Cardiomyopathies

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- Research focus:
  - Optimization of Heart Failure Disease Management
  - Clinical Trials of Novel Heart Failure Therapies
  - Management of Heart Failure with Preserved EF
  - Remote Monitoring
Disclosures

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Objectives

• Identify common etiologies of dilated cardiomyopathy and prognostic implications

• Discuss pathophysiology, diagnosis, risk stratification, and clinical management of patients with hypertrophic cardiomyopathy

• Discuss diagnosis and management of common infiltrative cardiomyopathies including amyloidosis and sarcoidosis
Etiologies of LV dysfunction

- Ischemic Heart Disease: 40%
- Dilated CMP: 37%
- Valvular: 11%
- HTN: 12%
- ‘Idiopathic’: 50%
- ‘Familial’: 40%
- Chemotherapy (adriamycin)
- Connective Tissue Disorder
- HIV
- Infiltrative
- Peripartum
- Toxins (ETOH, Cocaine)
- Myocarditis
- Other:
  - Tachycardia
  - Congenital HD
  - Stress-related
  - Chagas’ Disease

Baldasseroni, Am Heart J 2002; 143: 398
Ischemic ‘Cardiomyopathy’

• Significantly impaired LV function resulting from CAD
• Up to 40% of HFrEF
• Mechanisms
  – Irreversible loss of myocardium due to prior MI with ventricular remodeling
  – Partially reversible loss of contractility due to reduced function of ischemic, but still viable myocardium
Coronary Revascularization in Ischemic Cardiomyopathy – STICHES (STICH 10 year F/U)

Hypothesis: In patients with HF, LVEF ≤ 0.35 and CAD amenable to surgical revascularization to CABG added to intensive MED will decrease all-cause mortality compared to MED alone.

Surgical Revascularization and Medical therapy superior to medical therapy alone for those with CAD, LVEF<=0.35, and CAD amenable to revascularization

DCM: Prognosis according to etiology

Case #1:

- A 50-year-old man with prior history of hypertension and hyperlipidemia presenting with 3 month history of progressive exertional dyspnea.

- He takes only atenolol 25 mg once daily and simvastatin 20 mg once daily. He drinks one glass of wine with dinner each night, and denies use of tobacco or illicit drugs. His family history is notable for a paternal uncle who died suddenly in his 50s.

- PE: BP 170/80 mm Hg, P 80 bpm, JVP 12 cm H₂O, clear lungs to auscultation, and mild peripheral edema. Paradoxically split S₂, soft S₃ gallop, grade 2/6 apical holosystolic murmur.

- ECG: SR with LBBB

- Echocardiogram: dilated LV with global hypokinesis, and an EF of 25%.
Question 1

Which of the following factors is LEAST likely to be responsible for his HF?

A. Uncontrolled hypertension
B. Coronary artery disease
C. Alcohol use
D. Genetic factors
E. Myocarditis
Secondary Cardiomyopathy

- **Drugs of Abuse**
  - Alcohol (typically > 5 standard drinks/day x yrs)
  - Cocaine
  - Amphetamines
- **Anticancer Drugs**
  - Anthracyclines (doxorubicin, epirubicin, mitoxantrone)
  - HER2 antagonists (trastuzumab, pertuzumab)
  - Tyrosine Kinase Inhibitors (sunitinib)
  - Immune Checkpoint Inhibitors
- **Other Drugs**
  - Clozapine
  - Hydroxychloroquine
- **Toxins**
  - Heavy Metals (Cobalt), Solvents
Case #2

• 25 year old male presents in transfer with EF 10%, intubated, and with balloon pump

• Was completely healthy until 4 days prior when he developed a flu like syndrome. In fact, ran a marathon 2 weeks ago.

• History is notable for growing up in Guyana, moved to Connecticut 2 years ago, may have had a tick bite. Otherwise healthy.
Question 2

Which of the following is the most likely etiology of his cardiomyopathy?

A. Trypanosomiasis
B. Toxoplasmosis
C. Borrelia
D. Coxsackievirus B
Myocarditis: Clinical Presentation

- Acute Onset Heart Failure
- Viral Prodrome
- +/- Chest Pain
- + Cardiac Biomarkers
- ST segment abnormalities in absence of CAD
- Dx: Cardiac MRI, Endomyocardial Biopsy
Myocarditis: Etiology

• Infectious
  – Viral (e.g. coxsackievirus, COVID-19, parvovirus, HIV)
  – Bacterial
  – Rickettsia (B. Burgdorferi)
  – Fungal
  – Protozoal (T. Cruzi)

• Hypersensitivity (eosinophilic)

• Autoimmune (e.g. Connective Tissue Disease, Giant Cell Myocarditis, Vaccine-related)
Myocarditis: Immune Suppression not effective in general

