Overview

- Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances that cause the ventricular walls to become progressively rigid
  - Some infiltrative CMs cause increased wall thickness and diastolic dysfunction
  - Others cause chamber enlargement and wall thinning
- The clinical presentation, combined with morphologic and functional features are combined to establish a working diagnosis
  - ECG or echo often doesn’t fit the usual etiologies
  - Extra-cardiac manifestations are common
  - Tissue and/or serologic diagnosis is often required
## IC with increased LV mass/thickening

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age</th>
<th>Presentation</th>
<th>ECG</th>
<th>Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac amyloid</td>
<td>&gt; 30 years</td>
<td>HF, nephrotic syndrome, neuropathy</td>
<td>Low or nl QRS volts, pseudoinfarct</td>
<td>Biventricular thickening, BAE, speckling</td>
</tr>
<tr>
<td>Fabry</td>
<td>&lt; 40 years</td>
<td>Neuropathic pain, rash</td>
<td>Inc or nl QRS, short or long PR</td>
<td>Symmetric bi-V thickening, nl EF</td>
</tr>
<tr>
<td>Danon</td>
<td>&lt; 20 years</td>
<td>HF, myopathy, retardation</td>
<td>Inc or nl QRS, short PR</td>
<td>Severe LV thickening ± RV involvement</td>
</tr>
<tr>
<td>Friedrich ataxia</td>
<td>~25 years</td>
<td>Gait abnormality</td>
<td>NI QRS, VT</td>
<td>Inc LV septal and posterior wall thickness, nl EF</td>
</tr>
<tr>
<td>Cardiac oxalosis</td>
<td>&gt; 20 years</td>
<td>Urolithiasis, nephrocalcinosis</td>
<td>Inc or nl QRS, CHB</td>
<td>Symmetric bi-V thickening, patchy speckling</td>
</tr>
<tr>
<td>Muchopolysaccharidoses</td>
<td>1-24 years</td>
<td>Variable</td>
<td>Inc/Dec QRS, malignant arrhythmia</td>
<td>ASH, mitral/aortic stenosis/regurg, nl EF</td>
</tr>
</tbody>
</table>

## IC with LV dilation and thinning

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age</th>
<th>Presentation</th>
<th>ECG</th>
<th>Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>Young adult</td>
<td>HF, VT, HB</td>
<td>Atypical infarct, infrahissian block</td>
<td>Variable wall thickness, focal or global HK, LV aneurysm</td>
</tr>
<tr>
<td>Wegener</td>
<td>Young adult</td>
<td>Chronic upper and lower resp infections</td>
<td>A-fib, AV block, atypical infarct</td>
<td>Regional HK, pericardial effusion, reduced EF</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Hereditary: &gt; 30 Secondary: any age</td>
<td>LFTs, weakness, hyperpigmentation DM, arthralgias</td>
<td>SVT, AV block</td>
<td>LV dilation, global systolic dysfunction</td>
</tr>
</tbody>
</table>

- Differential dx: ischemic CM, idiopathic or other DCM

Seward JB et al, JACC 2010
Approach to suspected IC: MRI

- Provides information regarding structure and function
- Late gadolinium enhancement can be seen in extracellular protein deposition
- CMR can characterize the type of infiltrative disease based on the location and distribution of LGE
  - Also useful for assessing response to therapy

Kramer CM, J Nuc Med 2015

Hoey ETD et al, Quant Imaging in Med and Surg 2014
Endomyocardial biopsy

- Most commonly done via R IJ
  - Femoral, brachial access also possible
- At least 4-5 samples should be sent for light microscopy
- Recommended for:
  - Late AV block, arrhythmias, or refractory HF
  - Restrictive CM with inconclusive workup
  - Unexplained LV hypertrophy when a storage disease or amyloid is suspected and noninvasive workup is inconclusive
  - Generally not indicated for DCM without arrhythmias or heart block

