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**

Brigden W, Cardiovasc Clin 1972;4(1):187-201
Maron BJ, et al, Circulation 2006;113:1807-1816

Modern (but slightly inaccurate) Use

Cardiomyopathy is used to refer to any process that abnormally affects the myocardium

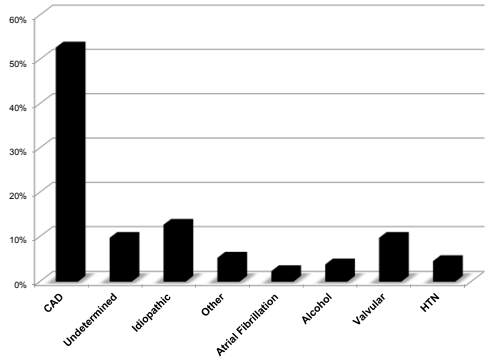
- **Ischemic Cardiomyopathy**
- **Non-ischemic Cardiomyopathy**

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**

Weintraub RG, et al, Lancet 2017 (in press)

Etiology of Heart Failure



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

Classifications

Primary	• Disease processes predominately within the heart
Secondary	• Systemic disorders with cardiac involvement

Primary Cardiomyopathies

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

Maron BJ, et al, Circulation 2006;113:1807-1816

Secondary Cardiomyopathy Examples

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

Maron BJ, et al, Circulation 2006;113:1807-1816

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

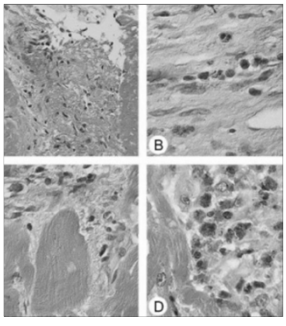
Genetic Basis for HCM

- 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



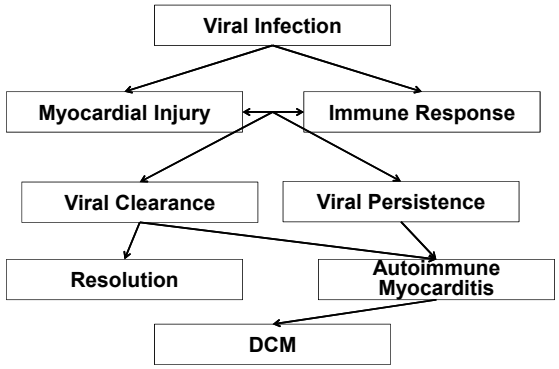
Magnani JW & William Dec G, Circulation 2006;113:876-890
openi.nim.nih.gov

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

Magnani JW & William Dec G, Circulation 2006;113:876-890

Myocarditis Pathogenesis



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

Giant Cell Myocarditis

- Previous viral infection my trigger response
- Associated autoimmiune 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	
Major Criteria	Paroxysmal nocturnal dyspnea Rales S3 gallop Radiographic cardiomegaly
Minor criteria	Dyspnea on ordinary exertion Nocturnal cough Tachycardia > 120 bpm Radiologic pleural effusion Weight loss > 4.5 kg in 5 days in response to diuretic treatment

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

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Cardiomyopathy: Clinical Parameters

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

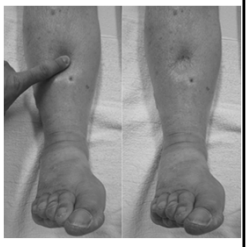
Fonarow GC. Rev Cardiovasc. Med. 2003
Gheorghiade M. JAMA 2008
Cleland JGF. Eur Heart J 2003

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

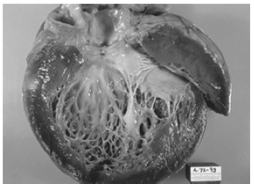
- **Provides evidence of extent of volume overload and cardiac output**
  - **Tachypnea**
  - **Tachycardia**
  - **Crackles or wheezing ("cardiac asthma")**
  - **Extra cardiac sounds (S3 and/or S4)**
  - **Elevated jugular venous pressure (use central lines for CVP)**
  - **Edema**
  - **Abdominal 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**



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Initial Testing

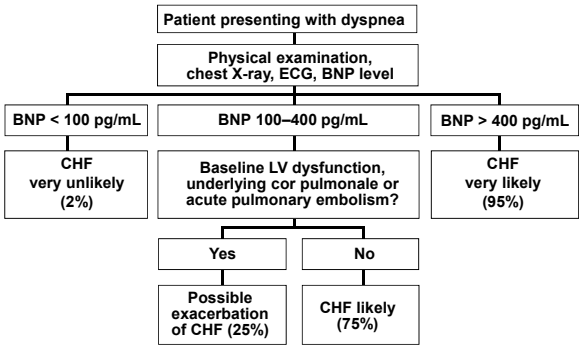
- EKG to identify underlying causes (LVH, ischemia, afib, heart block)
- CXR may reveal pulmonary vascular congestion, but <u>normal chest x-ray does not exclude ADHF</u>
- Initial blood tests
  - CBC to identify anemia or infection
  - Chemistries to evaluate for renal dysfunction, hyponatremia
  - 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
Advanced age
Anemia
Renal failure
OSA
PH
Critical illness
Bacterial sepsis
Severe burns
Toxic metabolic insults including chemotherapy

Use of BNP in Diagnosing Heart Failure



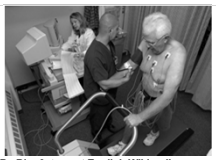
Maisel A. *Reviews in Cardiovascular Medicine*. 2002; 3(4):S13.

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



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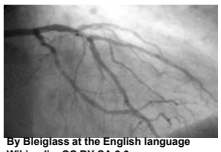

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Initial Testing - Ischemic Evaluation

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Underutilization of Coronary Artery Disease Testing Among Patients Hospitalized With New-Onset Heart Failure

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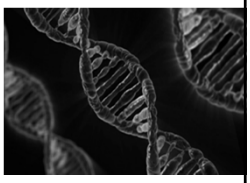
- 67,161 patients between 2010 – 2013
- 17.5% underwent ischemic evaluation during index hospitalization
- 27.4% by 90 days

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
Yancy, et al. Circulation 2013
Hershberger, etl al. J Card Fail 2009

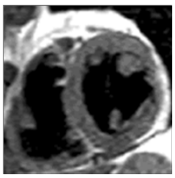
Additional Testing - Genetics

- 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

Hershberger, et al. Genetic Evaluation of Cardiomyopathy – HFSA Guideline. Journ Card Fail 2009

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



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Valle-Munoz A, et al. Eur J Echocardiogr 2009
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

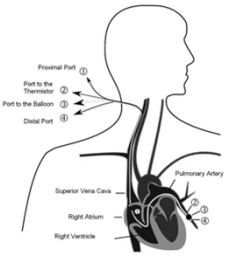
- Endomyocardial Biopsy
  - Can be useful if seeking specific diagnosis that would influence treatment
    - Rapidly progressive cardiomyopathy (giant cell, myocarditis)
    - Primary cardiac amyloid to determine specific chemotherapy
  - Routine use not recommended given limited diagnostic yield and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

Yancy, et al. Circulation 2013

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

Yancy, et al. Circulation 2013



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Additional Testing - RHC

Variable	Estimate of	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
JVP	RAP	48	78	60	69
Edema		10	94	55	60
Pulse Press	Cardiac Index	27	69	52	44
S3	PCWP	36	81	69	54
Dyspnea		50	73	67	57
Rales		13	90	60	48

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**

Levy, et al. Circulation 2016