Definition and classification of the cardiomyopathies

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Historical Context

- WHO: 1980 classification
  "heart muscle diseases of unknown cause"

- WHO 1995 classification
  "diseases of myocardium associated with cardiac dysfunction"
How should we define cardiomyopathies?

**BASED ON**

- origin?
- anatomy?
- physiology?
- biopsy histopathology?
- genetics?
Based on Origin

DILATED CARDIOMYOPATHY

- Idiopathic
- Familial/Genetic
- Viral
- Immune
- Alcoholic/Toxic
Based on Anatomy

Fabry

Cardiac amyloidosis

HCM
Based on physiology (Filling Pattern)
Based on physiology (restrictive pattern)
Based on physiology

- Restrictive cardiomyopathy
- Hypertrophic-restrictive cardiomyopathy

  Restrictive filling pattern
Based on biopsy histopathology
ARVC
Based on biopsy histopathology
HCM
DCM, male, 44-y-old
Light microscopy: Two myocardial samples with severe interstitial and endocardial fibrosis. Myocytes with irregular profiles, focal hypertrophia and myofibrillar lysis. No myocarditis; no extracellular accumulation; no endocardial thrombosis.

Ultrastructural findings on electron microscopic study: One myocardial sample from paraffin-embedded tissue processed for electron microscopy. Myocytes: myofibrillar lysis, mitochondrial cristolysis, lipid droplets, nuclei with irregular profiles. Interstitium: fibrosis with dense collagen bundles, absence of inflammatory cells. No extracellular accumulation.

Histology: Two myocardial showing findings similar to A, with sparse and focal inflammatory cells in one sample.

Ultrastructural findings on electron microscopic study: One myocardial sample showing findings similar to A, with more pronounced myofibrillar lysis. No amyloid.

Findings consistent with cardiomyopathy

Eloisa Arbustini
Classification Based Mainly on Molecular Genetics
B-myosin heavy chain gene mutations

DCM                HCM
Disease-causing mutations in the human \textit{beta-cardiac Myosin Heavy Chain} gene

- 194 hypertrophic cardiomyopathy mutations
- 13 dilated cardiomyopathy mutations
- 7 other mutations
- 7 variants of uncertain effect
- 15 polymorphisms
AHA Scientific Statement
Contemporary Definitions and Classification of the Cardiomyopathies
An American Heart Association Scientific Statement From the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention
Barry J. Maron, MD, Chair; Jeffrey A. Towbin, MD, FAHA; Gaetano Thiene, MD; Charles Antzelevitch, PhD, FAHA; Domenico Corrado, MD, PhD; Donna Arnett, PhD, FAHA; Arthur J. Moss, MD, FAHA; Christine E. Seidman, MD, FAHA; James B. Young, MD, FAHA
AHA: Definition of Cardiomyopathies

- 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.
New definition: basic characteristics

- **mechanical dysfunction** (diastolic or systolic dysfunction)
- **electrical dysfunction** (life-threatening arrhythmias)
- ion channelopathies (long-QT syndrome, Brugada syndrome)
- no histopathological abnormalities
- abnormalities at the molecular level in the cell membrane
Entities excluded from the new definition

pathological myocardial processes and dysfunction that are a direct consequence of

- valvular heart disease
- systemic hypertension
- congenital heart disease
- atherosclerotic coronary artery (ischemic cardiomyopathy)
- metastatic and primary intracavitary or intramyocardial cardiac tumors
- diseases affecting endocardium with little or no myocardial involvement
- hypertensive HCM.
AHA: Classification of Cardiomyopathies

*Primary cardiomyopathies*
- solely or predominantly confined to heart muscle
- genetic, nongenetic, acquired

*Secondary cardiomyopathies*
- pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders
- old definition: "specific cardiomyopathies" or "specific heart muscle diseases"
Hypertrophic Cardiomyopathy

**Definition:** Myocardial hypertrophy in the absence of any other cause capable to produce the magnitude of hypertrophy present

**Incidence:** 0.2% (1/500)
HYPERTROPHIC CARDIOMYOPATHY

diagnosis

1. Echo: maximal wall thickness > 14mm

2. Maximal wall thickness = 14 or 13 mm
   ECG changes compatible with HCM
   Positive family history

3. No hypertrophy
   Positive family history and abnormal ECG

4. Gross ECG abnormalities
Hypertrophic Cardiomyopathy

- firstly described by Teare in 1958
- incidence of familial form: 60-70% with autosomal dominant pattern of inheritance
- Remaining cases: sporadic
- Variable penetrance:
  - phenotype positive/ genotype positive
Familial Hypertrophic Cardiomyopathy

Disease of sarcomere characterized by mutations in the genes coding for contractile and regulatory proteins of contraction (H. Watkins)-1990
>500 HCM-causing gene mutations

