Definition of Cardiomyopathy

AHA Statement

Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic.

Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.

Secondary Cardiomyopathies

Nutritional deficiencies
- Beriberi
- Scurvy
- Pellagra
- Keratocoriodosis
- Siderosis
- Phenylketonuria
- Acatalasia

Infections
- Viral
- Fungal
- Parasitic
- Tumours

Toxicities
- Heavy metals
- Methyl alcohol
- Organophosphates

Medication-induced
- Digoxin
- Beta-blockers
- Calcium channel blockers
- Amiodarone

Sepsis

Vegetative

Other causes


definition of cardiomyopathy

European Society of Cardiology statement:

“A myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to explain the observed myocardial abnormality.”
Definition of Cardiomyopathy

European Society of Cardiology classification:
Genetic/familial vs non-genetic
Did not include the channelopathies

ESC Statement, Classification of Cardiomyopathies Eur Heart J 2008;29:270-6

Dilated, Hypertrophic and Arrhythmogenic Cardiomyopathy

Hershberger, Hedges, Morales Nature Review Cardiol 2013:10:531-47
### 65 The Dilated, Restrictive, and Infiltrative Cardiomyopathies

Rodney J. Folk and Ray E. Mitchell

**Phenotype; clinical characteristics, also pedigree**

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Dilated Cardiomyopathy (DCM)

**Definition**

- Left ventricular enlargement (LVE)
- Decreased systolic function (LV ejection fraction < 0.50)
- Other causes excluded

**Familial dilated cardiomyopathy may be present in 20-50% of IDC diagnoses**


**Lamin A/C mutations - CV phenotype**

Average age of onset - 40 years

Present with CSD and arrhythmia
- Initially, asymptomatic ECG changes: sinus/AV node dysfunction
- Progress to 1st, 2nd, 3rd degree HB;
  supraventricular arrhythmias, SSS, Aflutter/Afib,
  ventricular pacemakers/ICDs common

Progress to DCM - mild to severe
- progressive HF commonly requiring transplant
- occasional skeletal muscle disease overlap

Fatkin, et al, NEJM, 1999; 341:1715-24
Parks et al, Am Heart J 2008; 156:161-69
Burket, Hershberger, J Am Coll Cardiol, 2005; 45:969-81
**Lamin A/C in disease**

- **Muscular dystrophy**
  - AD Emery-Dreifuss muscular dystrophy (EDMD)
  - AR EDMD (rare)
  - AD limb girdle muscular dystrophy, type 1B (rare)
  - AD conduction system disease and DCM (usu w/o MD)

- **Partial lipodystrophy syndromes**
  - AD familial partial lipodystrophy
  - AR mandibuloacral dysplasia

- **Neuropathy**
  - AR Charcot-Marie-Tooth disorder type 2B1

- **Progeria syndromes** (Hutchinson-Gilford Progeria)

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**Disease Mutations in Lamin A/C**

- NH2
- COOH
- R225X
- K215P
- N195K
- Q6X
- R60G
- E203G
- E203K
- Coil 1a
- Coil 2
- Head
- Tail
- Rod
- Familial Dilated Cardiomyopathy
- Emery-Dreifuss Muscular Dystrophy
- Limb-girdle Muscular Dystrophy Type 1B
- Familial Partial Lipodystrophy

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**Lamin A/C in disease**

**Emery-Dreifuss Muscular Dystrophy**

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**Restrictive Cardiomyopathy**

**Physiological definition**

- Impaired filling with non-dilated ventricles, or
- Increased LV end-diastolic filling pressure to achieve a normal LV end-diastolic volume
Restrictive Cardiomyopathy

More tractable approach: non-dilated cardiomyopathy (normal LV size, normal or reduced ejection fraction; non-hypertrophied or hypertrophied).

Positive history: toxins (e.g., doxorubicin, other chemotherapy), radiation

Positive or negative history:
- Infiltrative: amyloid; sarcoidosis
- Storage diseases: hemochromatosis; Fabry disease
- Myocardial: familial/genetic, including HCM; idiopathic; endomyocardial fibrosis (Africa)

Rule out constrictive pericarditis

Amyloid Cardiomyopathy

Amyloid: extracellular deposition of protein beta-pleated fibrils usually 5-25kd, >25 human proteins

AL: primary, clonal plasma cell expansion, light chains
AA: secondary, many, amyloid A, transthyretin (TTR), etc

Cardiac: presents commonly as heart failure, congestive features predominate; restrictive physiology; narrow pulse pressure; ECG: low voltage despite LVH; echo: concentric LVH, non-dilated, small cavity

