Echocardiography for Patients with Restrictive Cardiomyopathy
Including Amyloid and Hypereosinophilic Syndrome
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Mayo Clinic Rochester

Heart Failure with Normal LV Chamber Normal Wall Thickness
- Restrictive cardiomyopathy
  - Idiopathic
  - Eosinophilic endomyocardial disease
  - Endomyocardial fibroelastosis
- Constriction

Restrictive Cardiomyopathy
- Idiopathic
- Eosinophilic endomyocardial disease
- Endomyocardial fibroelastosis
- Infiltrative (amyloid)

Clinical Profile and Outcome of Idiopathic Restrictive Cardiomyopathy
- Retrospective review
- 1979-1996
- 94 patients
- 57% women; 43% men
- 72% were ≥60 years old

Ammash NM: Circ 101; 2000

Restrictive Cardiomyopathy

Idiopathic Restrictive Cardiomyopathy
- Nondilated ventricles
- Normal to mildly increased ventricular wall thickness
- Marked atrial dilatation

Nondilated ventricles
Normal to mildly increased ventricular wall thickness
Marked atrial dilatation
**Diastolic Dysfunction**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Filling pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal or Low</td>
</tr>
<tr>
<td>Ia</td>
<td>Mildly ↑</td>
</tr>
<tr>
<td>II</td>
<td>Moderately ↑</td>
</tr>
<tr>
<td>III, IV</td>
<td>Severely ↑</td>
</tr>
</tbody>
</table>

**Assessment of Diastolic Function**

- Mitral E/A ratio
- Mitral deceleration time
- Mitral annular E’ velocity
- Mitral E/E’ ratio
- Mitral flow propagation velocity
- LA volume index

**94 Patients with Idiopathic Restrictive Cardiomyopathy**

<table>
<thead>
<tr>
<th>Mitral Doppler</th>
<th>Pt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>available for 51 pt</td>
<td></td>
</tr>
<tr>
<td>Decel time 70-250 msec (avg 144 msec)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MV decel time (msec)</th>
<th>Pt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;200</td>
<td>10</td>
</tr>
<tr>
<td>150-200</td>
<td>25</td>
</tr>
<tr>
<td>&lt;150</td>
<td>65</td>
</tr>
</tbody>
</table>

**24 Year Old Woman**

*Restrictive Cardiomyopathy*

- **Mitral PW Doppler**
  - $E = 0.8 \text{ m/sec}$
  - $A = 0.2 \text{ m/sec}$
  - $E/A = 4$
  - $DT = 78 \text{ msec}$

- **Mitral TDI (medial)**
  - $EE'' = 0.07 \text{ m/sec}$
  - $E/EE'' = 13$
  - $E' = 0.07 \text{ m/sec}$
  - $E/E' = 13$
24 Year Old Woman

Hepatic Vein PW Doppler

Large Atrial Reversal

Idiopathic Restrictive Cardiomyopathy

Survival vs Expected

Ammash NM: Circ, 2000

Echocardiography for Eosinophilic Endomyocardial Disease

Eosinophilic Endomyocardial Disease

- Temperate climates
- Idiopathic hypereosinophilia
- Tissue infiltration

Hypereosinophilic Syndrome

Diagnostic Criteria

- Peripheral blood eosinophilia >1500 cells/µL for > 6 months
- No other cause for eosinophilia
- Evidence of organ involvement by eosinophilic infiltration

Chusid MJ; Medicine (Baltimore); 1975

Eosinophilic Endomyocardial Disease

Mayo Experience

Ommen SR: AJC; 2000
Hypereosinophilic Syndrome

**Organ Involvement**
- Hematologic: 100%
- Cardiovascular: 58%
- Cutaneous: 56%
- Neurologic: 49%
- Pulmonary: 43%
- Splenic: 30%
- Hepatic: 23%
- Ocular: 23%
- Gastrointestinal: 23%

Hypereosinophilia

- Allergic
- Parasitic
- Drug hypersensitivity
- Vasculitis (Churg-Strauss)
- Eosinophilic leukemia
- Idiopathic

