortality and QOL
- Encourage communication between patients, family, and providers
Predictive Models

- Seattle Heart Failure Model
  - Derived and validated in broad HF population
  - Incorporates wide range of clinical variables including medications and devices
  - Provides estimates of 1 and 5 year mortality
  - Provides information about likely mode of death
  - Online calculator:
    www.SeattleHeartFailureModel.org