Treatment: challenging! Diuretics; avoid vasodilators, negative inotropes, CCBs. SCD usu from EMD, ICDs may not help. AL: CTX, bone marrow/heart transplant investigational. Transplant for TTR (liver, heart)

Amyloid Cardiomyopathy

Bi-mode echo cardiogram of amyloid cardiomyopathy

The bi-mode echocardiogram in a patient with amyloid cardiomyopathy shows a classic triad: severe LV systolic dysfunction, septal and lateral LV wall thinning, and intramyocardial calcium (amorphous-like calcium). PRV = interventricular septum; PNLV = posterior wall of the LV.
Amyloid Cardiomyopathy

Granulomatous disease, >90% pulmonary involvement

Clinical cardiac involvement 5%; at autopsy 30%

Conduction disease, Arrhythmias, Heart failure
- Early onset heart block, 1st, 2nd, 3rd degree
- SCD, syncope from ventricular tachyarrhythmias, heart block
- Progressive LV dysfunction, heart failure

Diagnosis: endomyocardial biopsy

Treatment: steroids; pacemaker/ICD; transplant

Sarcoid Cardiomyopathy

Granulomatous disease, >90% pulmonary involvement

Clinical cardiac involvement 5%; at autopsy 30%

Conduction disease, Arrhythmias, Heart failure
- Early onset heart block, 1st, 2nd, 3rd degree
- SCD, syncope from ventricular tachyarrhythmias, heart block
- Progressive LV dysfunction, heart failure

Diagnosis: endomyocardial biopsy

Treatment: steroids; pacemaker/ICD; transplant

Sarcoid Cardiomyopathy

Cardiomyopathy with Hemochromatosis

Hemochromatosis is usually genetic disease unless clear history of multiple blood transfusions

HFE gene, autosomal recessive inheritance

C282Y most common (60-90%) (C282Y/H63D 3-8%)

Screening: transferrin-iron saturation
- >60% males, > 50% females;
- Ferritin helpful but non-specific

Tissue diagnosis: MRI scanning; liver, heart biopsy

Treatment: phlebotomy
Fabry Disease

X-linked glycogen storage disease: deficient activity (<1%) of alpha-galactosidase activity; progressive deposition of globotriaosylceramide (GL-3)

Classic onset: male children/adolescents

Acroparesthesias: episodic crises, severe extremity pain

Angiokeratomas: vascular cutaneous lesions

Other: hypohydrosis; corneal/lenticular opacities

ESRD: initial proteinuria, ESRD 3rd - 5th decade

Cardiovascular: concentric LVH, angina with normal coronary arteries, aortic insufficiency/mitral regurgitation: suspect atypical Fabry disease with LVH and no obvious explanation, few/no other findings

Diagnosis: plasma alpha-galactosidase activity

Women carriers can manifest symptoms
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

Clinical Features

- Ventricular arrhythmias, sudden death
- Spectrum of no systolic dysfunction to heart failure
- Classically, RV myocardium replaced by fat, fibrosis
- LV involvement now recognized
- Positive family history
- Early onset (2nd - 4th decades) common
- Much less common than HCM, DCM

Treatment focused on arrhythmia, SCD prevention

3 genes account for most disease

- plakophilin-2 10-40%
- desmoglein-2 10-40%
- desmoplakin 5-15%
- desmocollin-2 rare
- plakoglobin rare
- ryanodine receptor 2 rare
- TGF beta 3 rare

Cardiac desmosome: ARVC is a disease of desmosomal proteins

Cardiac desmosomes are complexes of transmembrane proteins that anchor structural proteins to the actin cytoskeleton.
Left Ventricular Noncompaction (LVNC)

LVNC: Altered myocardial wall with prominent trabeculae and deep intrabecular recesses

No universally accepted criteria; has been declared a specific type of cardiomyopathy (?)

Widely variable clinical course, clinical implications

Some familial clustering, some association with DCM genes

Summary: overall clinical significance unclear

The Dilated, Restrictive and Infiltrative Cardiomyopathies: Clinical and Genetic Evaluation

Thank you!
Hypertrophic Cardiomyopathy

Unexplained left ventricular septal or global hypertrophy
- LV thickness > 13 mm; >18 mm pathopneumonic
- diagnosis by echocardiography
- characteristic cardiac myocyte disarray
- Presentation may include:
  - syncope or sudden death
  - chest pain
  - murmur
  - arrhythmia
- Symptoms may be subtle, minimal
- Natural history varies, childhood vs adult onset.