Eosinophilic Endomyocardial Disease

Eosinophilic infiltration
- Necrosis
- Thrombus formation
- Fibrosis

Eosinophilic Infiltrate

- May present as myocarditis
- Focal damage usually subendocardial

67-year-old woman

- Transferred to Mayo 9 hours after onset of severe chest pain
- ST elevation on ECG
- Cardiomegaly and pleural effusions on CXR

Physical Exam

- Afebrile
- BP = 114/60 mmHg
- Pulse = 104
- No murmurs
Active eosinophilic myocarditis

- Patchy endocardial involvement
- Intersitial fibrosis
- Dispersed protein strands deposited on myocardial fibers

Cardiac Involvement with Hypereosinophilic Syndrome

Major cause of morbidity and mortality

↑ Frequency of cardiac involvement in FIP1L1-PDGFRα-positive HES pts

1 Weller PF; Blood; 1994
2 Scheik J; Immunol/Allergy Clin N Am; 2007
Eosinophilic Endomyocardial Disease
Involves Inflow Portion of Ventricles
• Apical obliteration
• Entrapment of mitral/tricuspid leaflets

Eosinophilic Endomyocardial Disease
Involves Inflow Portion of Ventricles
• Apical obliteration
• Entrapment of mitral/tricuspid leaflets

67 Year Old Man
• Weight loss
• Weakness of extremities
• Peripheral edema

53 Year Old Woman with EED
Cardiac MRI
 SSFP and MDE
 Delayed Enhancement

Glockner JF; International J of Cardiol; 2008

Differential Diagnosis
• Apical hypertrophic cardiomyopathy
• Apical infarct with thrombus
• Noncompaction of the myocardium

MRI FINDINGS
• Inner layer of thrombus
• Thickened endocardium
• Endomyocardial delayed enhancement
• Increased endocardial T2 signal
• Thick walls
• Normal LV systolic function
Eosinophilic Endomyocardial Disease

**Treatment**

- Steroids
- Hydroxyurea
- Alpha-1-interferon
- Cytoxan, cyclosporin, IVIG, Methotrexate for refractory cases

**Treatment**

- Imatinib for Tyrosine kinase mutation (+)
- Bone marrow transplant for Imatinib resistant cases

**Imatinib**

- Fusion tyrosine kinase FIP1L1-PDGFR = target for Imatinib
- Small case series reported
- Eosinophilia, myelofibrosis resolve
- No effect on restrictive cardiomyopathy
- May be associated with an acute drug-induced cardiomyopathy
- Pre-treat with steroids if troponin is ↑ or other evidence disease is active

**Conventional drug treatment for heart failure**

- Surgical decortication for apical obliteration and/or chordal entrapment
- Valve replacement (bioprosthesis)
- Cardiac transplant

**Prognosis**

- 50% mortality in first 3 months, if untreated
- 70% 6 year survival with treatment

Klion AD; J Allergy Clin Immunol; 2006
Echocardiography for Cardiac Amyloid

71 year old Man

- CVA 13 months ago
- CHF identified one year ago
- Fatigue
- Peripheral edema
- Frequent thoracenteses for right pleural effusion
- Echo: “concentric LVH; LVEF 45%”

Given These Echo Findings
Which of the Following is Most Useful for Differential Diagnosis?

A) Complete blood count
B) Serum and Urine special protein studies
C) Serum angiotensin converting enzyme
D) Iron and iron binding capacity
E) 24 hr urine 5-HIAA

Cardiac amyloid
Infiltrative Disorder

Amyloid protein deposits between myocytes

Amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Protein</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (primary)</td>
<td>Monoclonal Light Chain</td>
<td>Plasma Cell Dyscrasia</td>
</tr>
<tr>
<td>AA (secondary)</td>
<td>Serum Amyloid A</td>
<td>Chronic Inflammatory Disorders</td>
</tr>
<tr>
<td>ATTR (familial)</td>
<td>Transthyretin</td>
<td>DNA mutation-single amino acid substitution</td>
</tr>
<tr>
<td>Senile – Atrial Deposition</td>
<td>Atrial Natriuretic Peptide</td>
<td>Production degradation mismatch</td>
</tr>
<tr>
<td>Senile – Ventricular Deposition</td>
<td>Wild type TTR</td>
<td>Production degradation mismatch</td>
</tr>
</tbody>
</table>
2D Echocardiography for Cardiac Amyloid
• Increased LV and RV wall thickness
• Granular myocardial appearance
• Atrial enlargement
• Thickened valves
• Pericardial effusion
• Pleural effusion

