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Cardiomyopathies: which classification we have to rely on?

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In 1957 Bridgen published his St Cyres Lecture on :

"Uncommon myocardial diseases - the non-coronary cardiomyopathies"

Lancet 1957;2:1174-1243

Population cross-sectional studies
overall estimated **prevalence** of all cardiomyopathies
is **at least 3%** in the general population worldwide.

PREVALENCE of the MOST COMMON CARDIAC CONDITIONS

	Children (1–puberty)	Adults (19–64 y)
HCM	Uncommon	1:250/500*
DCM	Uncommon†	1:250/500‡
ARVC	Uncommon	1:2000/5000
RCM	Uncommon	Uncommon
LQT	1:2000	1:2000
Brugada (type 1 ECG)	Uncommon	1:2000/5000§
CPVT	1:5000/10 000	1:5000/10 000

McKenna WJ et al. *Circ Res.* 2017;121:722-730.

CARDIOMYOPATHIES and SPECIFIC HEART MUSCLE DISEASES

***JF Goodwin* in 1961 and in 1964 proposed a definition and classification based on disorders of structure and function.**

The classification was modified (1973) to:

- ***Congestive***
- ***Hypertrophic obstructive***
- ***Restrictive (or obliterative)***

1980 - Report of the WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies.

***Br Heart J* 1980;44:672-3**

***Definition*:**

"Cardiomyopathies are heart muscle disease of unknown cause"

***Classification*:**

- **Dilated cardiomyopathy**
- **Hypertrophic cardiomyopathy**
- **Restrictive cardiomyopathy**

Specific heart muscle disease are heart muscle diseases of known cause or associated with disorders of other systems.

1995 - Report of the WHO/ISFC Task Force on the *Definition and Classification of Cardiomyopathies*

Circulation 1996;93:841-2

Cardiomyopathies **are defined as diseases of the myocardium associated with cardiac dysfunction.**

They are classified as :

- *Dilated Cardiomyopathy (DCM)*
- *Hypertrophic Cardiomyopathy (HCM)*
- *Restrictive Cardiomyopathy (RCM)*
- *Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)*
- *Unclassified Cardiomyopathies*

Specific Cardiomyopathies are heart muscle diseases associated with specific cardiac or systemic disorders.

SPECIFIC CARDIOMYOPATHIES

Report of the 1995 WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996; 93: 841-2.

- *Ischemic cardiomyopathy*
- *Valvular cardiomyopathy*
- *Hypertensive cardiomyopathy*
- *Inflammatory cardiomyopathy*
- *Metabolic cardiomyopathy* (endocrine, familial storage disease and infiltrations, deficiency and nutritional disorders, amyloid)
- *General system disease* (connective tissue disorders, infiltrations and granulomas)
- *Muscular dystrophies* (Duchenne, Becker type, myotonic dystrophies)
- *Neuromuscolar disorders* (Friedeich's ataxia, Noonan's syndrome, lentiginosis)
- *Sensitivity and toxic reactions* (alcohol, catecholamines, antracyclines, irradiation, miscellaneous)
- *Peripartal cardiomyopathy*

AHA Scientific Statement

2006 - Classification of the Cardiomyopathies.

Definitions

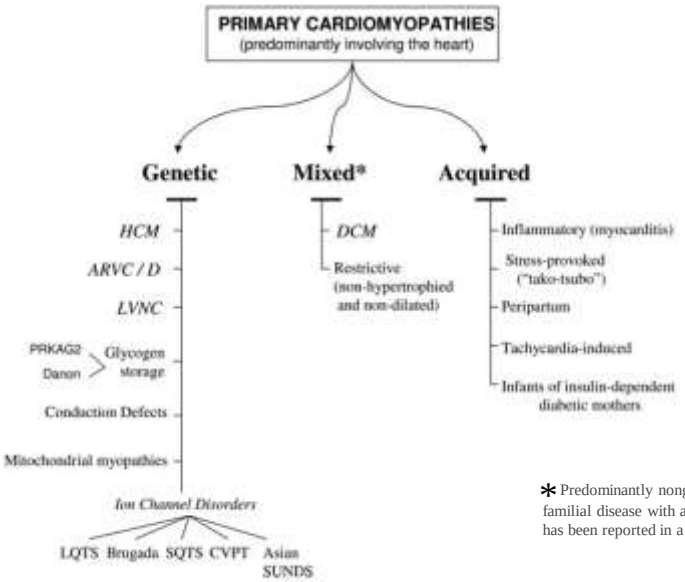
The expert consensus panel proposes this definition: *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety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

