Update in Cardiomyopathies: Their New Classifications and Importance of Mixed Phenotypes

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Cesarea, 2008

ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY

DONALD TEARE

From the Department of Pathology, St. George's Hospital

Received January 7, 1957

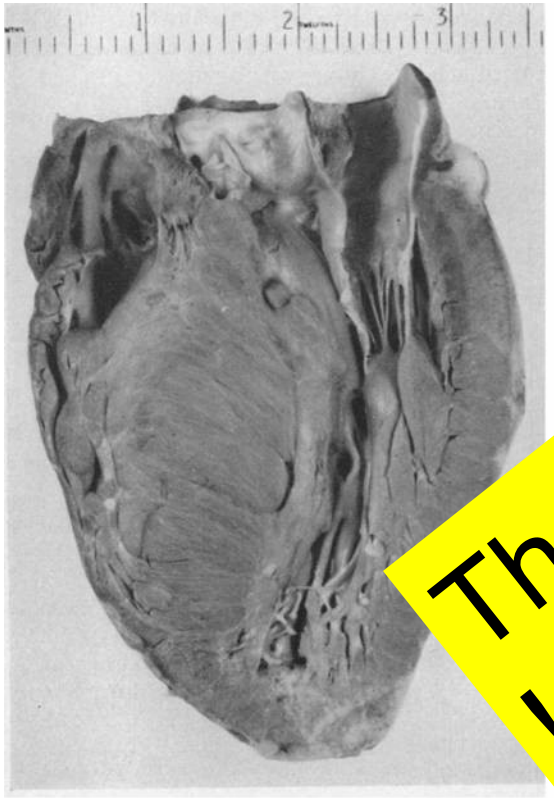


FIG. 1.—Case 1. Localized hypertrophy of the interventricular septum.

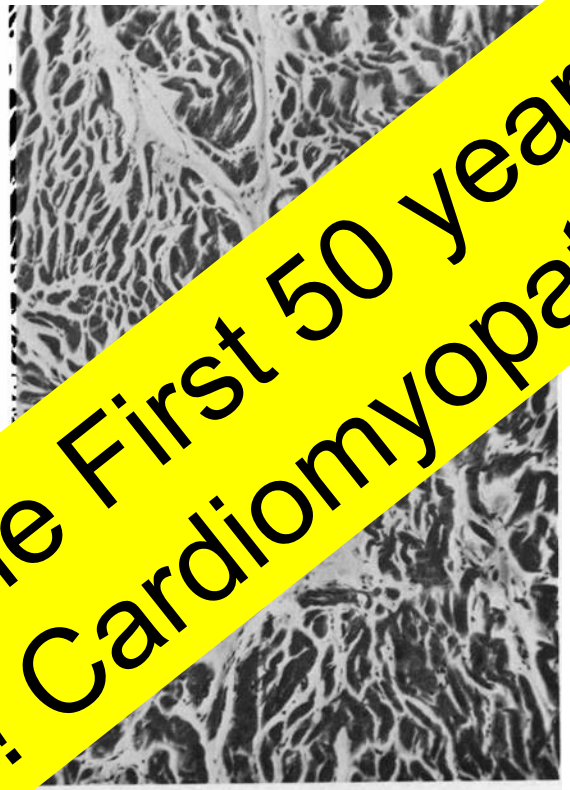
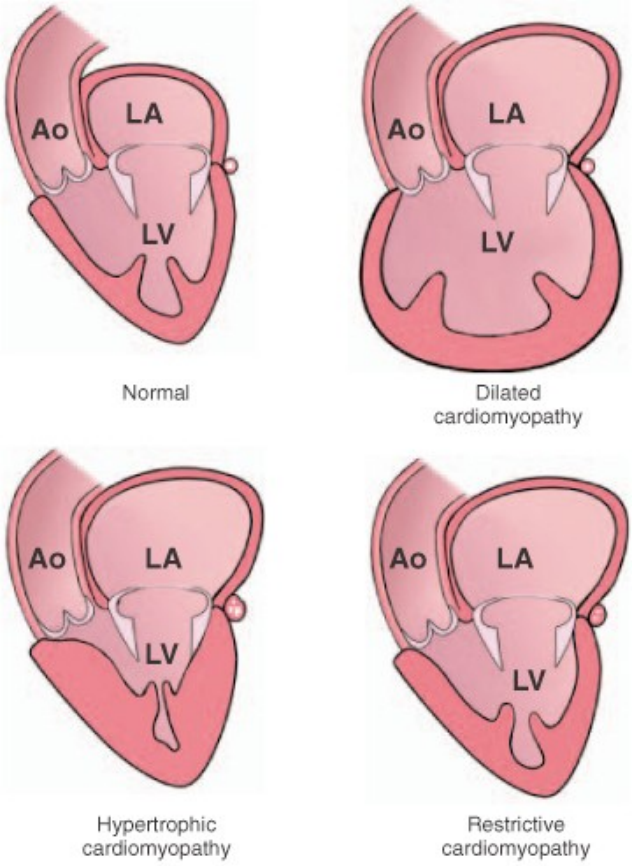


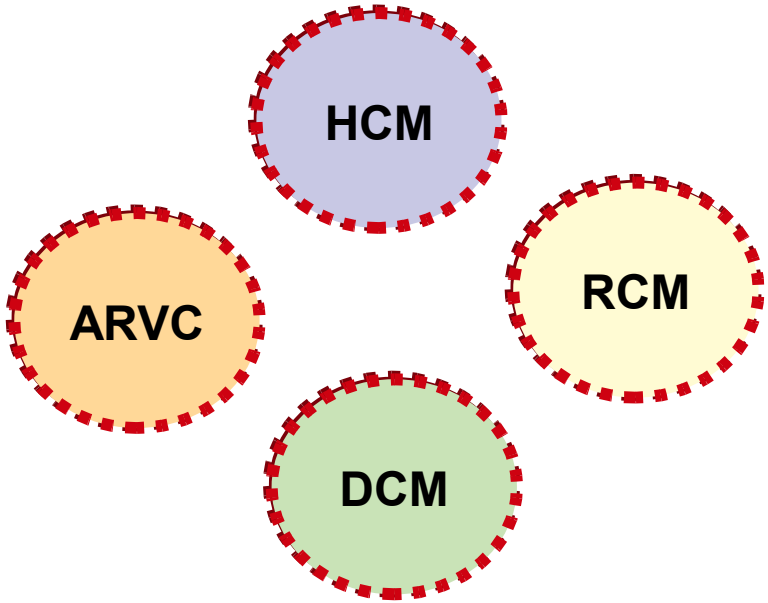
FIG. 2.—Case 1. Disordered arrangement of muscle bundles with variations in size of individual fibres (H & E × 80).

The First 50 years of ! Cardiomyopathies

Br Heart J 1958:20:1-8

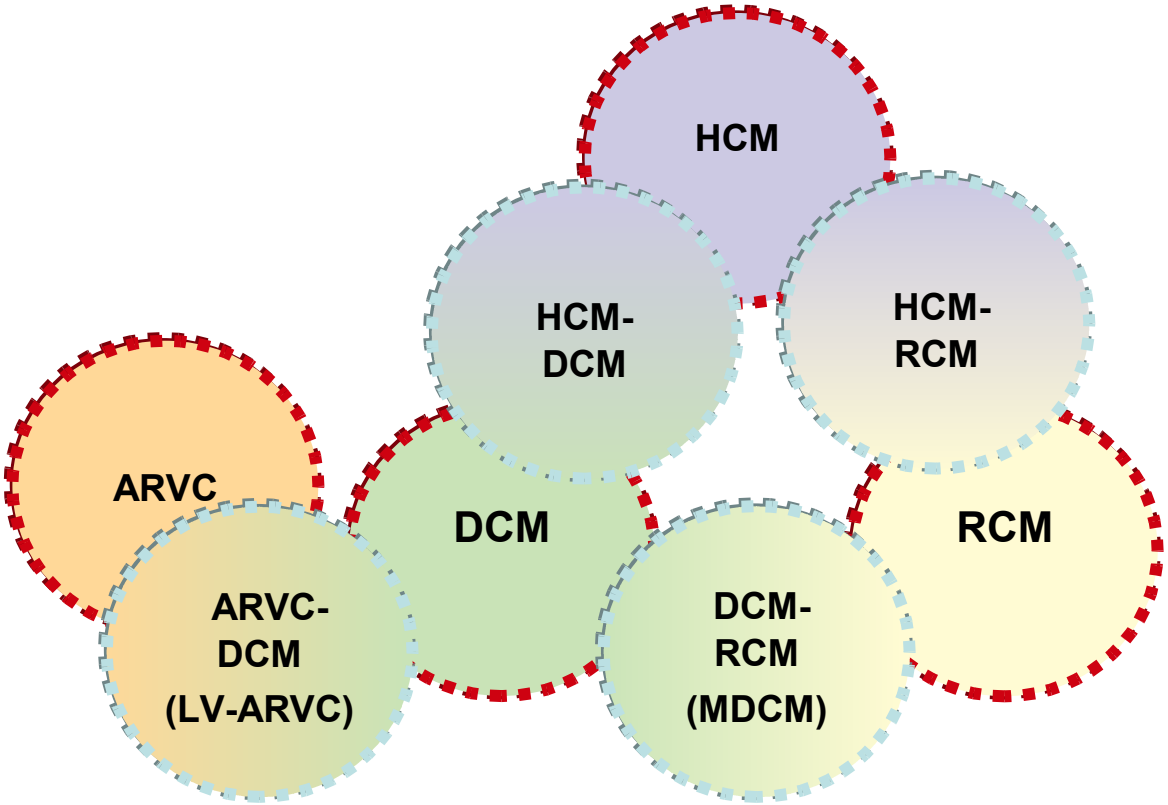
Initial Classification Into 4 Major Phenotypes