2D Echocardiography for Cardiac Amyloid
• LV ejection fraction
• Usually normal to moderately reduced

Spectral Doppler for Cardiac Amyloid
• Stroke volume
• Stroke volume index
• Cardiac output
• Cardiac index
• Diastolic function

Diastolic Dysfunction
Grade Filling pressure
I Normal or Low
Ia Mildly ↑
II Moderately ↑
III, IV Severely ↑
Assessment of Diastolic Function

- Mitral E/A ratio
- Mitral deceleration time
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Tissue Doppler Imaging (TDI)

Cardiac Amyloid

For patients with systemic amyloid these findings are as diagnostic as myocardial biopsy

Historically the Mayo Clinic Echo Lab has Studied Patients with Cardiac Amyloid to Verify the Utility of New Measurements

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Prognostic Measure</th>
<th>Decade</th>
</tr>
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<tbody>
<tr>
<td>Cueto-Garcia</td>
<td>LV wall thickness</td>
<td>1970s</td>
</tr>
<tr>
<td>Klein</td>
<td>Diastolic dysfunction</td>
<td>1980s</td>
</tr>
<tr>
<td>Chuwa Tei</td>
<td>Tei Index (LIMP)</td>
<td>1990s</td>
</tr>
</tbody>
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Doppler Index Combining Systolic and Diastolic Myocardial Performance: Clinical Value in Cardiac Amyloidosis

Chuwa Tei
Journal of the American College of Cardiology 28(3); September 1996

Evaluation of Right Ventricular Dysfunction in Patients with Cardiac Amyloidosis Using Tei Index

Won-Ho-Kim (senior author Chuwa Tei)
Journal of the American Society of Echocardiography 17(1); January, 2004
Intracardiac Thrombosis in Amyloid

- Primary Amyloid: 51% had intracardiac thrombus (17% afib hx)
- Other Amyloidoses: 16.7% had intracardiac thrombus (39.6% afib hx)

Feng D; Circ; 2007

Risk Factors for Intracardiac Thrombus in Amyloid

- Low ejection fraction
- Diastolic dysfunction (Grade 3-4)
- Increased RV wall thickness
- Atrial fibrillation
- Increased HR
- Primary myeloidosis

Interestingly, Not LA Volume

Feng D; Circ; 2007

AL Amyloid and NSTEMI

- Amyloid deposits; intramural coronary microvasculature
- Autopsy series: 63/96 patients (66%)
- Ischemic microscopic changes 86%
- Clinical ischemic syndromes 25%
- May be the first manifestation of AL
- Microvascular dysfunction has been demonstrated

Nebben-Wittich MA; Am J Med; 2005
Suwaidi JA; Am Int Med; 1999

Myocardial Contrast Echo in Amyloid

Abdelmonem S; Myocardial Contrast Echocardiography in Biopsy-Proven Primary Cardiac Amyloidosis; Echocardiography; 2008

Cardiac MR in Amyloid

- Diffuse infiltration of interstitium with amyloid
- Difficult to “null” the myocardium: global enhancement

Described by Maceira et al JACC 2005

Strain Imaging for Patients with Cardiac Amyloid

Doppler Myocardial Imaging Modalities

- Tissue velocity imaging (TVI)
- Strain rate imaging (SI)
- Strain imaging (SI)

Strain and Strain Rate Imaging

- Longitudinal (apical views)
- Radial (parasternal short axis views)
- Circumferential (parasternal short axis views)
- Transmural (difference between subendocardial and subepicardial strain or strain rate)
- Twist (basal and apical short axis views)

Directions of Cardiac Strain

- Longitudinal
- Radial
- Circumferential

Myocardial Strain

Used to describe elastic properties of cardiac muscle

\[
\text{Strain} (\varepsilon) = \frac{L_1 - L_0}{L_0}
\]

Strain Rate

Mirsky and Parmley: Circ Res, 1973
As Opposed to Tissue Velocity Imaging, Strain and Strain Rate Imaging can Discriminate between Actively Contracting Muscle and Muscle that is Moving because of Tethering.