*Cardiomyopathies either are confined to the heart **(Primary CM)** or are part of generalized systemic disorders (**Secondary CM**), often leading to cardiovascular death or progressive heart failure–related disability.*

Circulation 2006;113;1807-1816

AHA Scientific Statement

2006 - Classification of the Cardiomyopathies.



* Predominantly nongenetic; familial disease with a genetic origin has been reported in a minority of cases

Circulation 2006;113;1807-1816

AHA Scientific Statement

Circulation 2006;113;1807-1816

2006 - Classification of the Cardiomyopathies

SECONDARY CARDIOMYOPATHIES

Infiltrative*
Amyloidosis (primary, familial autosomal dominant†, senile, secondary forms)
Gaucher disease†
Hurler's disease†
Hunter's disease†

Storage‡
Hemochromatosis
Fabry's disease†
Glycogen storage disease† (type II, Pompe)
Niemann-Pick disease†

Toxicity
Drugs, heavy metals, chemical agents
Endomyocardial
Endomyocardial fibrosis
Hypereosinophilic syndrome (Löeffler's endocarditis)

Inflammatory (granulomatous)
Sarcoidosis

Endocrine
Diabetes mellitus†
Hyperthyroidism
Hypothyroidism
Hyperparathyroidism
Pheochromocytoma
Acromegaly
Cardiofacial
Noonan syndrome†
Lentiginosis†

Neuromuscular/neurological
Friedreich's ataxia†
Duchenne-Becker muscular dystrophy†
Emery-Dreifuss muscular dystrophy†
Myotonic dystrophy†
Neurofibromatosis†
Tuberous sclerosis†

Nutritional deficiencies
Beriberi (thiamine), pallagra, scurvy, selenium, carnitine, kwashiorkor

Autoimmune/collagen
Systemic lupus erythematosis
Dermatomyositis
Rheumatoid arthritis
Scleroderma
Polyarteritis nodosa
Electrolyte imbalance

Consequence of cancer therapy
Anthracyclines: doxorubicin (adriamycin), daunorubicin
Cyclophosphamide
Radiation

* Accumulation of abnormal substances between myocytes (ie, extracellular).

† Genetic (familial) origin.

‡ Accumulation of abnormal substances within myocytes (ie, intracellular).

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

AHA Scientific Statement

2006

Contemporary Definitions and Classification of the Cardiomyopathies

The AHA definition and classification of CM

- is rather a scientific scheme aiming to aid in understanding this complex group of diseases
- is the first genuine attempt to introduce a genetic basis of classification of CM
- includes the channelopathies as primary CM, despite the absence of gross structural abnormalities

Circulation 2006;113;1807-1816

European Heart Journal (2008) 29, 270–276
doi:10.1093/eurheartj/ehm342

ESC REPORT

2008

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*

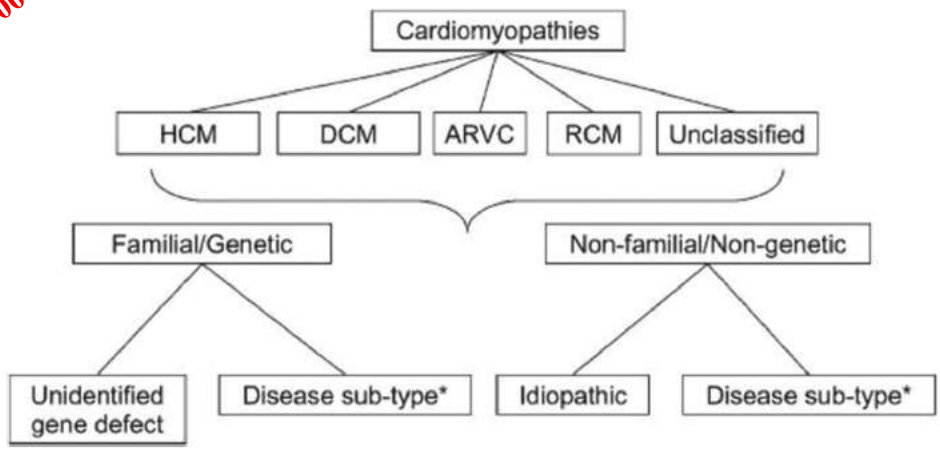
In this statement a cardiomyopathy is defined as:

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 cause the observed myocardial abnormality.

