Infiltrative cardiomyopathies, storage and endomyocardial diseases

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My declaration of interest:
I have nothing to declare
Infiltrative/storage Cardiomyopathies

Definition

- Characterized by the deposition of abnormal substances in intercellular space (Infiltrative) or in the cells (Storage)
- Progressively rigid ventricular walls
- Impaired ventricular filling
Infiltrative/storage Cardiomyopathies

- Relatively rare, but tend to be misdiagnosed, because of variable physiologic and morphologic characteristics
- Usually portend an adverse prognosis
- Early diagnosis can result in potentially curative treatment
### Classification of types of restrictive cardiomyopathy according to cause

#### Myocardial

1. **Noninfiltrative**
   - Idiopathic
   - Scleroderma

2. **Infiltrative**
   - Amyloid
   - Sarcoid
   - Gaucher disease
   - Hurler disease

3. **Storage Disease**
   - Hemochromatosis
   - Fabry disease
   - Glycogen storage

#### Endomyocardial

- Endomyocardial fibrosis
- Hyperesinophilic synd
- Carcinoid
- Metastatic malignancies
- Radiation, anthracycline

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*Cooper et al. JACC 2007; 50: 1914-31*
Restrictive Cardiomyopathy

Characterized by:
- impaired ventricular filling due to an abnormally stiff (rigid) ventricle
- intraventricular pressure rises precipitously with small increases in volume
- normal systolic function (early stage)

Cause: infiltration of myocardium by abnormal substance fibrosis or scarring of endocardium

Opie LH. Heart Physiology, Lippincott Williams & Wilkins 2004, 4th Ed.
Pathophysiology of Restriction

- Rigid Myocardium
- Diastolic ventricular pressure
- Venous congestion
- Venricular filling
- CO
- Jugular vein distension
- Hepatomegaly & ascites
- Peripheral edema
- Weakness
- Fatigue

Opie LH. Heart Physiology, Lippincott Williams & Wilkins 2004, 4th Ed.
When to suspect infiltrative/storage diseases?

- Peripheral neuropathy, neuropathic pain
- Skin rashes, hyperpigmentation
- Skeletal myopathy
- Arthralgia
- Mental retardation
- Chronic respiratory infection
- Nephrotic sy.
- Diabetes mellitus
When to suspect infiltrative/storage diseases?

- Symptoms of right (often) and left heart failure
- Elevated jugular venous pulse
- Peripheral edema, congestive hepatomegaly and ascites in advanced disease
- Normal or mildly reduced LV ejection fraction
How to make diagnosis?

- History and clinical presentation
- ECG and Holter monitoring
- Echocardiography/MRI
- Myocardial biopsy
## History and clinical presentation CVS

### Presentation
- dispnoea
- peripheral oedema
- syncope
- palpitation
- chest pain
- embolic events
- sudden death
- age at presentation

### Physical examination
- tachypnoea
- JVP ±Kussmaul`s sign
- gallop rhythm
- regurgitant murmors
- hepatomegaly
- ascites
- peripheral oedema
How to make diagnosis?

- History and clinical presentation
- ECG and Holter monitoring
- Echocardiography / MRI
- Myocardial biopsy
Without ECG or endomyocardial biopsy findings these two conditions can closely mimic each other.

Seward et al. JACC 2010;55:1769-79
Amiloidosis  Hypertrophic cardiomyopathy

Courtesy of Prof B. Vujisic-Tesic, Cardiology Clinic, Serbia

www.escardio.org/EAE
Decreased voltage ECG is seen when accumulation is within interstitium.

Hassan W. Tex Heart Inst J 2005:32:178-84
How to make diagnosis?

- History and clinical presentation
- ECG and Holter monitoring
- Echocardiography / MRI
- Myocardial biopsy
Differential diagnosis – ECG  HCM

- Increased voltage, repolarisation changes
- Thickened ventricular and atrial walls, abnormal-sparkling myocardial texture, atrial dilatation and pericardial effusion
- Unexplained ventricular hypertrophy
- Mutation in sarcomeric proteins
- » myocite disarrey, with or without fibrosis,
- SAM

Hassan W. Tex Heart Inst J 2005:32:178-84

www.escardio.org/EAE
Fabry Disease vs. HCM

Binary appearance of LV endocardium

Glycosphingolipids compartmentalization involving endocardium with enlarged and engulfed smooth muscle cells, subendocardial empty space and involvement of subendocardial myocardial layer, middle layer appears partially spared

Sn 94%, Sp 100%, PPV 100%, NPV 94%

ECG: LVH

HCM

Pieroni et al. JACC 2006;47:1663-71


www.escardio.org/EAE
Infiltrative/storage Cardiomyopathies (echocardiographic) hallmarks

