Heart in Systemic Disease: Sarcoid, Hemochromatosis, Hypereosinophilia

Muhamed Sarić MD, PhD, MPA
Director of Noninvasive Cardiology | Echo Lab
Associate Professor of Medicine

NYU Langone Medical Center
Disclosures

Speakers Bureau (Philips, Medtronic)
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**CARDIOMYOPATHY**

καρδιο-μυο-πάθεια = ‘disease of the myocardium’

*Any disease of the myocardium that cannot be explained by (1) coronary artery narrowing or (2) abnormal loading of the ventricles.*


And there is a very large number of such diseases of the myocardium...
Term was first used in 1956 in a lecture by Brigden, which was then published in Lancet in 1957.

Wallace Brigden (1916 – 2008)
English cardiologist

The common cause of isolated myocardial disease is coronary disease; but there are many other causes, notably obscure and relatively rare. When patients develop apparently causeless heart-failure, diagnosis of myocarditis is sometimes made, but usually the condition is attributed to a previous hypertensive or painless coronary disease. Often such patients die unexpectedly and pathological investigation may not reveal the cause of death.

The present study is concerned with these myocardial diseases which are either isolated, or nearly so, or else are involved in other systems to a greater or smaller degree and significant only as an aid to diagnosis. The term cardiomyopathy is used here to indicate isolated non-coronary myocardial disease.

Wallace Brigden: Hypertrophic cardiomyopathy
Br Heart J 1987;58:299–302

Cardiomyopathy

Thirty years later, Brigden was surprised how ubiquitous had become the term he had coined.

Jubilee Editorial

Hypertrophic cardiomyopathy

W Brigden

From the London and National Heart Hospitals, London

When I first used the expression “cardiomyopathy” in 1956 I did not realise that I had coined a term that would become widely applied. Experience, however, has confirmed its value in describing isolated non-coronary “myocardial disease” that may be seen in patients with dyspnoea and, occasionally, in those with left ventricular hypertension. The term “cardiomyopathy” is now used to describe a variety of conditions that affect the myocardium and result in symptoms and signs of heart failure.

Thus the strands of medical knowledge were con-
CARDIOMYOPATHY

Myocardial disease that is not ischemic, hypertensive or related to valvular disease.

Yet...

There is a widespread use of terms 'ischemic cardiomyopathy' or even 'hypertensive cardiomyopathy'.

The term 'ischemic cardiomyopathy' was first coined in 1970. 

CARDIOMYOPATHY CLASSIFICATIONS

<table>
<thead>
<tr>
<th>2006</th>
<th>American Heart Association Classification</th>
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<tbody>
<tr>
<td></td>
<td>Circulation 2006;113:1807-1816</td>
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<table>
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<tr>
<th>2008</th>
<th>European Society of Cardiology Classification</th>
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<tr>
<td></td>
<td><em>Eur Heart J</em> 2008;29:270–276</td>
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<table>
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<tr>
<th>2013</th>
<th>MOGES Classification</th>
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<td></td>
<td><em>J Am Coll Cardiol</em> 2013;62(22):2046-72</td>
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</table>

M - Morphology
O - Organ involvement
G - Genetics
E - Etiology
S - Status, clinical
CARDIOMYOPATHY CLASSIFICATIONS

All 3 classification systems move away from the classic trilateral subdivision of cardiomyopathies.

![Diagram showing HYPERTROPHIC, DILATED, and RESTRICTIVE categories]

SELECTED CARDIOMYOPATHIES

*Chamber morphology vs. inheritance matrix*

<table>
<thead>
<tr>
<th>'HYPERTROPHIC'</th>
<th>True Hypertrophy</th>
<th>Storage Disorder</th>
<th>DILATED</th>
<th>MISC (Peculiar morphology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMILIAL</td>
<td>• HCM / HOCM</td>
<td>• ATTR amyloidosis</td>
<td>• Idiopathic DCM</td>
<td>• ARVD</td>
</tr>
<tr>
<td></td>
<td>• Fabry's disease</td>
<td>• Hemochromatosis</td>
<td></td>
<td></td>
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<td></td>
<td>• Carnitine deficiency</td>
<td>• Hunter's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NON-FAMILIAL</td>
<td>• Athlete's heart</td>
<td>• AL amyloidosis</td>
<td>• Peripartum</td>
<td>• Takotsubo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ethanol abuse</td>
<td></td>
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</tbody>
</table>
Whenever there is inappropriate ventricular \textit{hypertrophy} or \textit{dilatation} (an increase in wall thickness or chamber size) unexplained by coronary, hypertensive or valvular disease.

