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

Classifications

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

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

Myocarditis

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

- Viral is the most common
  - Coxsackie virus 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


Myocarditis Pathogenesis

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

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

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

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>Paroxysmal nocturnal dyspnea</th>
<th>Rales</th>
<th>S3 gallop</th>
<th>Radiographic cardiomegaly</th>
</tr>
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<tr>
<td>Minor criteria</td>
<td>Dyspnea on ordinary exertion</td>
<td>Nocturnal cough</td>
<td>Tachycardia &gt; 120 bpm</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>
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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

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Cardiomyopathy: Clinical Parameters

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<tr>
<th>Parameter</th>
<th>ADHERE (150,000 pts)</th>
<th>OPTIMIZE-HF (48,612 pts)</th>
<th>EURO HF (11,327 pts)</th>
</tr>
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<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>Railes</td>
<td>68</td>
<td>65</td>
<td>N/A</td>
</tr>
<tr>
<td>Pulm. edema</td>
<td>60</td>
<td>65</td>
<td>23</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>&lt;90</td>
<td>2</td>
<td>&lt;8</td>
</tr>
<tr>
<td></td>
<td>90-140</td>
<td>48</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>&gt;140</td>
<td>50</td>
<td>48</td>
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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

Physical Exam

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

- EKG to identify underlying causes (LVH, ischemia, atrial fibrillation, heart block)
- CXR may reveal pulmonary vascular congestion, but a 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

Noncardiac Causes of Elevated Natriuretic Peptides

<table>
<thead>
<tr>
<th>Advanced age</th>
<th>Anemia</th>
<th>Renal failure</th>
<th>OSA</th>
<th>PH</th>
<th>Critical illness</th>
<th>Bacterial sepsis</th>
<th>Severe burns</th>
<th>Toxic metabolic insults</th>
</tr>
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Use of BNP in Diagnosing Heart Failure

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

Initial Testing - Ischemic Evaluation

- 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 antmyosin 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/
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 between ischemic and nonischemic
  - LGE: reflects fibrosis/scar
  - ICM characterized by subendocardial or transmural LGE
  - NICM has isolated mid-wall or epicardial LGE

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

Butler J. J Card Fail 2007
**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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**Variable** | **Estimate of Sensitivity (%)** | **Specificity (%)** | **PPV (%)** | **NPV (%)**
---|---|---|---|---
JVP | 48 | 78 | 60 | 69
Edema | 10 | 94 | 55 | 60
Pulse Press | Cardiac Index | 27 | 69 | 52 | 44
S3 Dyspnea | PCWP | 36 | 81 | 69 | 54
Rales | 50 | 73 | 67 | 57
PCWP | 13 | 90 | 69 | 48

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**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

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**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