European Heart Journal (2008) 29, 270–276
doi:10.1093/eurheartj/ehm342

Proposed classification system of the Cardiomyopathies

2008



Examples of different diseases that cause cardiomyopathies

ESC 2008

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations β myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe, PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hunter's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedemann syndrome Sayer's syndrome Other Phospholamban promotor Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex ORYAB Spectrin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β1 (TGFβ1)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desmin myopathy Pseudoxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infectious/autoimmune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphatemia, hypovitaminosis Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chemotherapeutic agents Drugs (anorexigens, methysergide, ergotamine, neuroleptic agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (antineoplastics)	Takotsubo cardiomyopathy

Eur Heart J 2008;29:270-276

European Heart Journal (2008) 29, 270–276
doi:10.1093/eurheartj/ehm342

2008 proposed classification system of the Cardiomyopathies

The proposal differs in several ways from the 1995 WHO/ISFC and the 2006 AHA classifications:

- Groupings of specific morpho-functional phenotypes is the basis of the clinical management (rather than putative pathophysiological mechanisms).
- Further sub-classification into familial and non-familial forms, so as to raise awareness of genetic determinants of CM and to orient diagnostic tests.
- Abandonment of the distinction between primary and secondary CM.
- Exclusion of ion channelopathies.

The aim of these proposals is to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses that may be useful for tailored clinical management of patients and their families.

THE CLASSIFICATIONS OF CARDIOMYOPATHIES (1980-2008)

Modified: from Sinagra et al. *G Ital Cardiol* 2008;9(5):309-313

	1980 *Br Heart J* WHO/ISFC Task Force	**1995** *Circulation* WHO/ISFC Task Force	**2006** *Circulation* AHA Scientific Statement	**2008** *Eur Heart J* ESC Position Statement WGMPD
Def.	**Heart muscle disease of unknown origin**	**Disease of the myocardium associated to cardiac dysfunction**	**Disease of the myocardium associated to mechanical and/or electric dysfunction, usually, but not ever, with inappropriate ventricualr hypertrophy or dilatation and due to a variety of causes, frequently genetic**	**A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of CAD, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality**
Types	▪ Hypertrophic CM ▪ Dilated CM ▪ Restrictive CM	▪ Hypertrophic CM ▪ Dilated CM ▪ Restrictive CM ▪ ARVD ▪ Non classified CM	***Primary CMPs*** (localized exclus. or predom. in the myocardium) ▪ ***Genetic*** - Hypertrophic CM - ARVD - LVNC - Glycogen storage diseases - Conduction defects - Mithocondrial myopathies - "Channellopathies" ▪ ***Mixed*** - DCM - RCM ▪ ***Acquired*** - Inflammatories CM - Stress CM(tako-tsubo) - Peripartum CM - Tachycardia CM - CM in infants of IDDM mothers ***Secondary*** *CM* (due to multiorgan disorders)	▪ Hypertrophic CM ▪ Dilated CM ▪ Restrictive CM ▪ ARVD ▪ Non classified CM *Every type further divided in* - Familiar/genetic - Non familiar/non genetic ***No difference*** *between primary and secondary form*
	Specific heart muscle diseases (of known cause or associated disorders of other systems)	Specific cardiomyopathies (associated to malattie cardiache specific cardiac disease or to other systems disorders)		
	Excluding: *m*yocardial disease caused by pulmonary or systemic hypertension, CAD, valvulopathies, congenital heart disease	***Including***: ischemic, valvular, hypertensive CMP	***Excluding***: myocardial disease caused by pulmonary or systemic hypertension, CAD, valvulopathies, congenital heart disease	***Excluding***: myocardial disease caused by pulmonary or systemic hypertension, CAD, valvulopathies, congenital heart disease, Channellop.