* * *

... especially when there is a family history of a similar disorder

* * *

... or when the ventricle has a peculiar morphology or motion.

\textbf{WHEN A CARDIOMYOPATHY SHOULD BE SUSPECTED?}

\textbf{CARDIOMYOPATHIES}
where echocardiography is diagnostic or nearly diagnostic.

\textbf{CARDIOMYOPATHIES}
where echocardiography is NOT diagnostic.

Clinical context, family history and other testing modalities are required to establish the diagnosis.
A Cardiomyopathy with Pathognomonic Appearance

23-year-old male graduate student

- Enlarged heart since childhood
- NYHA class II
- Recent episode of ventricular fibrillation
23-year-old male graduate student

- Diagnosed with HCM at age 12 by echo
- β Myosin heavy chain mutation
- ICD placed at age 15

23-year-old male graduate student

- Massive increase in LV wall thickness

EKG
Left ventricular hypertrophy
23-year-old male graduate student

- NYHA class II

MITRAL INFLOW

SEPTAL TISSUE DOPPLER

SPECTRAL DOPPLER
Grade I Diastolic Dysfunction

CONCLUSION

Hypertrophic Nonobstructive Cardiomyopathy
46-year-old man

TTE | Parasternal Long-Axis View
Systolic anterior motion (SAM) of the mitral valve

46-year-old man

- Family history of sudden death

TTE | Color Doppler
LVOT obstruction +
Late systolic mitral regurgitation
HOCM: SPECTRAL DOPPLER PATTERNS

**LVOT OBSTRUCTION**
Late peaking, dagger-shaped profile

**MITRAL REGURGITATION**
Late systolic, very high velocity

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**MID-VENTRICULAR OBSTRUCTION**
Lobster claw profile

**MITRAL TISSUE DOPPLER**
Premature cessation of S wave
CONCLUSION

Hypertrophic Obstructive Cardiomyopathy

57-year-old woman

- Asymptomatic
- Abnormal pre-employment EKG

EKG

Left ventricular hypertrophy with symmetric T wave inversions
57-year-old woman

- Hypertension
- Her nephew has hypertrophic cardiomyopathy

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33-year-old man

- Heart failure symptoms

---

TTE | Apical 4-Chamber View

Apical variant of hypertrophic cardiomyopathy
33-year-old man

- Heart failure symptoms

**TTE | Perflutren microbubble echo contrast**

Apical variant of hypertrophic cardiomyopathy

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**ORIGINAL DESCRIPTION OF APICAL HCM**

Japanese population | *Am J Cardiol.* 1979 Sep;44(3):401-12

**EKG**

Left ventricular hypertrophy with *giant* T wave inversions

**RAO Ventriculogram**

*Spade shaped* heart at end diastole
CONCLUSION

Apical Variant of Hypertrophic Cardiomyopathy

33-year-old man

- Recent heart failure symptoms

A4C View | Foreshortened
Correct diagnosis not fully visualized
33-year-old man

- Recent heart failure symptoms

**A4C View | Not Foreshortened**
Isolated LV Noncompaction cardiomyopathy

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**Noncompaction LV Cardiomyopathy**

**Apical SAX View | No Contrast**
33-y/o man | Noncompacted LV

**Apical SAX View | Echo Contrast**
46-y/o man | Noncompacted LV
LV NONCOMPACTION

Cardiac MRI

CONCLUSION

Isolated LV Noncompaction Cardiomyopathy
46-year-old man

- Hypertensive urgency

TTE | PARASTERNAL LONG-AXIS VIEW
Increased in LV wall thickness

46-year-old man

- Hypertensive urgency

EKG
Left ventricular hypertrophy
with typical repolarization changes
CONCLUSION

Hypertensive Heart Disease

53-year-old man
- Hypertension
- Chronic renal insufficiency

TTE | PARASTERNAL LONG-AXIS VIEW
Left ventricular hypertrophy?
53-year-old man

- Hypertension
- Chronic renal insufficiency

EKG
Left ventricular hypertrophy

TTE | Apical 4-Chamber View
Pacemaker wire | Mitral annuloplasty ring
ADDITIONAL FINDINGS