- Progressive diastolic dysfunction, which precedes overt systolic dysfunction
- Depressed Doppler myocardial relaxation velocity (mitral annular E tissue velocity)
- Atrial remodeling (increased LA volume index)
Normal diastolic pattern (E/A>1)  
Dec T=185ms, IRT=85ms

Abnormal relaxation pattern (E/A<1)  
Dec T= 277ms, IRT=120ms

Restrictive pattern (E/A>>>1)

Late stage of cardiac amyloidosis with severe restrictive pattern. Short DT (high LA pressure)

Austin B. et al. Am J Cardiol 2009;103:1429-33
Diastolic dysfunction with abnormal relaxation and abnormal Doppler Tissue imaging: low early diastolic motion E`=3.56 cm/s

Echocardiographic presentation

Increased LV mass and thick ventricular walls
- Amiloidosis
- Fabry
- Danon

Dilated LV and Infarct pattern
- Sarcoidosis
- Hemochromatosis
- Wegener disease

Diff Dg Hypertrophic CMP
- Hypertensive heart disease
- Functional resemblance to constrictive pericarditis

Diff Dg Ischemic CMP
- Idiopathic dilated CMP

www.escardio.org/EAE
How to make diagnosis?

- History and clinical presentation
- ECG and Holter monitoring
- Echocardiography/ MRI
- Myocardial biopsy
Tissue: Echo + biopsy

- Increased echogenicity: Sn 87%, Sp 81%

- Increased atrial thickness Sp 100%, conduction defects, atrial thrombus formation, thromboembolism

- Biopsy of noncardiac tissue (tongue, subcutaneous fat pads, kidney, bone marrow, gastric mucosa)

Hassan. W. Tex Heart Inst J 2005;32:178-84
Tissue: Echo/biopsy

**Fabry**
- Vacuolisation of myocytes
- Lamellar structure “zebra bodies”
- Mild fibrosis

Fukuzawa K et al. Journal of Cardiology 2009; 54: 139-143

**Sarcoidosis**
- Noncaseating, multinucleated giant cell granuloma surrounded by band of dense collagen fibers
- Endomyocardial biopsy is a gold standard for the detection of cardiac sarcoidosis: Sensitivity 20%

Main genes of interest in CMP for mutation screening in routine practice

<table>
<thead>
<tr>
<th>Cardiomyopathies</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>MYBPC3 (myosin-binding protein C), MYH7 (bêta myosin heavy chain), TNNT2 (troponin T), TNNI3 (troponin I), MYL2 (regulatory myosin light chain) ± TPM1 (alpha tropomyosin), MYL3 (essential myosin light chain), ACTC (actin)</td>
</tr>
<tr>
<td>With particular phenotype</td>
<td>PRKAG2 (AMP-activated protein kinase), LAMP2 (lysosome-associated membrane protein 2), GLA (alpha galactosidase), mitochondrial DNA</td>
</tr>
<tr>
<td>DCM</td>
<td>MYH7 (bêta myosin heavy chain), TNNT2 (troponin T) ± other sarcomeric genes</td>
</tr>
<tr>
<td>With particular phenotype</td>
<td>LVNA (lamin A/C), TAZ (tafazzin), DES (desmin), DMD (dystrophin), mitochondrial DNA</td>
</tr>
<tr>
<td>RCM</td>
<td>TNNI3 (troponin I) ± other sarcomeric genes</td>
</tr>
<tr>
<td>With particular phenotype</td>
<td>DES (desmin), TTR (transthyretin), HFE (haemochromatosis)</td>
</tr>
<tr>
<td>ARVC</td>
<td>PKP2 (plakophilin 2), DSP (desmoplakin), DSG2 (desmoglein 2), DSC2 (desmocollin 2)</td>
</tr>
<tr>
<td>LVNC</td>
<td>MYH7 (bêta myosin heavy chain) ± other sarcomeric genes</td>
</tr>
</tbody>
</table>

Amyloid heart disease

Restriction caused by replacement of normal myocardial contractile elements by infiltrative interstitial deposits

- ED-IVS >12mm
- Symmetrical increase in RV and LV wall thickness
- Increased thickness of AV valves
- Dilated RA and LA
- Increased thickness of IAS
- Sparkling appearance of the walls
- Pericardial effusion

Falk HR. Prog Cardiovasc Dis 2010;52:374-361
Amyloid heart disease

Courtesy of Prof B. Vujisic-Tesic, Cardiology Clinic, Serbia

www.escardio.org/EAE
Amyloid heart disease

Courtesy of Prof B. Vujisic-Tesic, Cardiology Clinic, Serbia
- Subendocardial deposition of amyloid reduce contraction, which contributes to longitudinal LV shortening
- Strain/SR imaging can detect longitudinal systolic dysfunction before the onset of heart failure
- Powerful prognostic factor of survival