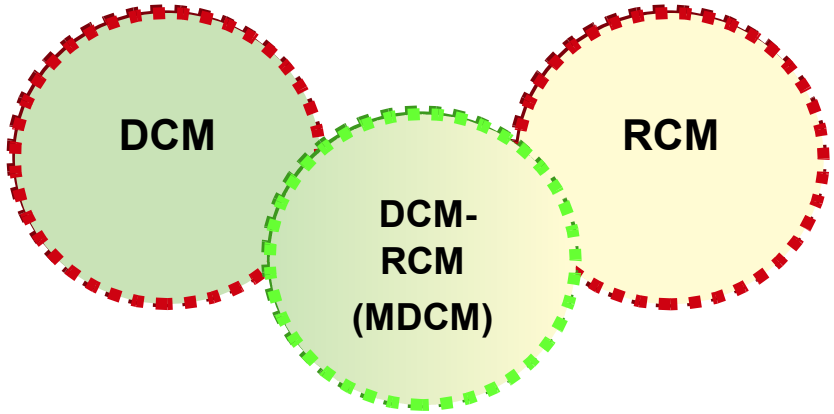


Modified from Roberts W, Human Path, 1975

Overlapping phenotypes

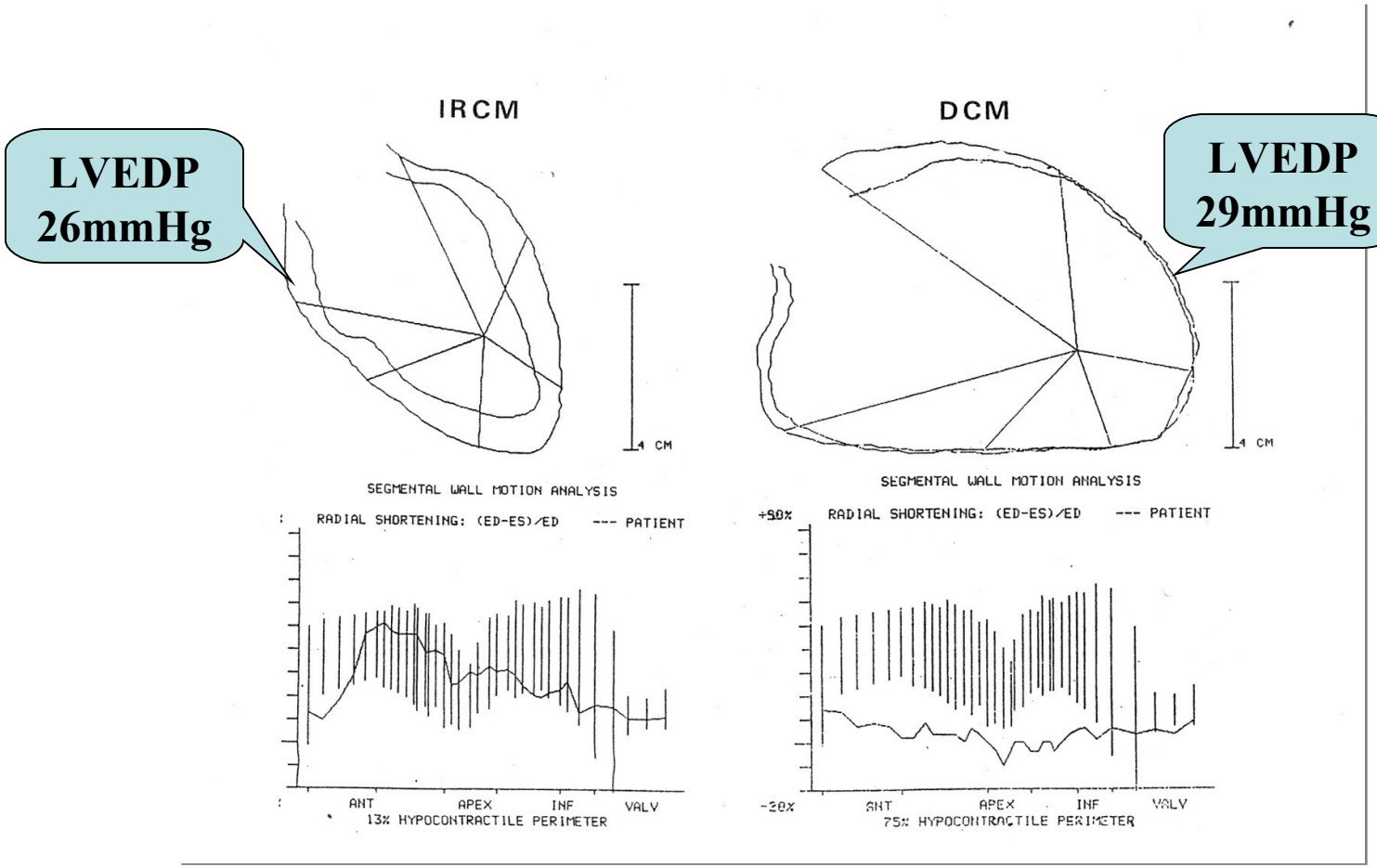


Overlapping DCM / RCM (Nondilated DCM (MDCM

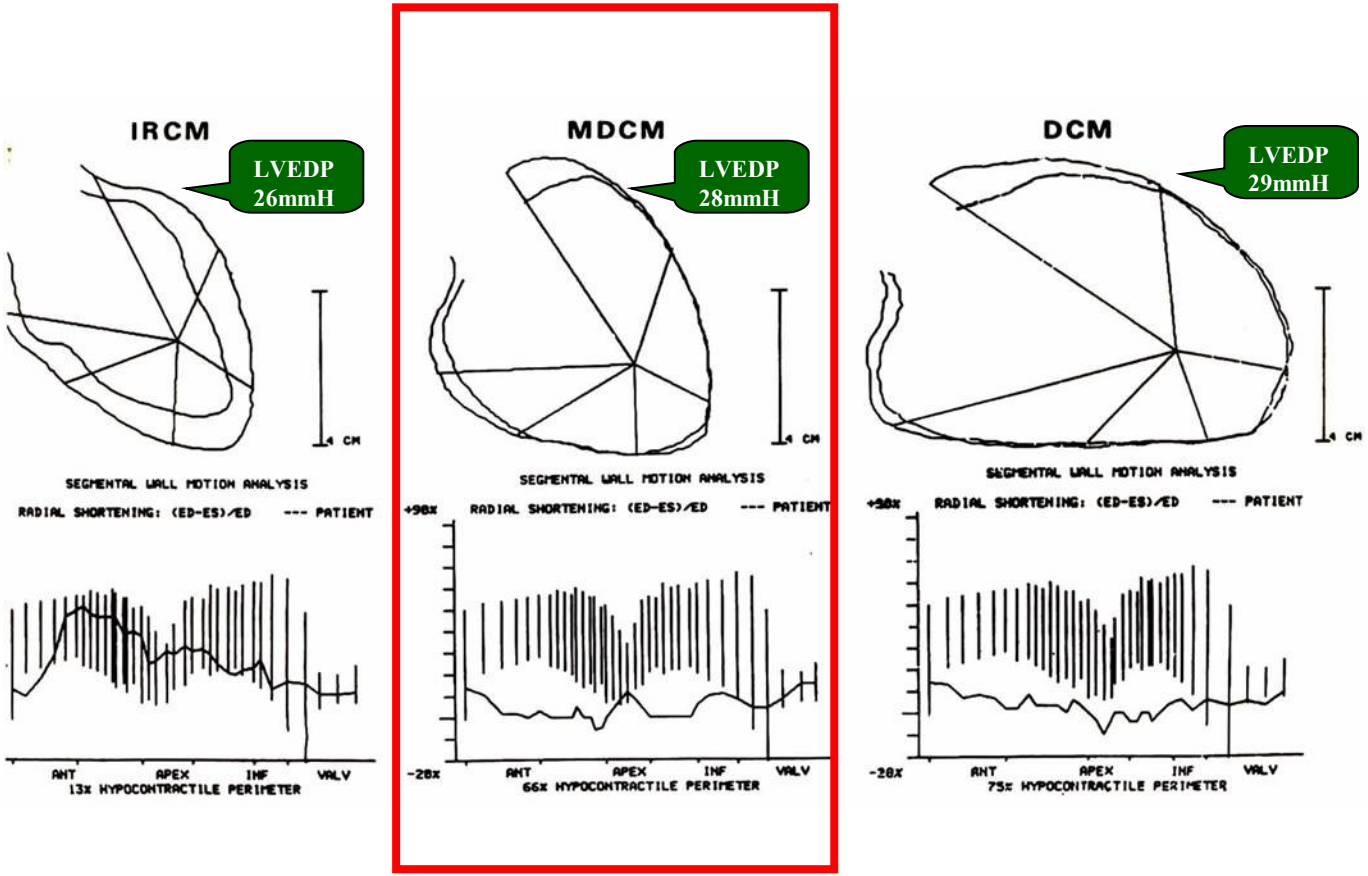


?Possible association with LMNA mutations

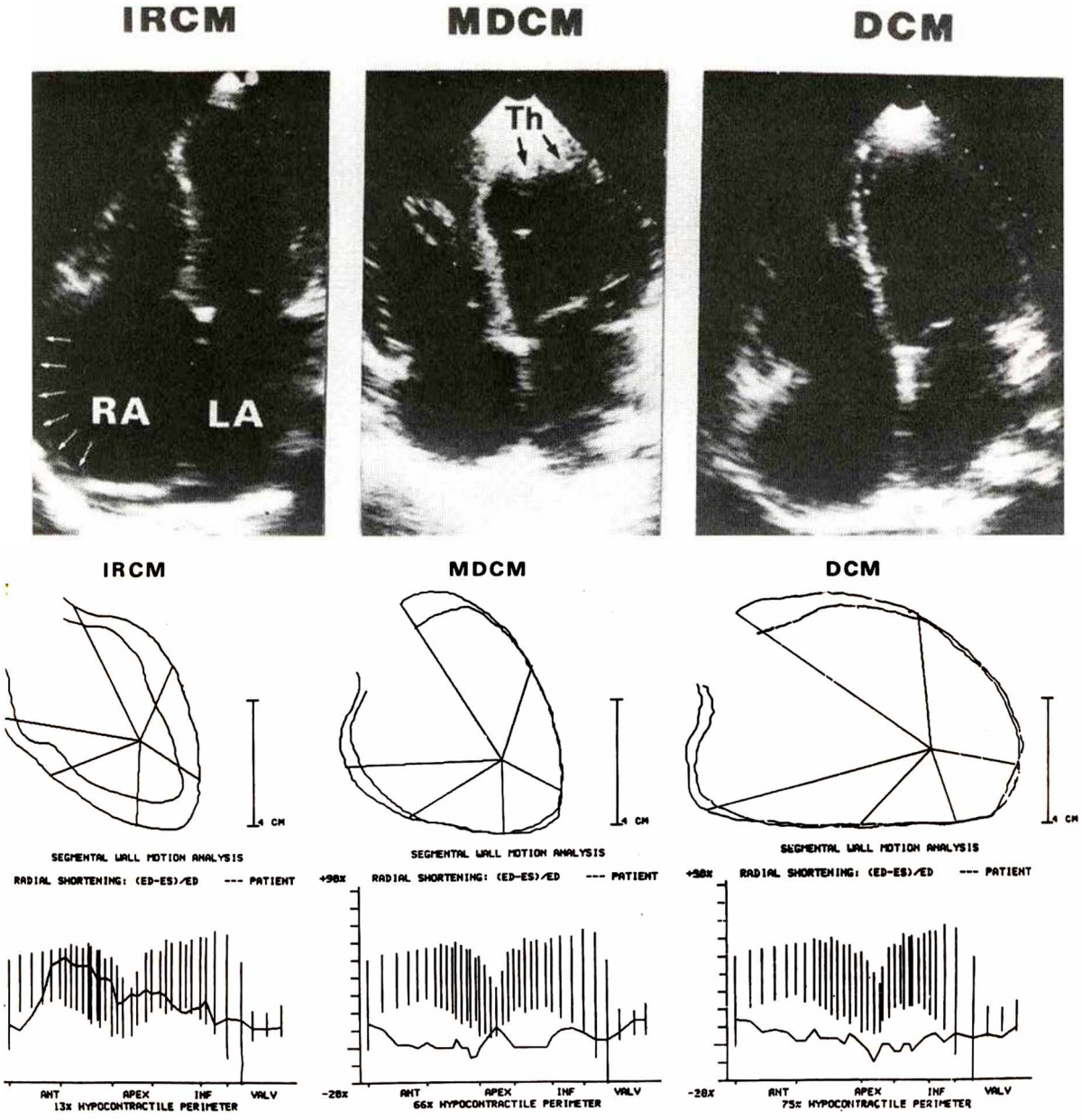