**SKIN**
Angiokeratomas

**CARDIAC MRI**
Fibrosis in the basal inferolateral LV

CONCLUSION

Fabry's Disease
Fabry, J. Ein Beitrag zur Kenntniss der Purpura haemorrhagica nodularis (Purpura papulosa haemorrhagica Hebrae)

[A contribution to the knowledge of Purpura haemorrhagica nodularis (Purpura papulosa haemorrhagica Hebrae)]


**Johannes Fabry**
German dermatologist (1860-1930)

**Fabry's Disease**
- X-linked recessive disorder
  - Male patient with affected maternal relatives
- Patients die in their 50's
- Alpha-galactosidase deficiency
  - Glycolipid accumulation in lysosomes of blood vessels
- No typical habitus or ethnic preference
- Cardiac manifestations
  - LVH (on EKG & Echo)
  - Fabry's disease may account for 3% of patients with LVH
  - Aortic root dilatation
  - Mitral valve prolapse
  - Conduction abnormalities
22-year-old woman

- Asymptomatic
- Referred for 'screening TTE'

TTE | Parasternal Long-Axis View
Left ventricular hypertrophy?

22-year-old woman

- Asymptomatic
- Abnormal pre-employment EKG

EKG
Left ventricular hypertrophy
with typical repolarization changes
22-year-old woman

- Asymptomatic
- Abnormal pre-employment EKG

Chest X-Ray
Pacemaker/Defibrillator

---

**FAMILY HISTORY**

**BROTHER**

*Homozygous* for carnitine transporter gene mutation.

Died as a teenager despite carnitine supplementation

**PATIENT**

*Heterozygous* for carnitine transporter gene mutation.

Marked improvement in cardiomyopathy post carnitine supplementation

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**CARNITINE**

- *Lysine* + *Methionine* derivative.
- *Essential for fatty acid transport into mitochondria*
- *Gene mutations in renal carnitine transporter gene >> carnitine wasting*
CONCLUSION

Cardiomyopathy Due to Carnitine Uptake Deficiency

61-year-old woman

- Hypertension
- Ethanol abuse
- Liver cirrhosis
- Shortness of breath

TTE | APICAL 4-CHAMBER VIEW
Cardiomyopathy?
Spectral Doppler

Restrictive mitral filling pattern + Severe pulmonary hypertension

LABORATORY DATA
Iron Studies

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRON</td>
<td>78</td>
</tr>
<tr>
<td>TIBC</td>
<td>96</td>
</tr>
<tr>
<td>FERRITIN</td>
<td>1110</td>
</tr>
<tr>
<td>TRANSFERRIN</td>
<td>66</td>
</tr>
</tbody>
</table>

**Iron Saturation**

\[
\text{Iron Saturation} = \frac{\text{Iron}}{\text{TIBC}}
\]

\[
= \frac{78}{96} = 81\% \text{ (normal <50\%)}
\]

**FERRITIN**

1110 ng/mL (normal <200)

Patient has iron overload
CONCLUSION

Hemochromatosis

59-year-old man

- Hemo-chromatosis

TTE | APICAL 4-CHAMBER VIEW
Dilated Cardiomyopathy
59-year-old man

- Hemo-chromatosis

M mode

Signs of severe LV systolic dysfunction

CONCLUSION

Hemochromatosis
54-year-old male physician

- Presents with recurrent palpitations
- 5 years earlier had an episode of exercise-induced RVOT ventricular tachycardia

TTE | PARASTERNAL LONG-AXIS VIEW
Cardiomyopathy?