Yancy CW et al, 2013 ACC/AHA heart failure guidelines

Sarcoidosis

- Multisystem inflammatory granulomatous disease
- 2-5% of patients will have clinical cardiac involvement
  - 27% at autopsy
  - Accounts for 13-25% of sarcoid-related deaths
- Presents as HF, SCD, heart block (CHB in 25-30% of cases)
- Affects the basal septum, AV node, His bundle, ventricular free walls, and papillary muscles
  - The location of involvement influences the clinical manifestations
- Echo may show wall thickening or thinning
  - Septal thinning
  - Segmental WMA in a non-coronary distribution

Dubrey SW et al, Postgrad Med J 2015
Cardiac Sarcoidosis: Diagnosis

Histological
- Myocardial biopsy showing non-caseating granuloma with no alternative cause identified

Clinical
- Histological dx of extracardiac sarcoid and
- Steroid-responsive cardiomyopathy or HB
- Unexplained low EF
- Unexplained VT
- Mobitz 2 or 3 AV block
- Patchy uptake on cardiac PET
- LGE on cardiac MRI
- Positive gallium uptake
- Other causes of cardiac sx excluded

Judson MA et al, Sarcoid Vasc Diff Dis 2014
Treaba DO, Mod Path 2005

Cardiac sarcoidosis: Management

- Early identification and treatment can yield resolution of heart block and improved survival
- Corticosteroids: used frequently, but little consensus regarding dose, duration, etc
  - Often maintained for 6+ months and then tapered
  - Much more effective when started before LV dilation and systolic dysfunction
- Immunosuppressive steroid-sparing regimens can be used
  - MTX, azathioprine, infliximab, etc
- Antiarrhythmics, pacemaker, ICD
- Heart transplantation for refractory cases
Cardiac amyloidosis

Amyloidosis

- Amyloid means ‘starch’ or ‘starch-like’
- A group of diseases characterized by the extracellular deposition of a proteinaceous material
  - Genetic mutations or excess production of misfolded proteins form β-pleated sheets
  - Insoluble fibrils, 7.5-10 nm in diameter
  - 24 heterogenous proteins have been discovered
- Deposition causes mechanical disruption and oxidative stress in affected organs
Amyloid: structural features

- Transferrin
- Apolipoprotein A-I
- Lysosome
- Immunoglobulin κ light chain

Key features include:
- 4.7 Å fibril width
- 10 Å fibril diameter

Merlini G and Bellotti V, NEJM 2003

Extra-cardiac manifestations of amyloidosis

- Renal
  - Proteinuria, nephrotic syndrome, CKD
- Gastrointestinal
  - Gastroparesis, hepatomegaly, constipation, malabsorption
- Tongue enlargement
- Neurologic
  - Peripheral and/or autonomic neuropathy, CTS, dementia, CNS bleed
- Hematologic
  - Bleeding
- Pulmonary
  - Pleural effusions, nodules, PH
- Skin
  - Ecchymoses, purpura
- Musculoskeletal
  - Arthropathy
Clinical presentation of cardiac amyloid

- Heart failure
- Small vessel disease
- Syncope/SCD
- Conduction system disease
  - More common in ATTR
- Pericardial disease
- Thromboembolism/stroke

Falk RH, *Circulation* 2005
- ECG: Low voltage, pseudoinfarct
- Echo: Concentric Bi-V thickening
  - Increased myocardial echogenicity
  - Bialtrial enlargement
  - Diastolic dysfunction