The paradigms of diastolic and systolic HF: Restrictive and Dilated Cardiomyopathy



Keren A, BillinghamME, Popp RL. J Am Soc Echo 1988;1:78-87



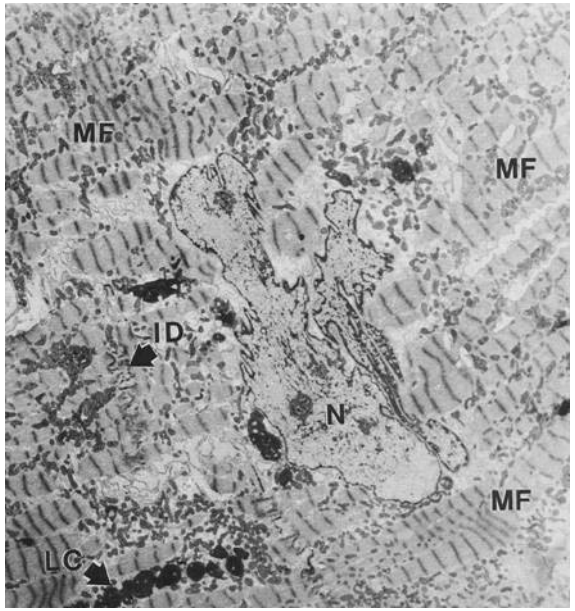
Keren A, BillinghamME, Popp RL. J Am Soc Echo 1988;1:78-87



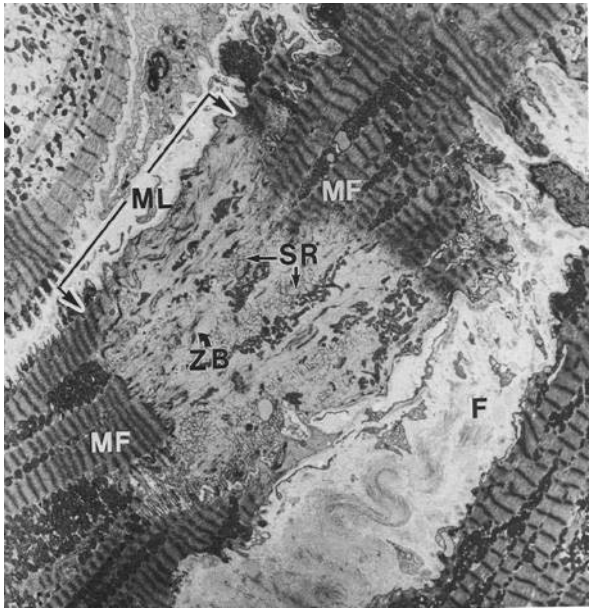
Keren A, BillinghamME, Popp RL. J Am Soc Echo 1988;1:78-87