54-year-old male physician

- Presents with recurrent palpitations
- 5 years earlier had an episode of exercise-induced RVOT ventricular tachycardia

TTE | APICAL 4-CHAMBER VIEW
No significant valvular disease, ASD or pulmonary hypertension
54-year-old male physician

- Presents with recurrent palpitations
- 5 years earlier had an episode of exercise-induced RVOT ventricular tachycardia

EKG
Peculiar RBBB

ARRHYTHMOGENIC RV DYSPLASIA

Congenital cardiomyopathy with **autosomal dominant** transmission

Mutations in proteins of **desmosomes** (structures connecting adjacent cells)

- Fibrofatty replacement of myocytes
- RA & RV dilatation & dysfunction without volume or pressure overload
ORIGINAL DESCRIPTION OF ARRHYTHMOGENIC RV DYSPLASIA

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

This is a previously unrecognized form of cardiomyopathy mainly localized to the right ventricle and is usually associated with little or unappreciable alteration in myocardial contractility (34). Isolated cases suggestive of this syndrome have been reported by others (60-42). We have documented a total of 23 cases of this type; 9 of these who were resistant to drug therapy have been treated surgically (Table 27.5). A possible familial form has also been encountered.

The diagnosis may be based on the following criteria:

- **ECG:** The ECG was completely normal in only a small number of cases. In most of the cases, ECG recordings during sinus rhythm indicated right ventricular abnormality on the basis of delayed right ventricular activation, negative or biphasic T waves in the right precordial leads, and...

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Table 1. Criteria for Diagnosis of Right Ventricular Dysplasia (5)

<table>
<thead>
<tr>
<th>Category</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Global and/or regional dysfunction and structural alterations</td>
<td>Severe dilatation and reduction of right ventricular ejection fraction (RVFEF) with no (or only mild) left ventricular impairment</td>
<td>Localised right ventricular aneurysms (infarct or dyskinetic areas with diastolic bulging)</td>
</tr>
<tr>
<td>II. Tissue characterization of wall</td>
<td>Severe dilatation of the right ventricle</td>
<td>Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle</td>
</tr>
<tr>
<td>III. Repolarization abnormalities</td>
<td>Regional right ventricular hyperkinesis</td>
<td>Mild segmental dilatation of the right ventricle</td>
</tr>
<tr>
<td>IV. Depolarization/conduction abnormalities</td>
<td>Inverted T waves in right precordial leads (V1 and V2) in people age ≥12 years, in absence of right bundle branch block</td>
<td>Inverted T waves or localised prolongation (≥110 ms) of the QRS complex in right precordial leads (V1-V2)</td>
</tr>
<tr>
<td>V. Anion gap</td>
<td>Late potentials (signal-averaged ECG)</td>
<td>Late potentials (signal-averaged ECG)</td>
</tr>
<tr>
<td>VI. Family history</td>
<td>Left bundle branch block. Type ventricular tachycardia (malignant and nonmalignant) by ECG, Holter, or exercise testing</td>
<td>Frequent ventricular extrasystoles (≥1,000/24 h) (Holter)</td>
</tr>
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Echocardiography

CONCLUSION

ARVD/ARVC is an **autosomal dominant** inherited cardiomyopathy

♦

Regional or global
RV and RA dilatation & dysfunction
without volume or pressure overload

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54-year-old man

- Hypertension
- Clinical signs of heart failure

**TTE | PARASTERNAL LONG-AXIS VIEW**

Left ventricular hypertrophy?
Discrepancy between apparent LVH on echo and no LVH on EKG is often the first clue in diagnosing cardiac amyloidosis.

54-year-old man

- Hypertension
- Multiple myeloma (AL amyloid)

TTE | APICAL 4-CHAMBER VIEW
Left ventricular hypertrophy?
Amyloidosis: LV Diastolic Dysfunction

**Mitral Inflow**

RESTRICTIVE FILLING PATTERN
E/A > 2
E wave deceleration time < 150 msec

**Mitral Inflow with Respirometry**

NO RESPIRATORY VARIATIONS IN E WAVE
(in contrast to constriction)

Cardiac Amyloidosis: LV Diastolic Dysfunction

**Pulmonary Vein Flow**

S << D
(indicative of high LA pressure)

**Mitral Annular Tissue Doppler**

LOW MEDIAL & LATERAL VELOCITIES
(indicative of diminished longitudinal LV function)
Amyloidosis: Longitudinal Strain

Despite globally diminished longitudinal strain, apical strain is relatively preserved.

Cardiac Amyloidosis

Global longitudinal peak systolic strain = –10%

Apical sparing – typical finding in amyloidosis
Cardiac Amyloidosis: Tissue Diagnosis

Typical biopsy sites
- Abdominal wall fat pad
- Endomyocardium

CONCLUSION

Cardiac Amyloidosis
Thank You!

New York University Langone Medical Center