2013

The MOGE(S) Classification of Cardiomyopathies - Premise

- **Knowledge of the genetics** of cardiomyopathies has evolved exponentially

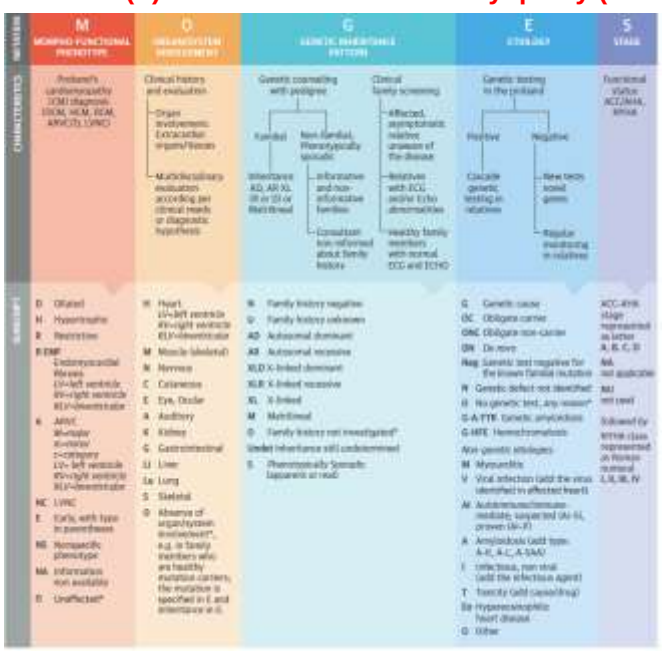
- **At least 60 disease genes** has been either confirmed or suspected as candidate gene

- A **genetic heterogeneity** is well established
- Implementation of **Next Generation Sequencing** is further expected to increase the pool of knowledge

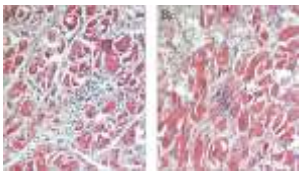
- The diagnosis based on **phenotype** is <u>still clinically useful, but not sufficient</u> for prognosis stratification in CM caused by mutations in different genes
- **Grouping per disease gene** <u>could provide a basis</u> for implementation of disease-specific research

2013

The MOGE(S) Classification of Cardiomyopathy (WHF)



Arbustini E et al. *J Am Coll Cardiol* 2014;64:304-18.



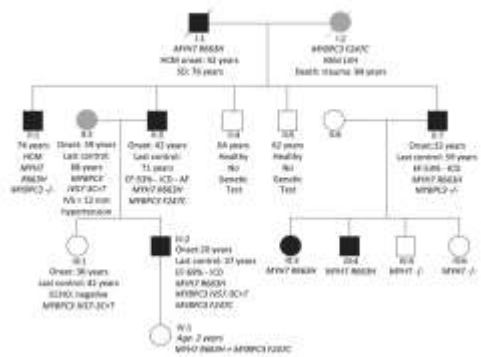
a patient with an early AV block and subsequent severe CHF due to an autosomal dominant familial dilated cardiomyopathy (DCM) and a pathological mutation in the LMNA gene.

$M_{D(AVB)}$ O_{H} $G_{G(AD)}$ $E_{G\text{-}LMNA\ [p.Arg190Trp]\ +\ Focal\ inflammation}$ $S_{D\text{-}IV}$

MOGE(S) describes

- **M m**orpho-functional phenotype (D with conduction defect AVB);
- **O o**rgan involvement, the heart (H) as unique organ involvement;
- **G g**enetic transmission (G), autosomal dominant (AD) transmission pattern;
- **E e**tiology, genetic associated with an LMNA pathological (red) mutation;
- **S s**tage D with NYHA functional class IV.