Electronmicrographic Patterns

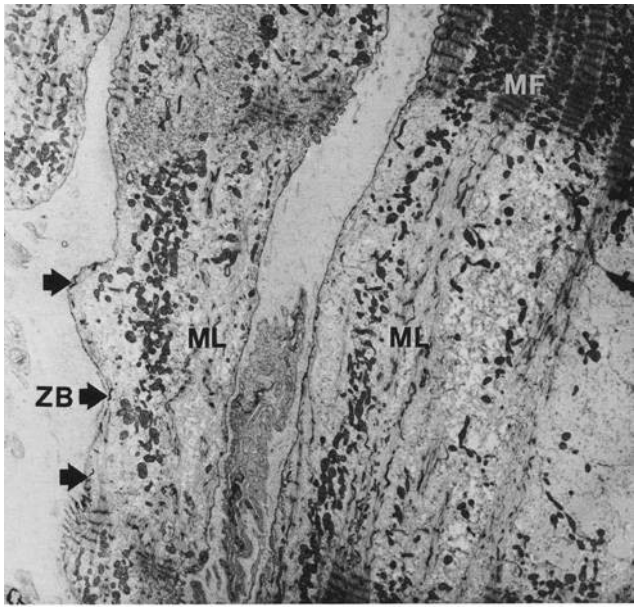
IRCM



MDCM



DCM

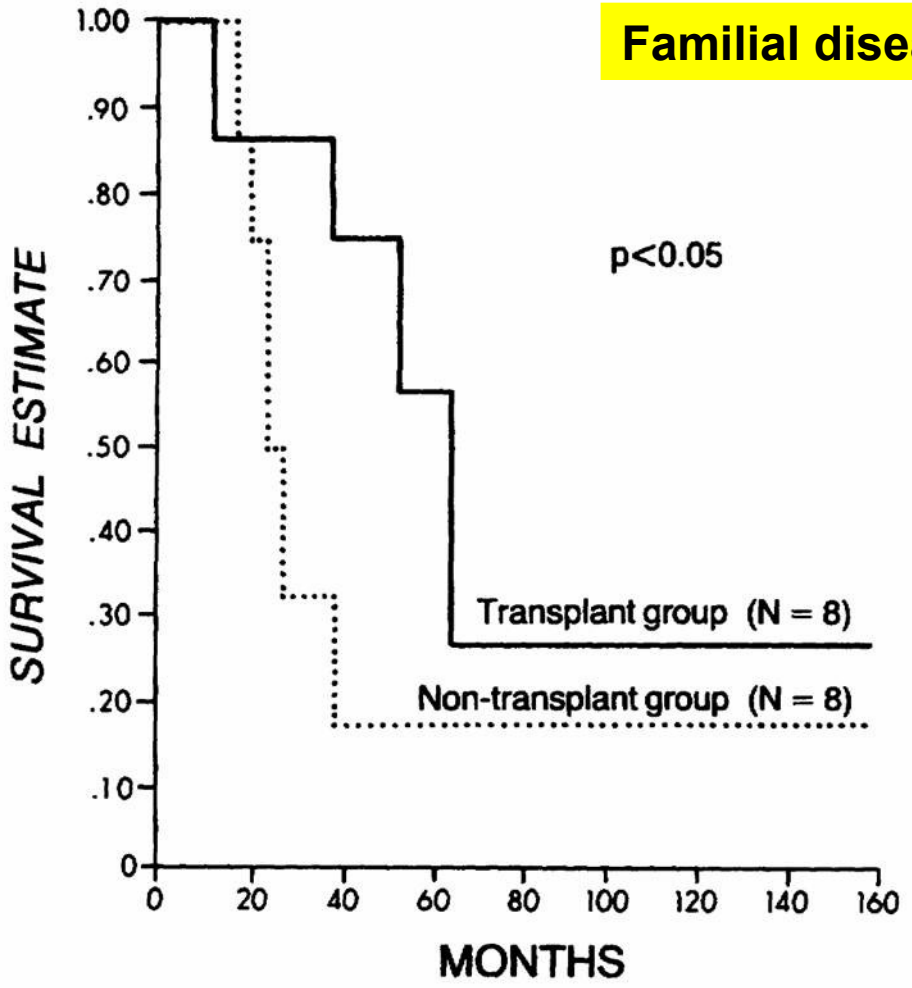


MYOFIBRILLAR LOSS MAXIMAL IN DCM, LESS IN MDCM, ABSENT IN IRCM

Keren A, BillinghamME, Popp RL. et al. Circulation 1985

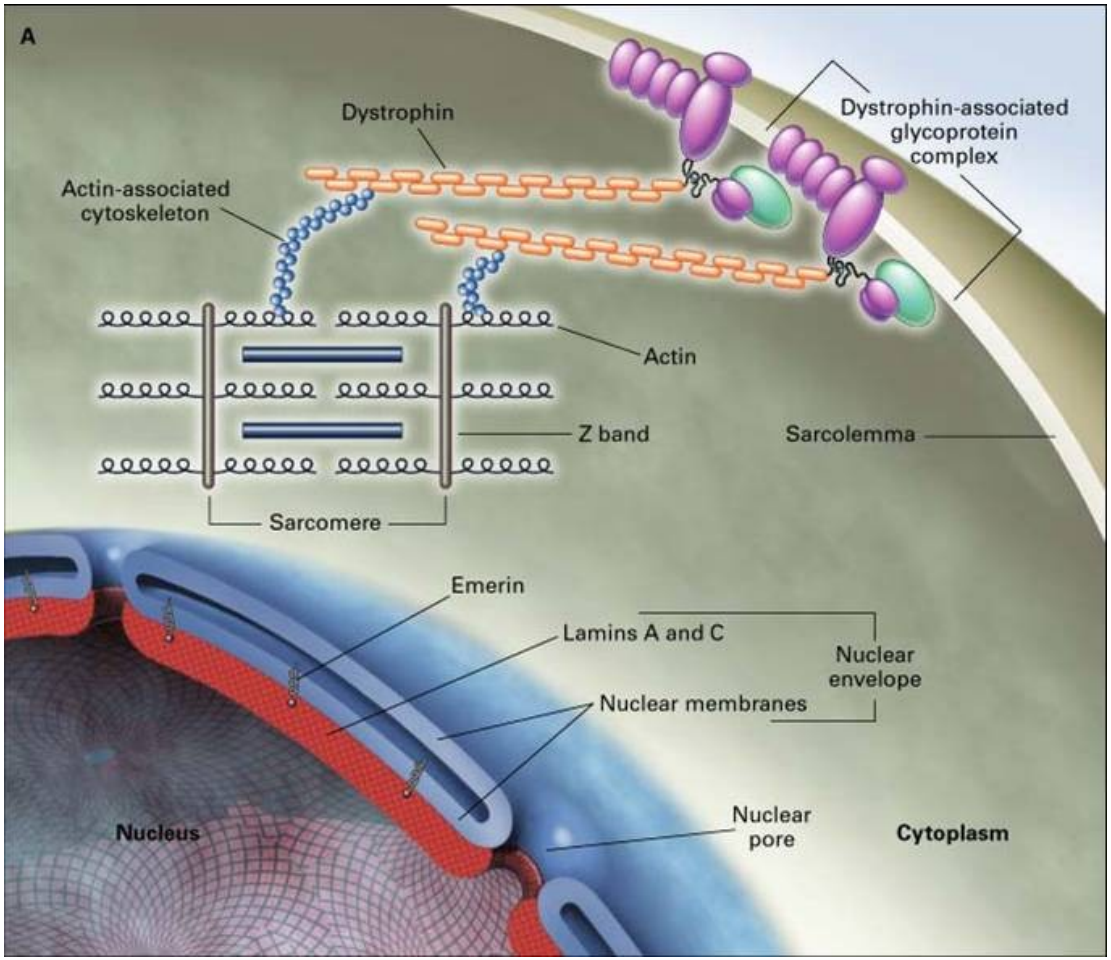
Keren et al **Mildly Dilated Congestive Cardiomyopathy**

Familial disease in 50%



Circulation 1990;81:506-17

Lamin A/C



- **DCM**
- **Atrial arrhythmias, sinus bradycardia, heart block**
- **Sudden death**

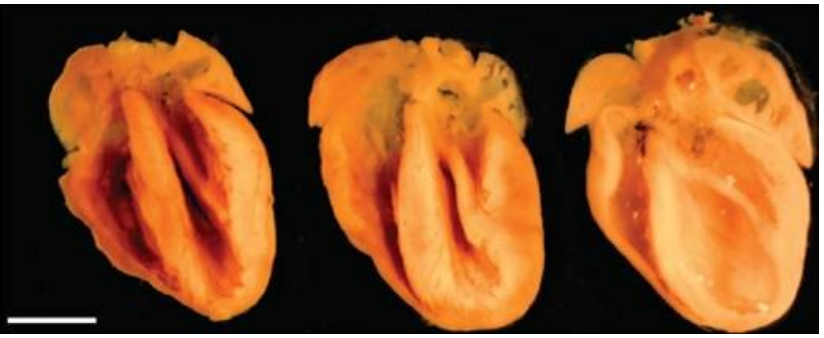
Fatkin et al: NEJM 1999

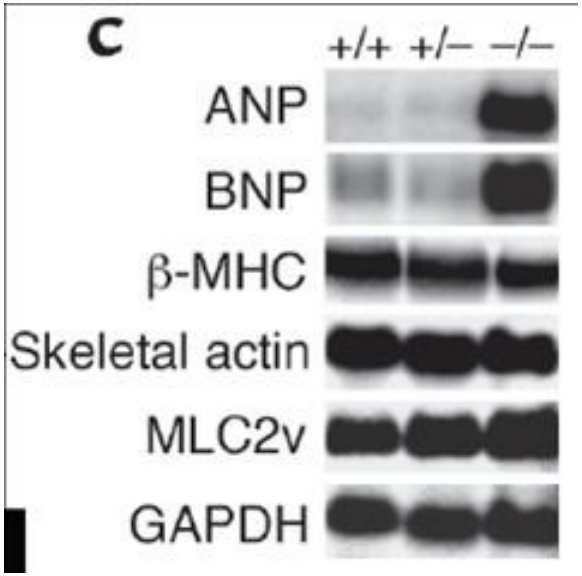
Lamin A/C Phenotypes

- DCM with skeletal muscle involvement (MDDC1)
- Severe DCM (early onset, sudden death)
- Progressive conduction disease – late DCM
- Variable mild skeletal muscle involvement
- Partial lipodystrophy
- Progeria
- Charcot-Marie-Tooth disease