Prolongation of IVCT because of conduction disturbance
Prolongation of IVRT due to myocardial infiltration

Early identification of the cardiac involvement in various systemic amyloidosis may influence the choice of therapies

Koyama and Falk. JACC Cardiovascular imaging 2010;3:383-42
Cardiac Sarcoidosis

- Granulomatous disease affects basal septum, AV node, focal regions of Ventricular free walls, papillary muscles

- 2-D echo: wall thickening (>13mm) due to granulomatous expansion and Wall thinning (<7mm) due to fibrosis, scar retraction = anurysms

- Segmental wall motion abnormality do not conform to any particular coronary Distribution

- Diff Dg. DCM dyskinetic segments are interspersed with normokinetic segments

- Doppler: Assessment of pulmonary pressures and RV function to detect Early signs of pulmonary hypertension

PA end-diastolic pressure (capillary wedge pressure)
Diastolic PA pressure = 4V_{end PR}^2 + estimated RAP
Sites of cardiac involvement

Cardiac Sarcoidosis

Courtesy of Dr M. Petrovic, Cardiology Clinic, Serbia
Fabry disease

- X-linked recessive glycosphingolipid storage disorder caused by deficiency of the lysosomal enzyme α-galactosidase A
- Accumulation in heart, skin, kidneys, vascular endothelium (heart attack or stroke)
- LV hypertrophy (concentric, asymmetrical, apical)
- Valvular disease: deposit and fibrosis
- Systolic and dyastolic dysfunction
- Supraventricular and ventricular arrhythmias
- Diff. Dg HCM: Binary appearance of LV endocardial border

Fukuzawa K et al. Journal of Cardiology 2009; 54: 139-143
TDI in Fabry disease

TDI can be useful in female carriers
Often without systemic manifestation
And usually considered spared by the Disease
Patients with mutation in a-Gal A gene had reduction in TDI velocities Sa, Ea,Aa, lowest in LVH

Lateral and septal Sa<10cm/s, Sn and Sp 100% in identifying mutation positive pt without LVH.
Lateral Ea and septal Ea <10 cm/s, have Sn 100% and Sp 90%

Cardiac hemochromatosis (iron heart)

- Weak heart with systolic dysfunction
- Hereditary (genetic) or secondary
- Diff dg. DCM
- Biopsy: sarcoplasmatic iron
- Other signs: Cirrhosis, bronze skin pigmentation,
diabetes, heart failure
- Definitive test: liver biopsy
- Th: phlebotomy, chelation th
Endomyocardial Fibrosis

Characterized by obliteration of LV cavity by shaggy coat of thrombus superimposed on a fibrotic thickened endocardium

Hypereosinophilic syndrome (Loffler’s endocarditis) caused by cation proetin release from eosinophils in circulation

- Thickening of basal inferior wall
- Apical obliteration
- 80-90% die within 1-2 years

Endocardial deposition of thrombus
Mitral regurgitation


www.escardio.org/EAE
Reduction of the LV volume
Calcified wall
MR

MRI: Late enhancement signal of fibrosis
Non enhanced areas of calcification

Restrictive cardiomyopathies vs. constrictive pericarditis

Importance lies in its differentiation from operable constrictive pericarditis

History can provide important clues

- Constrictive pericarditis
  - history of TB, trauma, pericarditis, collagen vascular disorders

- Restrictive cardiomyopathy
  - amyloidosis, hemochromatosis

- Mixed
  - mediastinal radiation, cardiac surgery

Rademakers F. In ESC Textbook of Cardiovascular Imaging, Springer-Verlag 2010: 502-519

www.escardio.org/EAE
Common features:
- non dilated ventricles
- ventricular filling limited to early diastole
- dilated inferior caval vein, reduced inspiratory collapse

Important differences
- Larger atria in RCMP
- Myocardial reflectance increased
- Pericardial thickening in CP
- Respiratory changes in mitral E velocity, reciprocal in tricuspid in CP
- Early diastolic septal bounce in CP
- Hepatic vein reversal flow with inspiration in RCMP and expiration in CP

Rademakers F. In ESC Textbook of Cardiovascular Imaging, Springer-Verlag 2010: 502-519
Restrictive cardiomyopathies vs. constrictive pericarditis

- In restrictive CMP reduction in LV relaxation is a result of primary myocardial disease with a resultant decrease in E` velocity

- In constrictive pericarditis, there is no myocardial dysfunction, and TDI E` velocity is not reduced