- **Myocarditis Treatment Trial**
- **N=111**
- histologically proven myocarditis and LVEF<0.45
- 24 weeks treatment with prednisone + cyclosporine or azathioprine

Treatment generally supportive

Peripartum Cardiomyopathy

• Heart failure without other obvious etiology occurring 1 month prior to delivery or up to 5 months after

• Rare complication of pregnancy occurring in 1:2000 to 1:4000 live births in the US (incidence may be increasing)

• Inflammatory and genetic etiologies suspected, but recent data suggests a vascular hypothesis as well
Peripartum CM: Risk factors

• Age > 30
• Multiparity
• African American race
• Pregnancy with multiple fetuses
• Hypertension, preeclampsia
• Cocaine
• Prolonged tocolytic tx with beta agonists
Outcome of PPCM in the US

182 Patients

- Recovery: EF ≥ 50% (at last f/u) 49%
- Persistent LV dysfxn (at last f/u) 41%
- Cardiac Transplantation 6%
- Death 7%

Goland et al. J Cardiac Fail 2009;15:645
Risk of Subsequent Pregnancy (SSP)

PERSISTENT LV DYSFUNCTION

- Higher Risk of Relapse with SSP
- ~50% with further deterioration in LV function
- Increased morbidity and mortality with SSP
- Premature delivery and abortion more common

RECOVERED LV FUNCTION

- Better prognosis with SSP compared to persistent LV dysfunction
- ~20% have a relapse
- Higher rate of recovery, mortality is lower
- Likely to have a normal pregnancy

Hypertrophic Cardiomyopathy

- Clinical Diagnosis: Unexplained LVH
- Pathological Hallmarks: Myocyte disarray and fibrosis
- Normal Longevity in most
- Serious outcomes in some
  - Sudden Death
  - Heart Failure

Prevalence: ~1:500
~600,000 cases in US
A Disease of the Sarcomere

14+ defective genes with hundreds of different mutations
Management of HCM

- Symptom Control
- SCD Risk Stratification
- Counseling/Family Screening

Courtesy Carolyn Ho, MD
Symptoms in HCM

Obstruction
SAM / MR
~70%

Diastolic Sequelae
~100%

C.O.
MR
Ischemia
C.O.
LA p
Dyspnea
Chest Pain or Pressure
Dyspnea
Fatigue
Dizziness
Fatigue
Dizziness

Courtesy Steve Ommen, MD
LV Outflow Obstruction

- Obstruction Worse with
  - More Contractility
  - Decreased Afterload
  - Decreased Preload

All of these occur with physical exertion

Courtesy Steve Ommen, MD
HCM: Approach to Therapy

No Symptoms → No Therapy

No Obstruction

Medical Therapy
- β-blocker
- CaCh Blocker
- Diuretics for Congestion

Symptomatic Obstruction

Establish Mechanism

Correct Exacerbating Factors
- Volume depletion
- Vasodilators

Avoid:
- ARBs, ACE-I's, Nitrates,
- Dihydropyridine
- CaChBl, PDE5-inhibitors

Medical Therapy
- Cautious diuretics for Congestion
- β-blocker
- CaCh Blocker
- Disopyramide

Refractory Symptoms

Advanced HF Management
- Limited options for severe restrictive physiology
- Cardiac Transplantation

Invasive Septal Reduction Therapy
- Myectomy
- Alcohol Septal Ablation

Mavacamten?

Courtesy Carolyn Ho, MD
Management of HCM

Symptom Control

SCD Risk Stratification

Counseling/Family Screening

Courtesy Carolyn Ho, MD
SCD Risk Predictors

- Unexplained Syncope
- Family history of ≥1 SCD event
  - Consider family size, proportion of affected individuals, reliability of information
- Severe LVH (>30mm; should probably consider as continuous variable)
- Abnormal BP response to exercise (<25 mmHg rise or >15 mmHg fall) in patients <40-50 yrs
- NSVT on Holter, especially in children

Courtesy Carolyn Ho, MD
Management of HCM

- Symptom Control
- SCD Risk Stratification
- Counseling/Family Screening
  - Family Evaluation
  - Genetic Counseling and Testing
Exercise Guidelines in HCM

- **Moderate recreational activity**
  - Conversational pace
  - Avoid sprint/burst
  - Avoid heavy isometric weight lifting

Differential Diagnoses

Thick Walls

Physiologic Left Ventricular Hypertrophy
Hypertrophic Cardiomyopathy
Renal failure
Infiltrative Disease (Amyloidosis, Hemochromatosis)
Storage disease (Gaucher, PRKAG2, LAMP2)
Anderson-Fabry disease
Freidreich’s ataxia
Amyloidosis

- Group of disorders characterized by extra-cellular deposition of fibrillar protein
- Deposits composed of amyloid fibrils → progressive end-organ dysfunction
- > 20 proteins form amyloid fibrils in vivo
- 2 predominant types involve the heart:
  - Transthyretin (TTR)-associated: hereditary and wild-type
  - AL: typically associated with plasma cell dyscrasia
# Cardiac Amyloid: A Rare Condition?