Lamin A/C Knockout Model

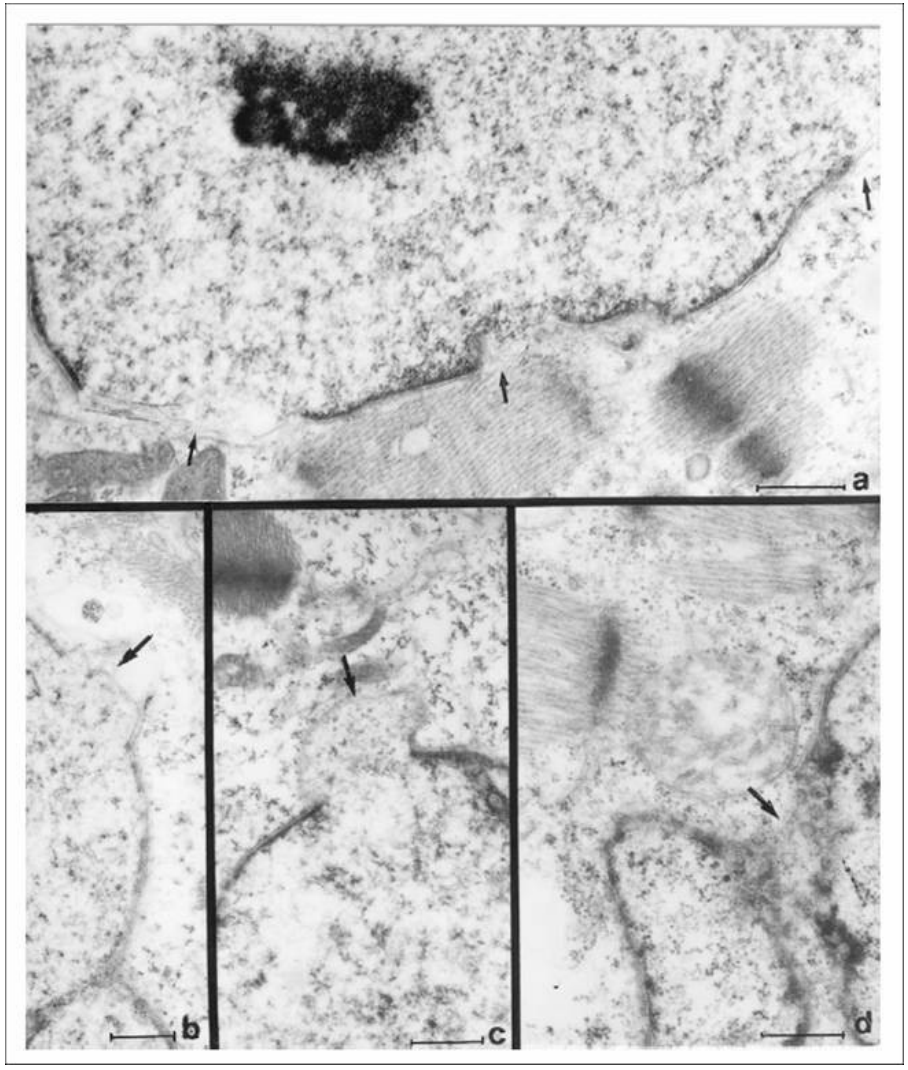
WT LMNA +/- LMNA -/-



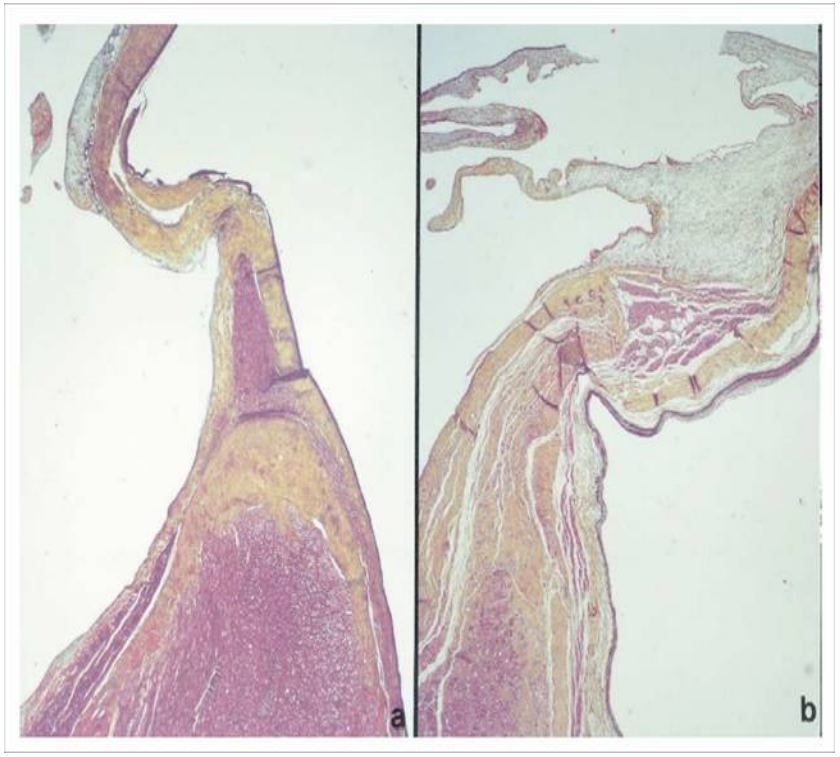


Nikolova V et al. J Clin Invest 2004;113:357-369

LMNA Gene Defects : Nuclear Membrane Fragmentation and Pathologic Degeneration of the AV Junction

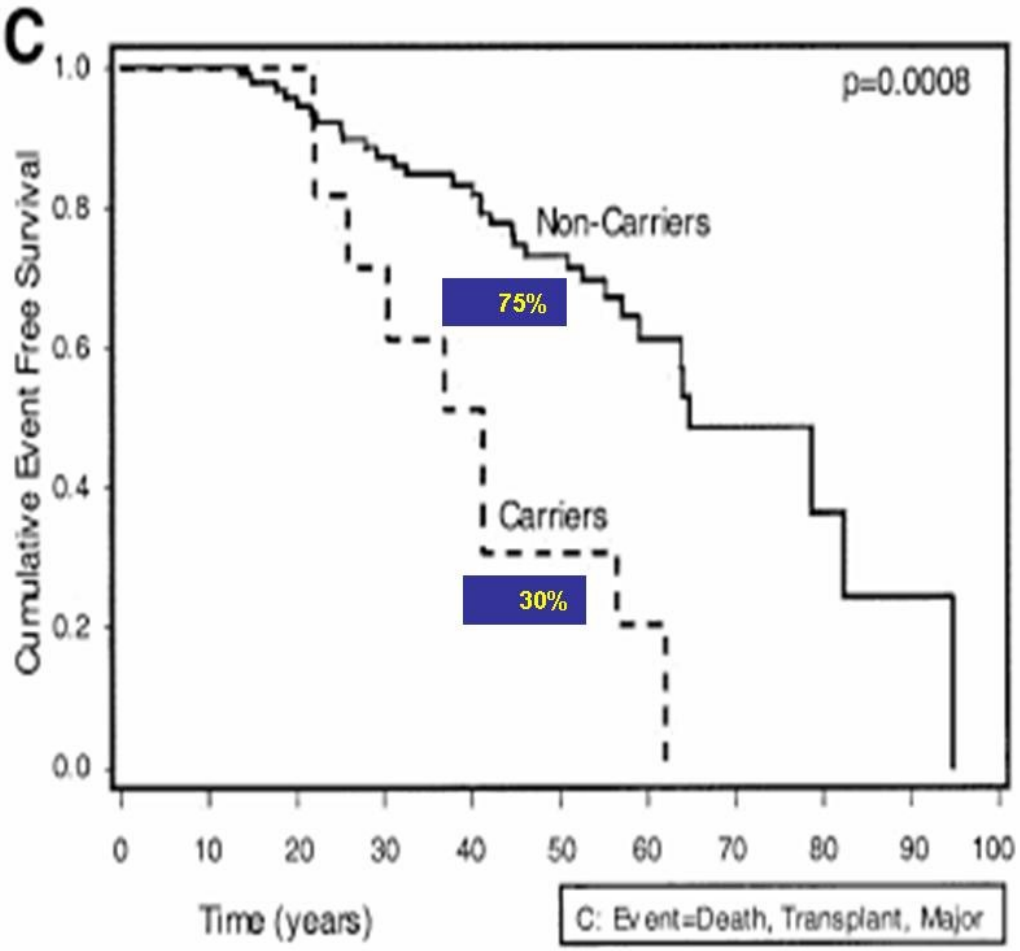


DCM



Arbustini E et al.
JACC 2002;39:981-90

Survival in Lamin A/C Mutation



Taylor M et al. JACC 2003;41:771-80

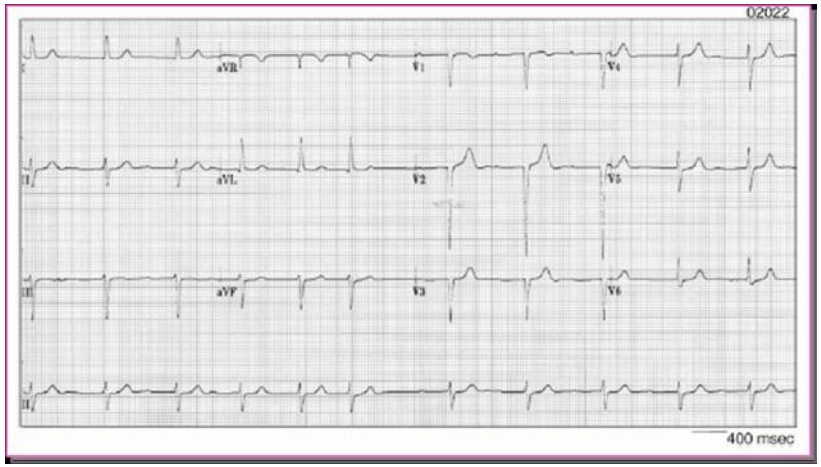
Familial DCM Registry Research Group

Predictors of LMNA Mutation

- Skeletal muscle invvolvement (p<0.001)
- Supraventricular arrhythmias (p=0.003)
- Conduction defect (p=0.01)
- “Mildly DCM” (p=0.006)