(Sarcomere protein gene mutation data base
available
at:http://www.cardiogenomics.med.harvard.edu)
# Genes Responsible for Human Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Gene</th>
<th># Mutations</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>b-myosin heavy chain</td>
<td>194</td>
<td>30-50%</td>
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<tr>
<td>myosin binding protein C</td>
<td>149</td>
<td>30-50%</td>
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<td>cardiac-troponin T</td>
<td>31</td>
<td>4%</td>
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<tr>
<td>cardiac-troponin I</td>
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<td>a-tropomyosin</td>
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<td>essential myosin light chain</td>
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<tr>
<td>regulatory myosin light chain</td>
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<td>1%</td>
</tr>
<tr>
<td>cardiac- actin</td>
<td>7</td>
<td>1%</td>
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</table>
Non-Sarcomeric Genes Responsible for Human Hypertrophic Cardiomyopathy

- gene for muscle LIM protein (MLP)
- The genes encoding the gamma-2 regulatory subunit of adenosine monophosphate-activated protein kinase (PRKAG2)
- the gene encoding lysosome-associated membrane protein 2 (LAMP2)
- The gene for titin
- The gene for the protein titin-cap (T-cap/telethonin)
Gene Mutation Forms in Familial Hypertrophic Cardiomyopathy

- Missense (δυσυνθετικές)
- Deletions (ελλείψεις)
- Insertions (προσθήκες)
- Truncated (ακρωτηριαστικές)
B-Myosin Heavy Chain Gene

Codon

AATCGTATGC\{TAC\}TGTGCATAATCG...

exon

22,000 bp
A: Adenine
T:Thymine
C:Cytocine
G:Guanine
B-Myosin Heavy Chain Gene

EXON 23

codon 403

↓

AATGCA\textcolor{green}{TGCT}TTGAGTCTGAC: MHC gene

↓

............. Arg................... b-MHC protein
B-Myosin Heavy Chain Gene

EXON 23

codon 403

AATGCA\textbf{TGC}TTGAGTCTGAC:MHC gene

\textbf{TAC}mutant gene

\textbf{Gln}b-MHC protein

\textbf{Arg}403\textbf{Gln}
B-Myosin Heavy Chain Gene

EXON 23

codon 403

AATGCA

TGC

TTGAGTCTGAC: b-MHC gene

......... TAC .........................mutant gene

......... Gln ...........................b-MHC protein

Arg403Gln
Healthy Carriers in HCM

- Up to 30% of genetically affected adults, are not identified by conventional criteria (Healthy Carriers)
- The majority of them will develop some form of HCM before the age of 50 years
HCM pathophysiology

Clinical assessment

Sarcomeric protein defect
↓
↓ Myofibrilar shortening
↓
Disarray
↓
Hypertrophy

None

Doppler, TVI

ECG

Echo
Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

- 1:5000
- involves predominantly the right ventricle with progressive loss of myocytes and fibrofatty tissue replacement
Pathogenesis

- The replacement of the right ventricular myocardium by fibrofatty tissue is progressive (epicardium or midmyocardium and then transmural)

- Progression then leads to wall thinning and aneurysms, typically located at the inferior, apical, and infundibular walls (so-called triangle of dysplasia), the hallmark of ARVC
ECG IN ARVC

The diagram shows ECG traces in different leads (I, II, III, AVR, AVL, AVF, V1, V2, V3, V4, V5, V6) highlighting the presence of an Epsilon wave, which is a characteristic feature in ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy).
Dilated Cardiomyopathy

Increased ventricular chamber size with reduced contractility in the absence of CAD, valvulopathy, pericardial disease.

Prevalence: 40/100,000 persons

Natural history: • heart failure
  • leading cause of heart transplantation
  • high rate of SCD
  • high mortality rate: 50%
    5 years after initial diagnosis
DILATED CARDIOMYOPATHY

- Idiopathic
- Familial/Genetic
- Viral
- Immune
- Alcoholic/Toxic
Familial Dilated Cardiomyopathy (FDC)

- Incidence: 50% (familial history)
- Patterns of inheritance: autosomal dominant, autosomal recessive, X-linked, matrilineal (mitochondrial DC)
The phenotype can be characterized by an isolated cardiac dysfunction (isolated DCM) or include conduction defects (atrioventricular block or sinus node dysfunction) and/or skeletal muscular disorders.
Genetic causes of DCM

**Sarcomere**

- β-Myosin heavy chain \((MYH7)\)
- Troponin T \((TNNT2)\)
- Troponin I \((TNNI3)\)
- Troponin C \((TNNC1)\)
- Cardiac-actin \((ACTC)\)
- Tropomyosin \((TPM1)\)
- Myosin-binding protein C \((MYBPC3)\)
Genetic causes of DCM

Sarcomere and Z-disc associated proteins

- Titin (TTN)
- Titin-cap/telethonin (TEL)
- Muscle LIM protein (CRP3)
- Metavinculin (VCL)
- Cypher/ZASP (LDB3)
Cytoskeleton
- Dystrophin (*DMD*)
- Sarcoglycan (*SGCD*)
- Intermediate filaments
  - Desmin (*DES*)
  - Lamin A/C (*LMNA*)

Genetic causes of DCM
Channel and channel-associated proteins

- Cardiac sodium channel (SCN5A)
- ATP-sensitive potassium channel (SUR2A/ABCC9)
- Phospholamban (PLN)
Mitochondria

- Tafazzin (*G4.5*)
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