Normal LVEF Does Not Always Mean That Systolic Function Is Normal!

42 Patients with Systemic (AL) Amyloid
- Normal LV wall thickness
- Normal e’ velocity of the medial mitral annulus
- Compared to 36 age- and gender-matched controls

Bellavia D; Am J Cardiol 4/08
42 Patients with Amyloid and No Evidence of Cardiac Involvement by Standard 2D and Doppler Echo

Demonstrating Systolic LV Dysfunction for Patients with Systemic Amyloid and Normal LV Wall Thickness and Mitral e' Velocity vs Controls

- Strain imaging and strain rate imaging demonstrated significant LV longitudinal systolic dysfunction in the patients.
- The global average for all 16 segments was best for making this distinction (followed closely by the average for the 6 basal segments).

Not evident from longitudinal tissue velocity imaging.
Radial and circumferential strain and strain rate imaging did not demonstrate this difference.

ROC Curve Analysis
Systolic DMI Measurements
Amyloid-Normal-Echo Patients vs Controls

Average LV Longitudinal Peak Systolic Strain
16 LV Segments

- Normal = greater than (more negative than) -18%
- Borderline = -16% to -18%
- Abnormal = less than (less negative than) -16%

Doppler Myocardial Imaging Compared to Standard 2D and Doppler Echo for Assessment of Diastolic Function in Patients with Systemic Amyloid

- Average longitudinal diastolic e' from myocardial velocity imaging
- Average longitudinal diastolic e' from myocardial strain rate imaging
**ROC Curve Analysis**
Average TVI-E and SR-E from 16 LV Segments
Non-Advanced Amyloid vs Controls

- **Sensitivity**
- **1-specificity**
- **AUC TVI-E 0.60**
- **SR-E 0.60**

0.0 0.2 0.4 0.6 0.8 1.0

- **Decreased longitudinal systolic strain is a very sensitive method for detecting ventricular dysfunction for these patients**

**For Cardiac Amyloid**
Longitudinal Systolic Function May Fail Before Diastolic Function

- **Speckle Tracking for Myocardial Strain**
  - ROI in image at t0
  - Search area in image at t1
  - Best match in image at t1

**Cardiac Amyloid**
**Differential Diagnosis**
- Hypertensive heart disease
- Athlete's heart (isometric athletic)
- Hypertrophic cardiomyopathy
- Fabry's
- Cardiac oxalosis
- Glycogen storage diseases
- Chloroquine toxicity

**2D Strain**
We Have Converted to 2D Strain as the Primary Modality for Assessing Longitudinal Function
We continue to use Doppler Myocardial Imaging as a back-up technique

**We Have Converted to**
2D Strain
as the Primary Modality for Assessing Longitudinal Function

Amundsen: JACC 47(4) 2/21/2006
Deformation Analysis
(Strain, Strain Rate)

Left Atrial Dysfunction
Independent of global LV systolic and diastolic function and LA size

Cardiac Amyloid
Treatment
- High dose Melphalan plus prednisone
- Peripheral blood stem cell transplantation (PBSCT)

50 year old Woman
Class IV Heart Failure

Given These Echo Findings
Which of the Following is Most Useful for Differential Diagnosis?
A) Complete blood count
B) Serum and Urine special protein studies
C) Serum angiotensin converting enzyme
D) Iron and iron binding capacity
E) 24 hr urine 5-HIAA

Sun et al. Differentiation of Hypertrophic Cardiomyopathy and Cardiac Amyloidosis from Other Causes of Ventricular Wall Thinning by Two-Dimensional Strain Imaging Echocardiography. AJC 2009

Modesto K et al. Left atrial myopathy in cardiac amyloidosis: implications of novel echocardiographic techniques. Eur heart J 2005
Cardiac Hemochromatosis

Storage disease

Iron accumulates within myocytes