Taylor M et al. JACC 2003;41:771-80
Familial DCM Registry
Rresearch Group

Meta-analysis of Clinical Characteristics of 299 Carriers of LMNA Gene Mutations



	Published patients (n=299)
Dysrhythmia	61%
LVEDD (mm)	52
FS	28%
No. of patients died	75
Age at death (years)	46
Sudden death	46%
With pacemaker	46%
Without pacemaker	54%

van Berlo JH, Pinto YM et al.
J Mol Med 2005;83:79-83

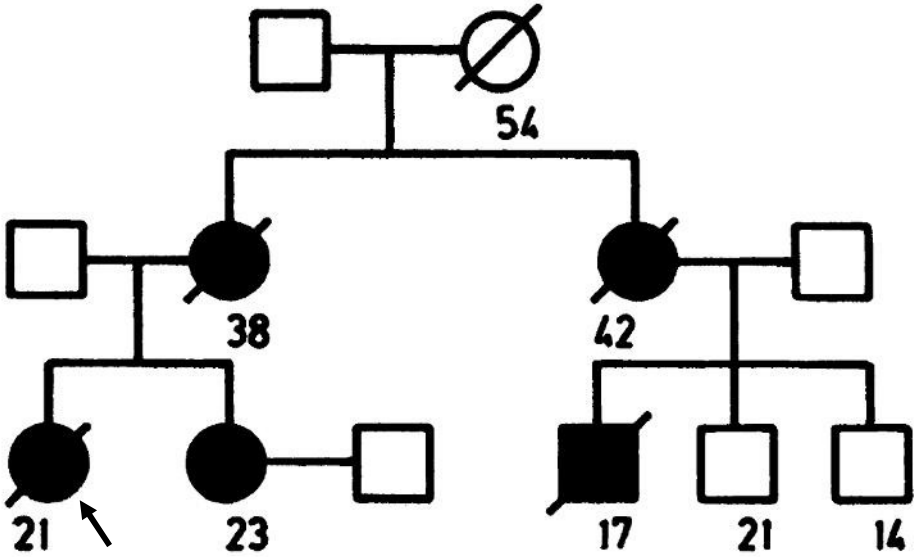
MDCM
((Non-dilated DCM

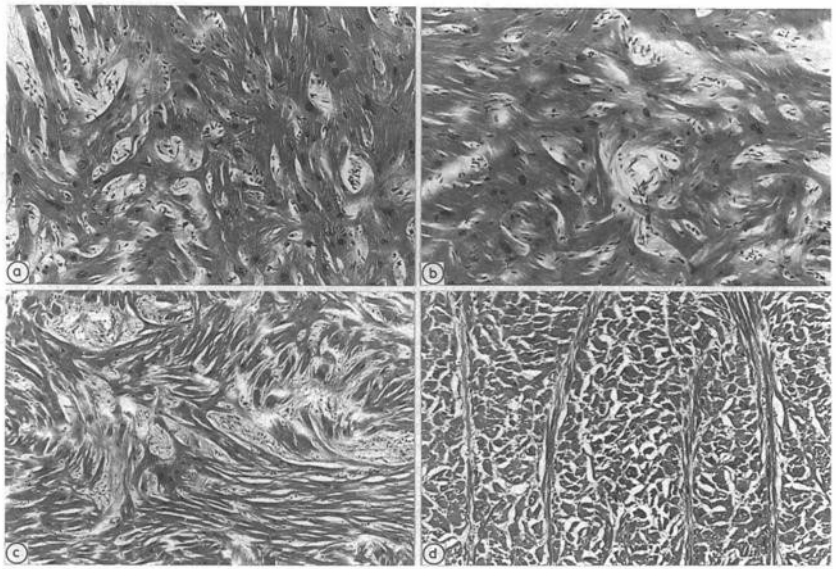
- Rare entity with familial occurrence in 50% of cases
- Poor prognosis despite preservation of the heart size
- In some, but not all series, LMNA mutations were associated with typical MDCM phenotype

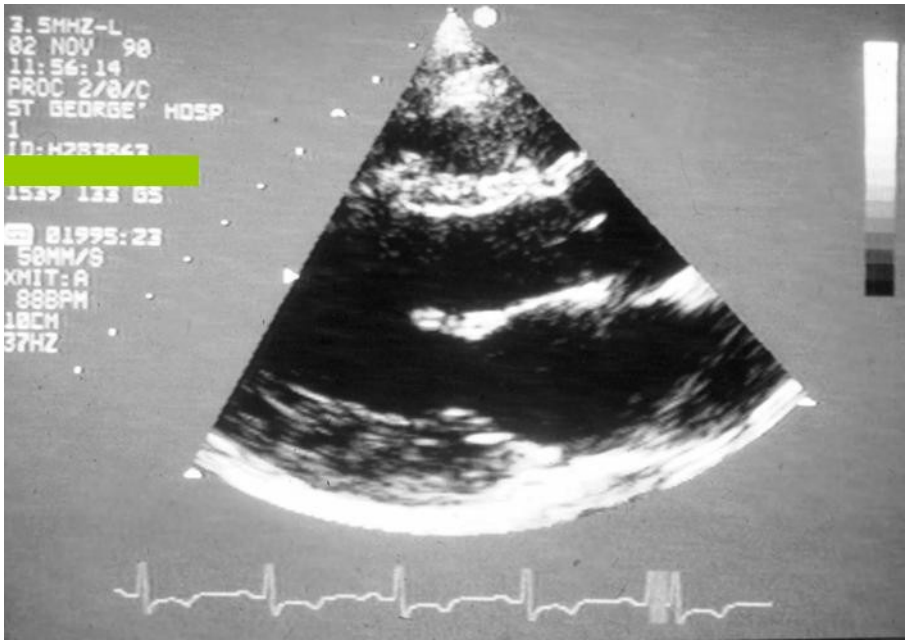
Br Heart J 1990;**63**:287–90

Hypertrophic cardiomyopathy without hypertrophy: two families with myocardial disarray in the absence of increased myocardial mass