<table>
<thead>
<tr>
<th>Distribution of LV thickening</th>
<th>Amyloid</th>
<th>Hypertensive Heart Disease</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF</td>
<td>Global</td>
<td>Low-normal or mildly reduced</td>
<td>Often hyperdynamic</td>
</tr>
<tr>
<td>LV cavity size</td>
<td>Normal or small</td>
<td>Normal, may dilate end stage</td>
<td>Normal, may dilated end stage</td>
</tr>
<tr>
<td>RV thickness</td>
<td>Often increased</td>
<td>Normal</td>
<td>Rarely increased</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Often increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Longitudinal strain/tissue Doppler</td>
<td>Severely reduced</td>
<td>Mild/moderately reduced</td>
<td>Regionally reduced</td>
</tr>
<tr>
<td>Valves</td>
<td>May be uniformly thickened</td>
<td>No specific abnormality</td>
<td>MR if SAM present</td>
</tr>
<tr>
<td>Diastology</td>
<td>Often restrictive</td>
<td>Usually grade I/II</td>
<td>No specific pattern</td>
</tr>
<tr>
<td>CMR</td>
<td>Widespread LGE, including RV/atria</td>
<td>Mild or no LGE</td>
<td>Varies, often mild, localized to LV</td>
</tr>
<tr>
<td>ECG voltage</td>
<td>Low in limb leads</td>
<td>LVH</td>
<td>LVH</td>
</tr>
</tbody>
</table>
### Types of amyloid

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Precursor of Amyloid Fibril</th>
<th>Organ Involvement</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Immunoglobulin light chain</td>
<td>Heart, Kidney, Liver</td>
<td>Chemotherapy</td>
<td>Plasma cell dyscrasia related to (but usually not associated with) multiple myeloma.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral/sympathetic nerves, soft tissue, gastrointestinal system</td>
<td></td>
<td>Heart disease occurs in 1/3 to 1/2 of AL patients; heart failure tends to progress rapidly and has a very poor prognosis.</td>
</tr>
<tr>
<td>ATTR (familial)</td>
<td>Mutant transthyretin</td>
<td>Peripheral/sympathetic nerve, heart</td>
<td>Liver transplantation, new pharmacological strategies to stabilize the TTR</td>
<td>Autosomal dominant; amyloid derived from a mixture of mutant and wild-type TTR; if present before, cardiac amyloid may progress despite liver transplantation.</td>
</tr>
<tr>
<td>AAPO1</td>
<td>Mutant apolipoprotein</td>
<td>Kidney, heart</td>
<td>Liver transplantation</td>
<td>Kidney disease is the commonest presentation; heart involvement rare.</td>
</tr>
<tr>
<td>Senile systemic amyloid</td>
<td>Wild-type transthyretin</td>
<td>Heart</td>
<td>Supportive therapy, new pharmacological strategies to stabilize the TTR</td>
<td>Almost exclusively found in elderly men; slowly progressive symptoms.</td>
</tr>
<tr>
<td>AA</td>
<td>Serum amyloid A</td>
<td>Kidney, heart (rarely)</td>
<td>Treat underlying inflammatory process</td>
<td>Heart disease rare and, if present, rarely clinically significant.</td>
</tr>
<tr>
<td>AANP</td>
<td>Atrial natriuretic peptide</td>
<td>Localized to the atrium</td>
<td>None required</td>
<td>Very common; may increase risk of atrial fibrillation and/or be deposited in greater amounts in the fibrillating atrium.</td>
</tr>
</tbody>
</table>

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### Survival in AL amyloid: significance of cardiac involvement

- Survival is significantly worse in those with CHF compared to those without

  Dubrey SW, 1998
Evaluation of suspected amyloid cardiomyopathy


Novel imaging for cardiac amyloid

- Nuclear medicine offers the opportunity to specifically target amyloidosis in the heart and other organs
- $^{18}$F-florbetapir was recently approved for imaging $\beta$-amyloid in the brain
  - Very high sensitivity
  - Also binds amyloid in other organs

Dorbala S *Eur J Nucl Med Mol Imaging* 2014
18F-florbetapir in cardiac amyloidosis

A. AL Lung Amyloid  B. TTR-Heart Failure


99mTc-PYP

Bokhari S et al, Circ CV Imaging 2013
Treatment of HF due to amyloid cardiomyopathy