## Incidence/Prevalence

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence/Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° AL Amyloid</td>
<td>~2500 Cases per year</td>
</tr>
<tr>
<td>(plasma cell dyscrasia)</td>
<td>50% have cardiac involvement</td>
</tr>
<tr>
<td>ATTRmutant</td>
<td>4% of African Americans are carriers</td>
</tr>
<tr>
<td>(Familial)</td>
<td>25,000-120,000 US patients</td>
</tr>
<tr>
<td>ATTRwt</td>
<td>~10-25% of adults &gt;80 years</td>
</tr>
<tr>
<td>(Senile)</td>
<td>~1 million</td>
</tr>
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<td></td>
<td>~13% of Hospitalized HFpEF</td>
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</table>
When to Suspect Amyloidosis

<table>
<thead>
<tr>
<th>History/ Exam Clues</th>
<th>Imaging Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HFPEF without hypertension</td>
<td>• Thick septum and granular sparkling on TTE</td>
</tr>
<tr>
<td>• Unexplained right-sided heart failure</td>
<td>• Low voltage to mass ratio on ECG</td>
</tr>
<tr>
<td>• Autonomic neuropathy</td>
<td>• Low tissue Doppler velocities, strain, or strain rate</td>
</tr>
<tr>
<td>• Bilateral carpal tunnel syndrome</td>
<td>• Apical sparing on strain rate imaging</td>
</tr>
<tr>
<td>• Macroglossia</td>
<td>• Diffuse LGE and suboptimal myocardial nulling on MRI</td>
</tr>
<tr>
<td>• Periorbital bruising</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac Amyloidosis: Diagnosis

- Serum immunofixation for light chains (not SPEP/UPEP)
- Endomyocardial biopsy

Falk RH. Circulation 2005;112:2047-60.
Noninvasive Dx of TTR Amyloidosis

Bone scintigraphy ($^{99\text{m}}\text{Tc}$-PYP)

- TTR amyloid fibrils are Ca$^{2+}$ avid
- Bone scintigraphy (e.g., Tc-PYP) differentiates TTR from AL cardiac amyloid
- Heart/contralateral lung ratio:
  - $>$ 1.5 diagnostic*, $<$ 1.0 ruled out
  - $>$ 1.6 $\rightarrow$ poor prognosis
- Must first rule out AL amyloidosis with serum/urine immunofixation, free light chains
Treatment of Cardiac Amyloidosis

• Treat Congestion
• Avoid Digoxin
• Low threshold for anticoagulation to prevent stroke (particularly if AF)

• AL Amyloidosis
  – Manage underlying plasma cell dyscrasia to reduce light chain production
  – Selected patients may be eligible for sequential heart and stem cell transplantation

• TTR Amyloidosis
  – ATTR-wt: TTR stabilizers – Tafamadis
  – ATTR-mutant: RNAi/antisense oligonucleotides: Patisiran, Inotersen; heart/liver transplant
Sarcoidosis

• Inflammatory disease of unclear etiology
  – Pathologic Hallmark: Non-caseating granulomas

• Typical onset prior to age 60
  – ↑ prevalence in Scandinavians, African-Americans

• Many Systemic Manifestations
  – Interstitial lung disease, Lymphadenopathy (hilar), Iritis, Erythema nodosum

• Cardiac involvement in up to 25%
  – High Grade AV block, Ventricular arrhythmias, Syncope +/- LV dysfunction/Heart Failure
  – Isolated Cardiac Disease Possible
  – Endomyocardial biopsy is gold standard, but sampling error limits sensitivity
Cardiac Imaging for Sarcoid

Cardiac MRI

LGE + T2 hyperenhancement
+/- LV dysfunction

\(^{18}\text{F-FDG} \ PET\)

Increased FDG uptake in myocardium and other affected tissues

diagnosis, prognostication, and monitoring response to therapy

Management of Cardiac Sarcoidosis

- **Consider Immune Suppression**
  - Prednisone 30-40 mg/day tapered gradually
  - MTX 15-20 mg/wk + leucovorin/folic acid for steroid-sparing
  - Other agents: azathioprine, leflunomide, infliximab, cyclosporine
  - Most effective in symptomatic patients with high grade AV block, ventricular arrhythmias, or HF/LV dysfunction

- **Consider ICD if...**
  - Cardiac Arrest or Sustained VT
  - EF<35% despite immune suppression
  - Indication for permanent pacing
  - Unexplained Syncope
  - Inducible VT/VF on EP testing
Thank You!