W J McKenna, J T Stewart, P Nihoyannopoulos, F McGinty, M J Davies



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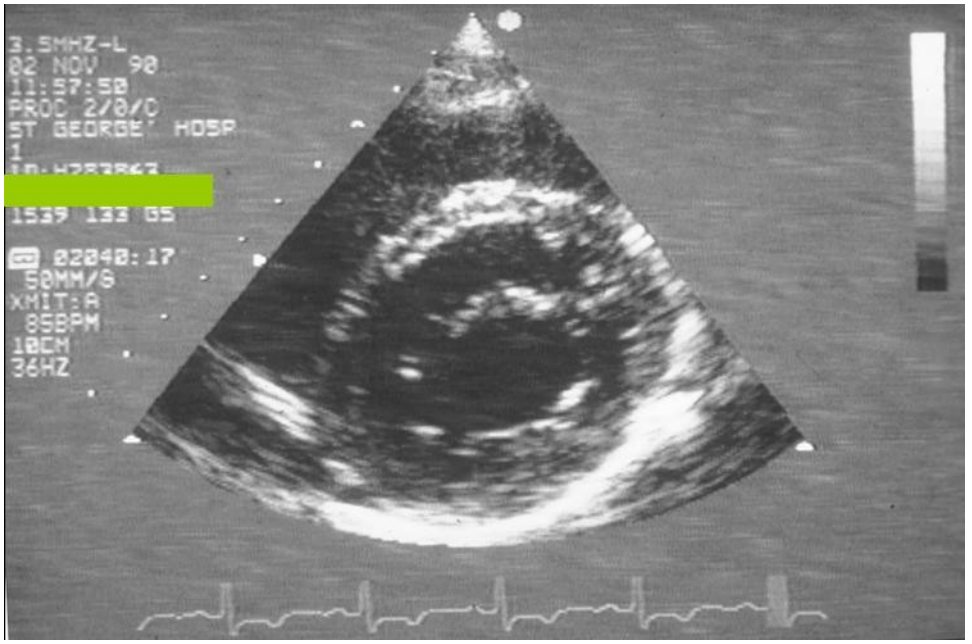
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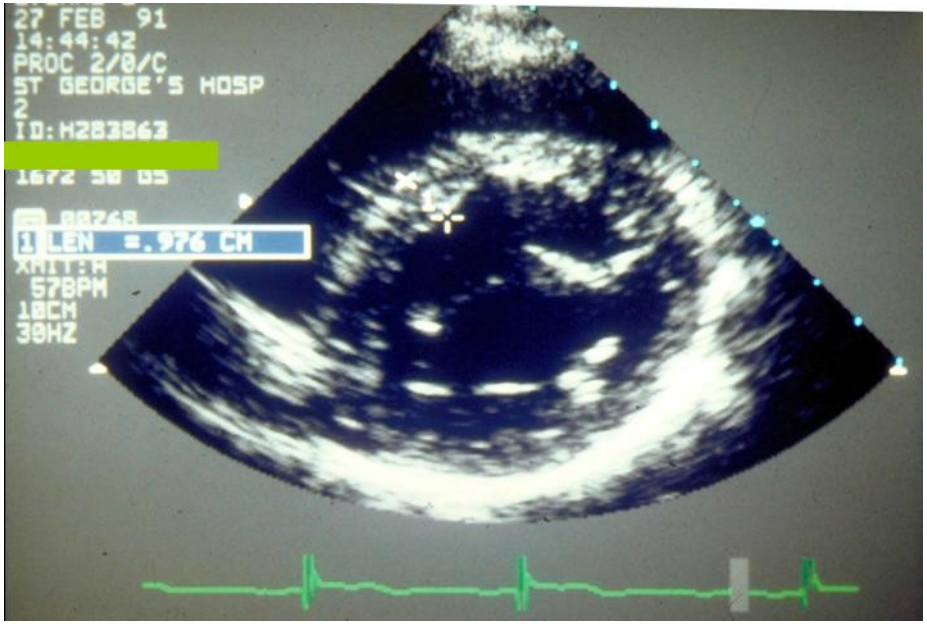
27 FEB 91
14:44:42
PROC 2/0/C
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1672 50 05
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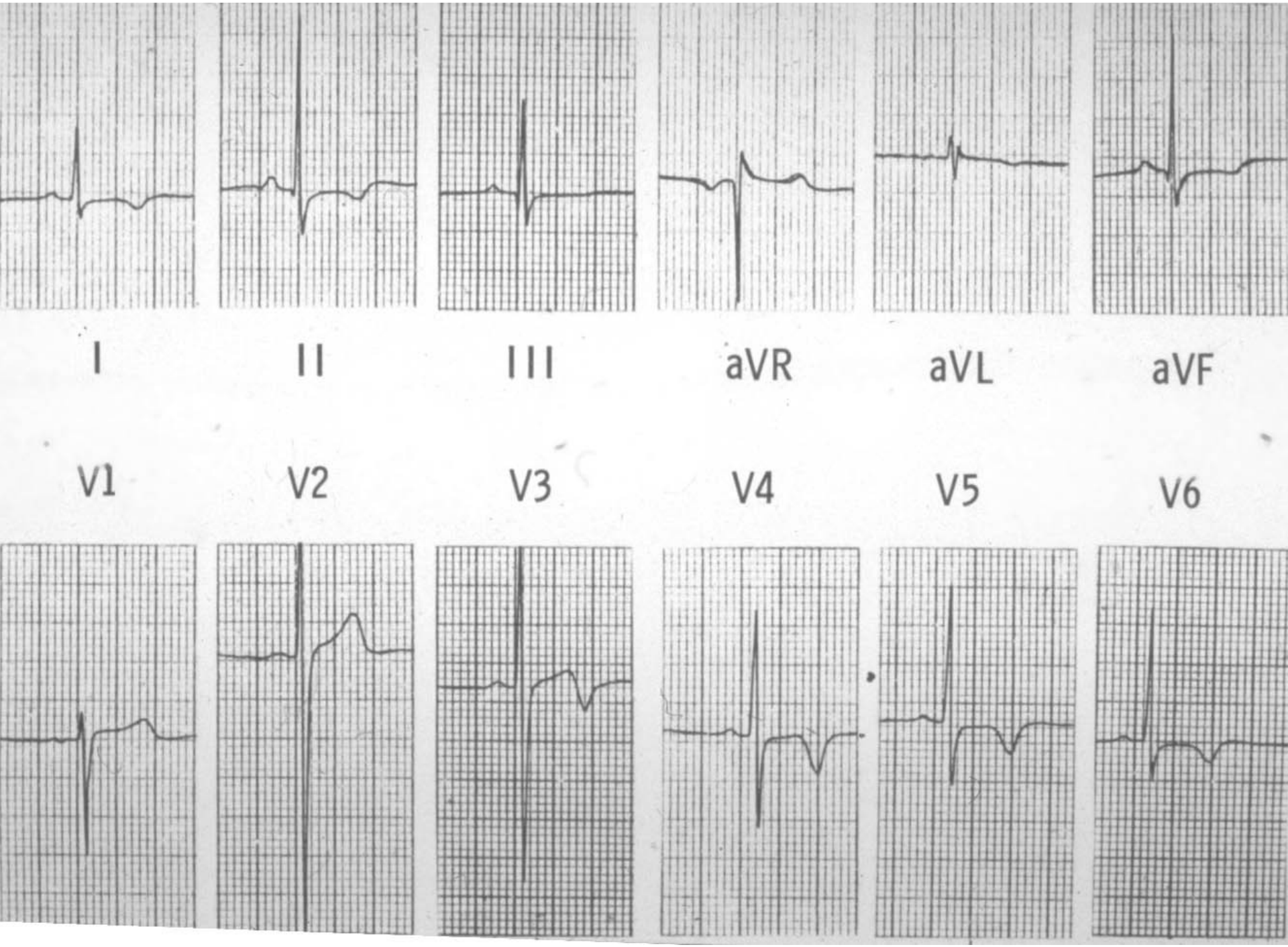
XMIT:A
57BPM
10CM
39HZ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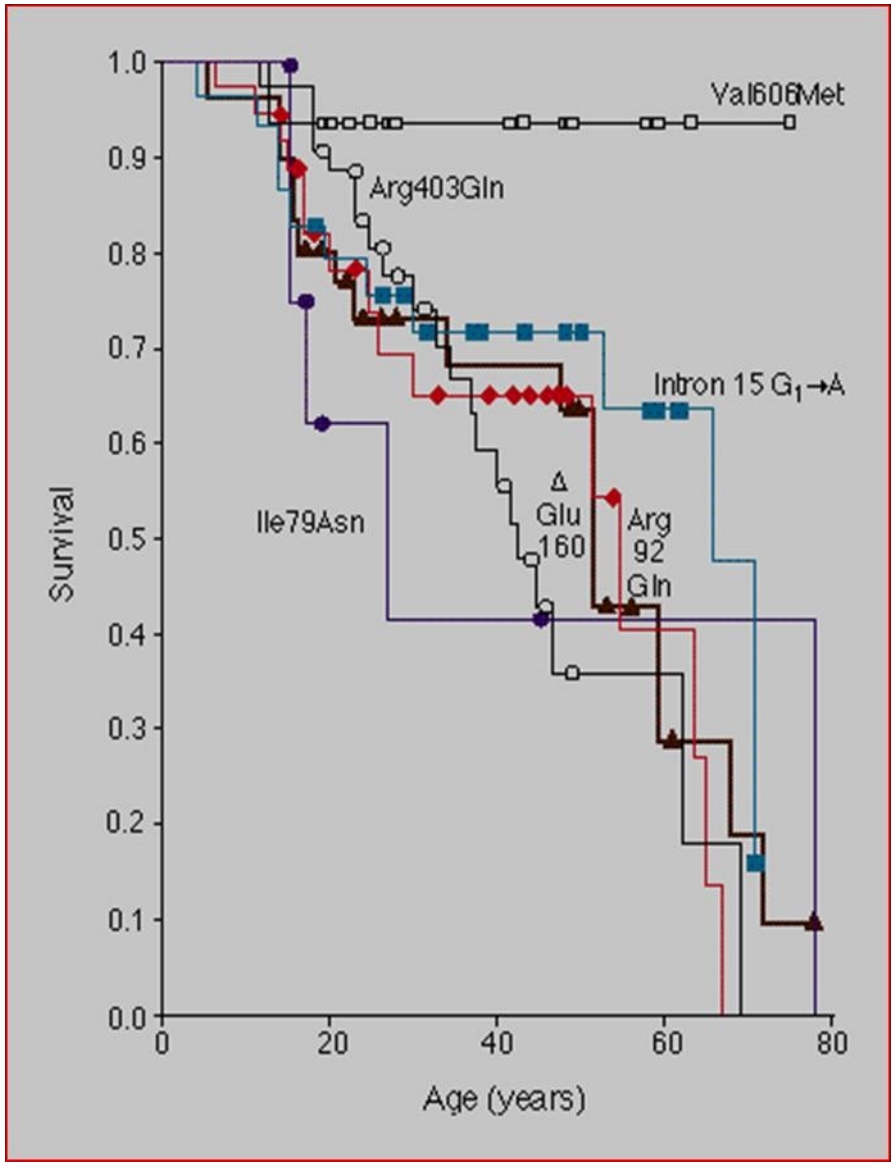
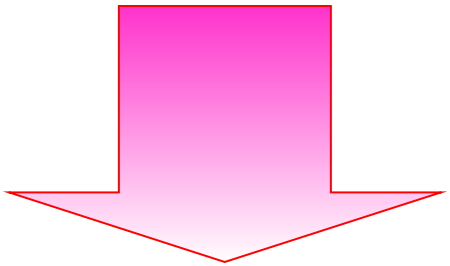
V5
V6

Troponin T Mutations & Survival



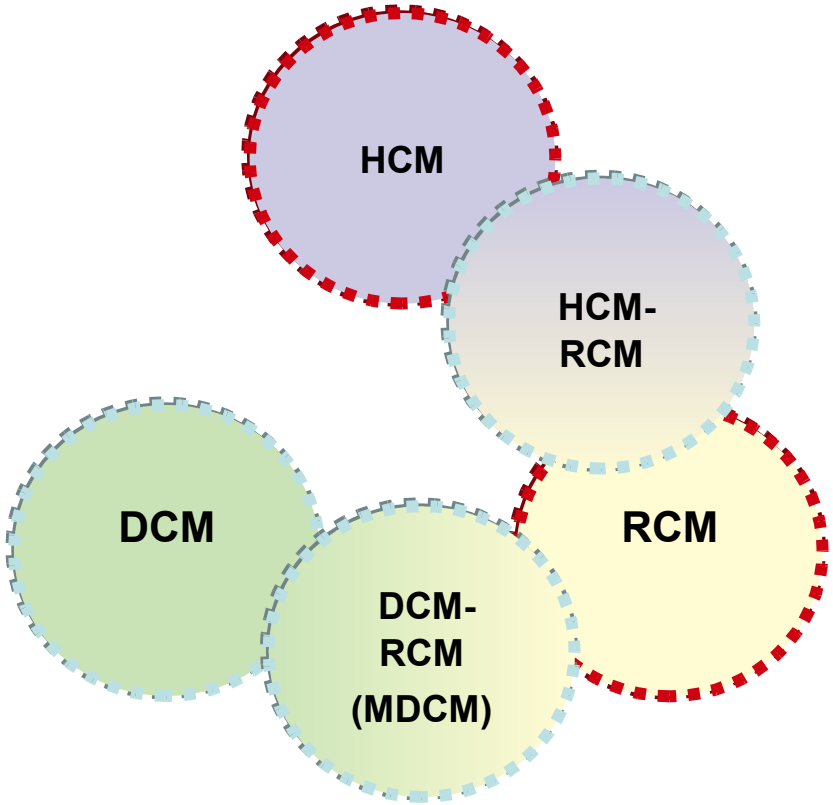
Troponin T

- Mild or absent LVH, severe myocyte disarray
- abnormal vascular responses
- premature sudden death