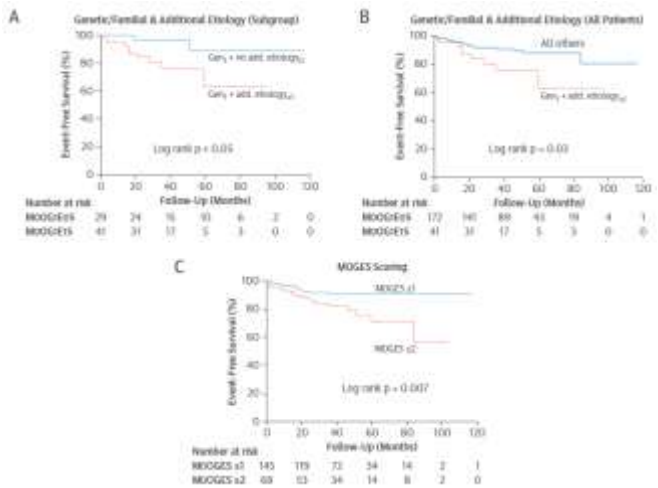
Arbustini et al. **The MOGE(S) Classification** *JACC* 2013;62(22):2046-72



Family member	M O G E
II:1*	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]}$
II:2	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]}$
II:1	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]\ +\ MYBPC3}$
II:2*	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}MYBPC3\ [IVS7\text{-}2C>T]}$
II:3	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]\ +\ MYBPC3\ [IVS7\text{-}2C>T]}$
II:4	$M_{D}\ O_{H}\ G_{AD}\ E_{G}$
II:5	$M_{D}\ O_{H}\ G_{AD}\ E_{G}$
II:7	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]}$
III:1	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}MYBPC3\ [IVS7\text{-}2C>T]}$
III:2	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]\ +\ MYBPC3\ [IVS7\text{-}2C>T]}$
III:3	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]}$
III:4	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]}$
III:5	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}neg}$
III:6	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}neg}$
IV:1	$M_{D}\ O_{H}\ G_{AD}\ E_{G\text{-}LMNA\ [p.R190W]\ +\ MYBPC3\ [IVS7\text{-}2C>T]}$

Event-Free Survival Curves for Pts with DCM (n=213) according to additional etiological/environmental factors and to the MOGE(S) scoring

Hazebroek MR et al. *J Am Coll Cardiol* 2015;66:1313–23



Web application for MOGE(S) nomeclature can be accessed from mobile phones and other devices (http://moges.biomeris.com)

$M_0\,O_0\,G_0\,E_0\,S$

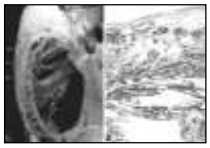
The **MOGE(S) Classification** for a Phenotype–Genotype Nomenclature of Cardiomyopathy Endorsed by the **World Heart Federation** (2013)

- Descriptive Nosology adressing 5 simple attributes of CM disorder
- Ability to integrate comprehensive data into a single descriptor
- As with the universal TNM staging for tumors, it is expected that this description will be improved, revised, modified, and made more comprehensive and user friendly

If a classification is merely a bridge between ignorance and knowledge, it must be pro-active and modified to meet new problems.

A classification that never changes is no longer a classification, but merely a monument to past endeavour.

John F. Goodwin
Emeritus Professor of Clinical Cardiology



ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

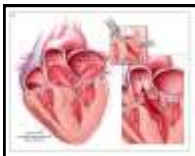
Report of the 1995 WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies *Circulation 1996;93;841-2.*

- ***Arrhythmogenic right ventricular cardiomyopathy*** is characterized by progressive fibro-fatty replacement of right ventricular myocardium, initially with typical regional and later global right and some left ventricular involvement with relative sparing of the septum.
- **Familial disease is common** with autosomal dominant inheritance and incomplete penetrance, a recessive form is described.
- Presentation with arrhythmias and sudden death is common, particularly in the young.

DILATED CARDIOMYOPATHY

Report of the 1995 WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies *Circulation 1996;93;841-2.*

- ***Dilated cardiomyopathy*** is characterized by dilatation and impaired contraction of the left ventricle or both ventricles.
- **It may be** idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage.
- **Histology is nonspecific.**
- **Presentation is usually with heart failure,** which is often progressive. Arrhythmias, thromboembolism, and sudden death are common and may occur at any stage.