- No strong evidence-based therapies
- Diuretics as needed
- No data to support neurohormonal blocking agents
- Patients often don't tolerate beta-blockers or ACE-I
- Avoid CCB and digoxin
  - May be used in A-fib with RVR
- Pacemakers often required for heart block
- Role of ICD is unclear in amyloid cardiomyopathy

Treatment of TTR cardiomyopathy

- Hereditary amyloidosis: Liver transplant
  - Disease may progress due to ongoing deposition of wild-type amyloid
- Senile (wild-type) amyloid:
  - No current disease-specific treatment
New therapies for TTR-CM

- TTR mRNA
- Block Synthesis: Small Interfering RNA (siRNA), Antisense Oligonucleotides (ASO)
- Stabilize Tetramer: Diffuseal, Tafamidis
- Folded dimers
- Folded monomer
- Misfolded amyloidogenic monomer
- Mature Fibrils
- Remove Fibris: Doxycycline + TUDCA, EGCG (Green Tea), Anti-SAP Antibodies

Hanna M, Current Heart Fail Rep 2014

Novel therapies: tafamidis

Functional forms of TTR
- Tetramer kinetically stabilized by tafamidis
- Free tetramer
- Folded dimers
- Folded monomer
- Amorphous Oligomers
- Spherical Oligomers
- Misfolded amyloidogenic monomer

TTR structures associated with pathology
**Tafamidis for TTR amyloid**

- A trial of tafamidis for familial amyloid polyneuropathy was negative overall, but there was suggestion of improvement in QOL and disease activity measures
- The ATTRACT trial will evaluate the effect of tafamidis in patients with documented TTR amyloid cardiomyopathy
- Enrollment closed
- Estimated completion date: August 2018

**RNA interference for TTR amyloid cardiomyopathy**

- Small interfering RNAs bind to and silence selected mRNA
  - Prevents disease-causing proteins from being made
- “Stopping the flood by turning off the faucet” rather than “mopping up the floor”
- Revusiran is an siRNA that blocks production of both mutant and wild-type TTR
- ENDEAVOUR is a phase 3 RCT, now randomizing subjects with mutant TTR cardiomyopathy to Revusiran vs placebo
**Treatment of AL amyloid cardiomyopathy**

- Chemotherapy to abolish or reduce the production of amyloidogenic monoclonal light chains
- Resolution of light chain production is associated with a reduction in serum NT-proBNP and survival
- Melphalan followed by ASCT is often used
  - Treatment associated mortality is highest among those with cardiac involvement

**Heart transplantation in AL amyloid cardiomyopathy**

- Historically: rarely done, many centers will not consider
- More recently, centers are doing OHT followed by ASCT
  - Reasonable outcomes reported in very small, generally single-center reports
  - Some centers use extended donor hearts
- Patient selection is key
- No guidelines for selection or management currently exist
**AL amyloidosis: novel therapies**

- NEOD001 is a an antibody that specifically targets AL amyloid
  - Binds to deposited insoluble amyloid and induces macrophages to phagocytose amyloid fibrils
  - Neutralizes and disaggregates circulating soluble amyloid
- In phase 1/2 studies of cardiac amyloid, NEOD001 was associated with a > 30% decrease in serum NT-proBNP in 57% of subjects
- The global phase 3 VITAL study is now enrolling patients with newly diagnosed cardiac amyloid
  - NEOD001 vs placebo as an adjunct to chemotherapy
- Immunotherapy may present a new platform for the treatment of AL amyloid

**Conclusions**

- Infiltrative cardiomyopathies are caused by extracellular deposition of abnormal substances in the ventricular walls
- May present with LV thickening or dilation/thinning
- A combination of clinical presentation, ECG, and echo will offer clues to an underlying infiltrative cardiomyopathy
- cMRI, nuclear imaging, and endomyocardial biopsy help confirm the diagnosis
- Novel therapies targeting amyloid production or deposition may offer disease-specific treatment of cardiac amyloid
- Consider referring patients with confirmed or suspected cardiac amyloid for clinical trials
- Heart transplantation is an increasingly viable option