- E` value of ≥8cm/s, Sn 89%, Sp 100%

- S` value of ≥6 cm/s has addictive value
E  0,74 m/s
A  0,36 m/s
E`  19 cm/s
S   7 cm/s
E/E` = 3

Treat underlying cause
amyloid (melphalan/prednisone/colchicine)
Endomyocardial Fibrosis (steroids, cytotoxic drugs, surgical th, MVR
Hemochromatosis (chelation, phlebotomy)
Sarcoidosis (steroids)
Fabry (enzyme replacement)

Diuretics for congestive symptoms, but ↓ LV/RV filling ⇔ ↓ CO
Antiarrhythmics for afib, amiodorone; AV synchrony is critical as stroke volume is small, and fixed
Pacemaker for conduction system disease
Anticoagulation for thrombus (esp in atrial appendages)
Stem cells transplantation
Treatment response

Amyloid
Stem cell transplantation
5 years

Hemochromatosis
Repeated phlebotomy
6 years

Seward et al. JACC 2010; 55: 1769-79
Prognosis depends on Etiology

Felker GM. NEJM 2000;342:1077
Summary

Early diagnosis of this types of CMP is critical, since once clinically significant heart disease is present prognosis is poor.

Suspect! when EF is normal in the presence of congestive heart failure, thick walls, dilated atria

Doppler suggest an elevated LVEDP and/or restrictive LV filling pattern

TDI and strain, strain rate show impairment of longitudinal contraction

Review history, echo and ECG findings to make correct diagnosis
Hemodynamic

- The characteristic hemodynamic feature in both conditions is a deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole.

- → **dip and plateau** → due to noncompliant myocardium
### Classification of the common amyloidoses

<table>
<thead>
<tr>
<th>Type</th>
<th>Primary Constituent</th>
<th>Site of Production</th>
<th>Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Light chains</td>
<td>Bone marrow</td>
<td>Kidney, Heart, Nervous system, Liver, Soft tissue</td>
</tr>
<tr>
<td>Familial</td>
<td>Mutant transthyretin</td>
<td>Liver</td>
<td>Nervous system, Heart</td>
</tr>
<tr>
<td>Senile (SSA)</td>
<td>Wild type transthyretin</td>
<td>Liver</td>
<td>Heart</td>
</tr>
<tr>
<td>Secondary (AA)</td>
<td>SAA</td>
<td>Acute phase reactant</td>
<td>Liver, Kidney</td>
</tr>
<tr>
<td>Isolated atrial amyloid (IAA)</td>
<td>Atrial natriuretic peptide</td>
<td>Atria</td>
<td>Atria</td>
</tr>
</tbody>
</table>

Falk R et al. Prog Cardiovasc Dis 2010; 52: 347-361
Early stage of cardiac amyloidosis with impaired Relaxation pattern, reversal E/A ratio

Late stage of cardiac amyloidosis with severe restrictive pattern. Short DT (high LA pressure)

- Severe atrial infiltration may lead to atrial standstill in the presence of sinus rhythm
- In such cases prevalence of atrial thrombus formation is high and thromboembolism may be the initial manifestation of the disease
- Atrial arrhythmias tend to occur late in the disease

Hassan W. Tex Heart Inst J 2005; 32:178-84
Falk H, Dubrey S. Prog Cardiovasc Dis 2010; 52:347
The pathogenesis of amyloid fibrils is related to amino acid substitutions in prefibrillar proteins and to protein instability. Protein instability can be provoked by different chemical, electrical, and mechanical stimuli and precipitate out of the serum into the extracellular matrix as amyloid. Five different types of amyloidosis have been described according to the underlying disease:

1) Immunoglobulin Amyloidosis. Immunoglobulin (AL) amyloidosis, found in all cases where the building block of the amyloid fibril is an immunoglobulin light chain protein, includes primary amyloidosis, multiple myeloma, and other plasma cell dyscrasias such as B-cell lymphoma and Waldenström macroglobulinemia. Primary amyloidosis is a plasma cell disorder in which approximately 5% to 10% of bone marrow plasma cells have clonal dominance of a light chain isotype. The number of plasma cells and the degree of clonality and marrow infiltration of those

The light chain isotype in primary amyloidosis does not generally affect survival. Immunoglobulin amyloidosis constitutes about 85% of all newly diagnosed cases of amyloidosis. Common presenting features include nephrotic syndrome, sensorimotor peripheral neuropathy, hepatomegaly, splenomegaly, and, less often, macroglossia.
Histopathology showing significant myofiber disarray and interstitial fibrosis

Metachromatic appearance of amyloid

Hassan W. Tex Heart Inst J 2005;32:178-84
Falk HR. Prog Cardiovasc Dis 2010;52:374-361