HYPERTROPHIC CARDIOMYOPATHY

Report of the 1995 WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;93;841-2.

- ***Hypertrophic Cardiomyopathy*** is characterized by left and/or right ventricular hypertrophy, which is usually asymmetric and involves the interventricular septum.
- Typically, the left ventricular volume is normal or reduced. Systolic gradients are common.
- **Familial disease with autosomal dominant inheritance predominates.** Mutations in sarcomeric contractile protein genes cause disease.
- **Typical morphologic changes** include myocyte hypertrophy and disarray surrounding areas of increased connective tissue.
- **Arrhythmias and sudden death are common.**

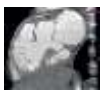
RESTRICTIVE CARDIOMYOPATHY

Report of the 1995 WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies *Circulation 1996;93;841-2.*

- ***Restrictive cardiomyopathy*** is characterized by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near normal systolic function and wall thickness.
- Increased interstitial fibrosis may be present.
- **It may be idiopathic or associated with other disease** (e.g. amyloidosis, endomyocardial disease with or without hypereosinophilia).

2008 proposed classification system of the Cardiomyopathies

European Heart Journal (2008) **29**, 270–276
doi:10.1093/eurheartj/ehm342



UNCLASSIFIED CARDIOMYOPATHIES

LEFT VENTRICULAR NON-COMPACTION (LVNC)

- **LVNC** is characterized by prominent LV trabeculae and deep inter-trabecular recesses. The myocardial wall is often thickened with a thin, compacted epicardial layer and a thickened endocardial layer. In some pts, LVNC is associated with LV dilatation and systolic dysfunction, which can be transient in neonates.
- It is not clear whether LVNC is a separate cardiomyopathy, or merely a congenital or acquired morphological trait shared by many phenotypically distinct cardiomyopathies. LVNC occurs in isolation and in association with congenital cardiac disorders such as Ebstein's anomaly or complex cyanotic heart disease and some neuromuscular diseases.
- The population prevalence of isolated LVNC is not known, but it is reported in 0.014% of consecutive echocardiograms. In large paediatric series, LVNC is reported to be the commonest cause of unclassified cardiomyopathies.
- LVNC is frequently familial, with at least 25% of asymptomatic relatives having a range of echocardiographic abnormalities. Genes in which causative mutations have been identified include G 4.5 encoding taffazin (X-linked), alpha dystrobrevin, ZASP, actin, lamin A/C and a locus on chromosome 11 p 15.

2008 proposed classification system of the Cardiomyopathies

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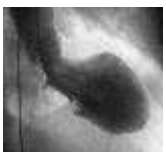

UNCLASSIFIED CARDIOMYOPATHIES

TAKOTSUBO CARDIOMYOPATHY

- ***Transient left ventricular apical ballooning syndrome or takotsubo cardiomyopathy*** is characterized by transient regional systolic dysfunction involving the LV apex and/or mid-ventricle in the absence of obstructive coronary disease on coronary angiography.
- Pts present with an abrupt onset of angina-like chest pain, and have diffuse T-wave inversion, sometimes preceded by ST-segment elevation, and mild cardiac enzyme elevation. Originally described in Japan, the condition is reported in Caucasian populations in Europe and North America, mostly in post-menopausal women.
- Symptoms are often preceded by emotional or physical stress. Norepinephrine concentration is elevated in most pts and a transient, dynamic intraventricular pressure gradient is reported in 16% of cases. LV function usually normalizes over a period of days to weeks and recurrence is rare.

INFLAMMATORY CARDIOMYOPATHY

Report of the 1995 WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies *Circulation 1996;93;841-2.*

- ***Inflammatory Cardiomyopathy*** is defined by myocarditis in association with cardiac dysfunction.
- ***Myocarditis*** is an inflammatory disease of the myocardium and is diagnosed by established histological, immunological, and immunohistochemical criteria.
- Idiopathic, autoimmune, and infectious forms of inflammatory cardiomyopathy are recognized.
- Inflammatory myocardial disease is involved in the pathogenesis of dilated cardiomyopathy and other cardiomyopathies, eg, Chagas' disease, HIV, enterovirus, adenovirus, and cytomegalovirus.