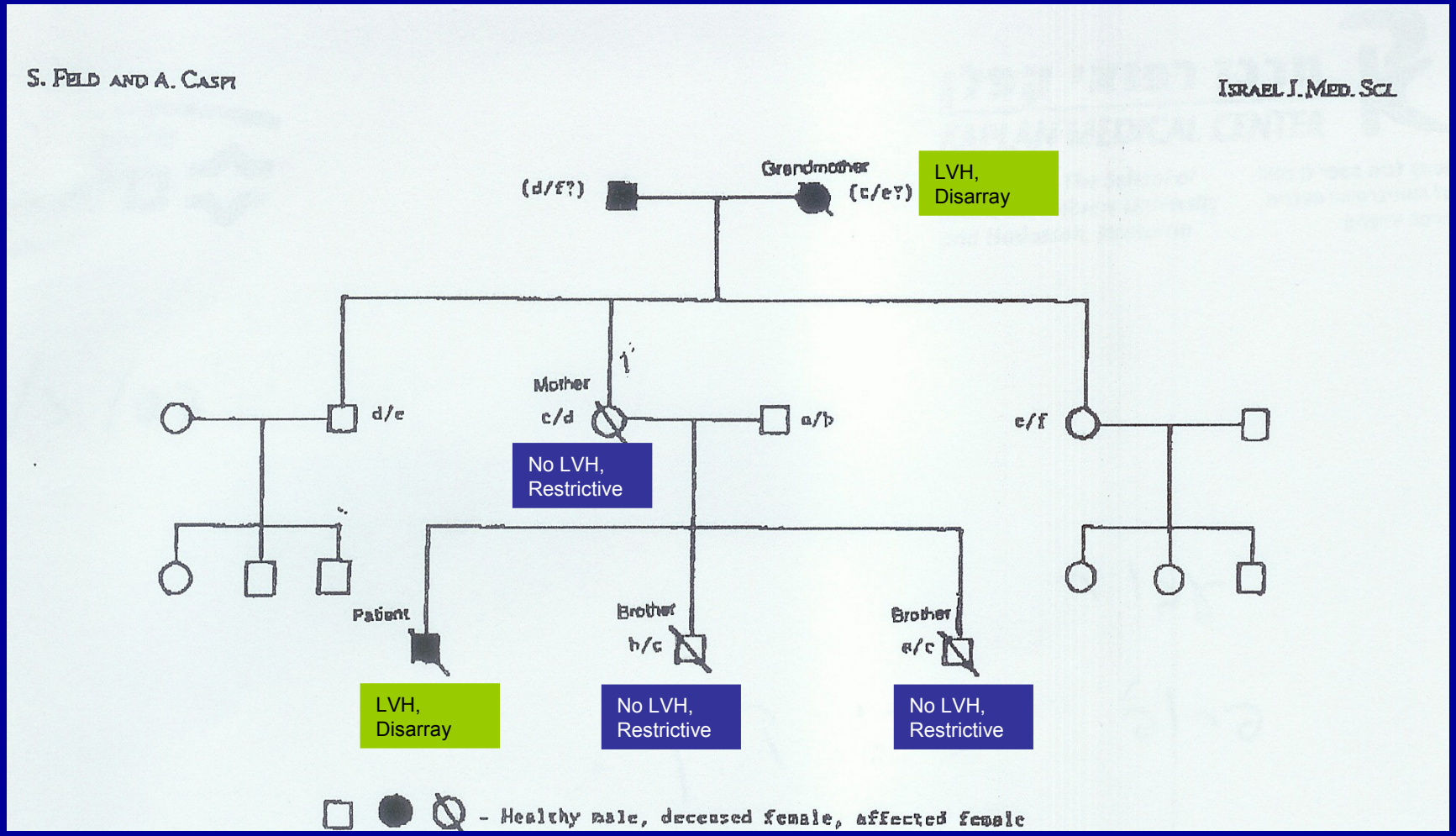


Severe Prognosis

Overlapping HCM/RCM

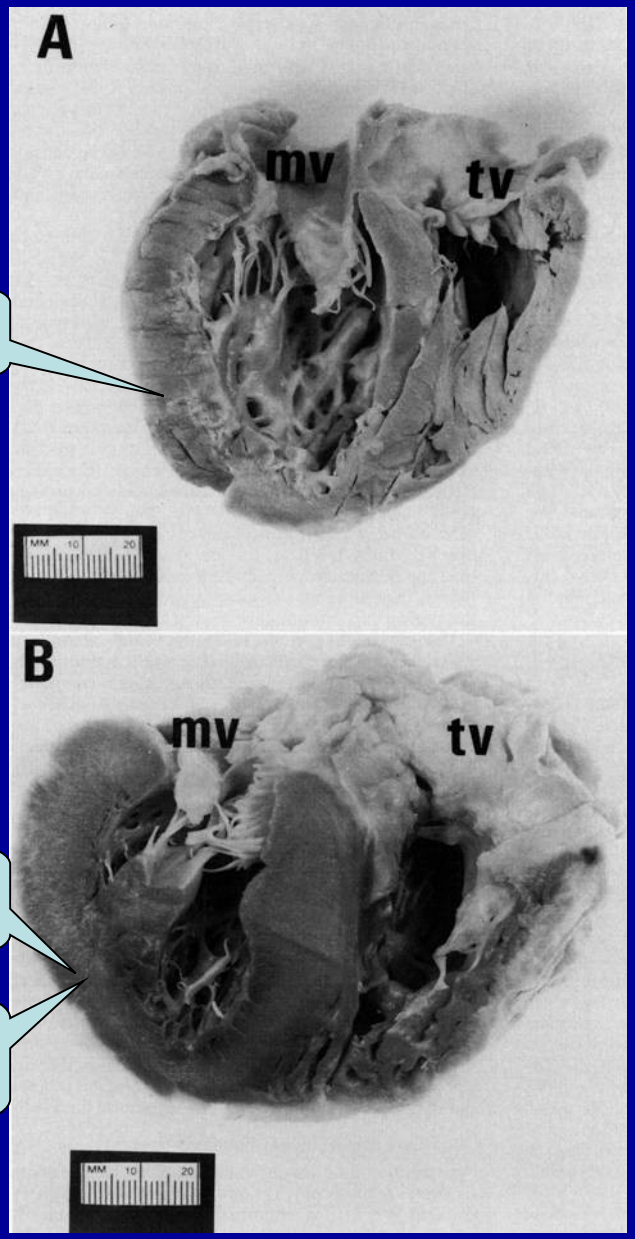


Common HLA Haplotype Associated with HCM or RCM



Isr J Med Sci 1992;28:277-80

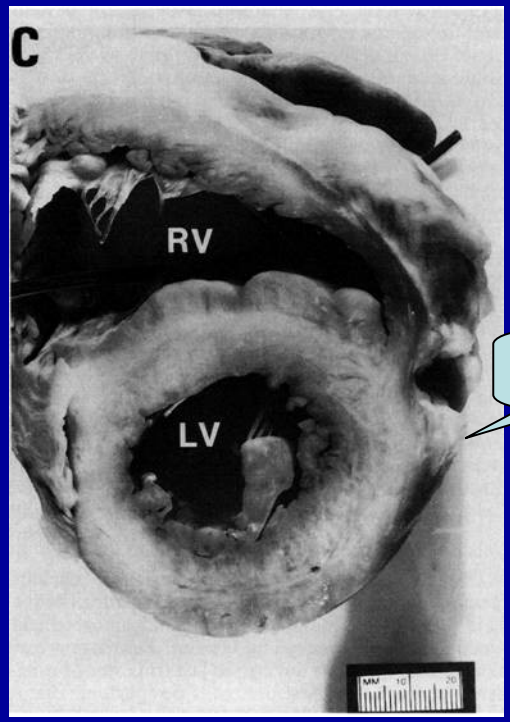
OVERLAPPING HCM/ RCM FEATURES



IRCM

IRCM

Restr
?HCM



HCM

Keren A, Popp RL.
Circulation 1992;86:1622-33

Morphologic Spectrum of Primary Restrictive Cardiomyopathy

Annalisa Angelini, MD, Vittorio Calzolari, MD, Gaetano Thiene, MD, Giovanni M. Boffa, MD, Marialuisa Valente, MD, Luciano Daliento, MD, Cristina Basso, MD, Fiorella Calabrese, MD, Renato Razzolini, MD, Ugolino Livi, MD, and Raffaello Chioin, MD

- 7 heart specimens of pts fulfilling morphologic and hemodynamic criteria of Primary RCM

- 4 with NORMAL mass/volume (PURE RESTRICTIVE)
  2 with INCREASED mass/volume (HYPERTROPHIC-RESTRICT)

- Histology: interstitial fibrosis and *myocardial disarray in all*

PRIMARY RCM

- may present with or without ***hypertrophy***

- may present with or without ***myocardial disarray***

Am J Cardiol 1997;80:1046-1050

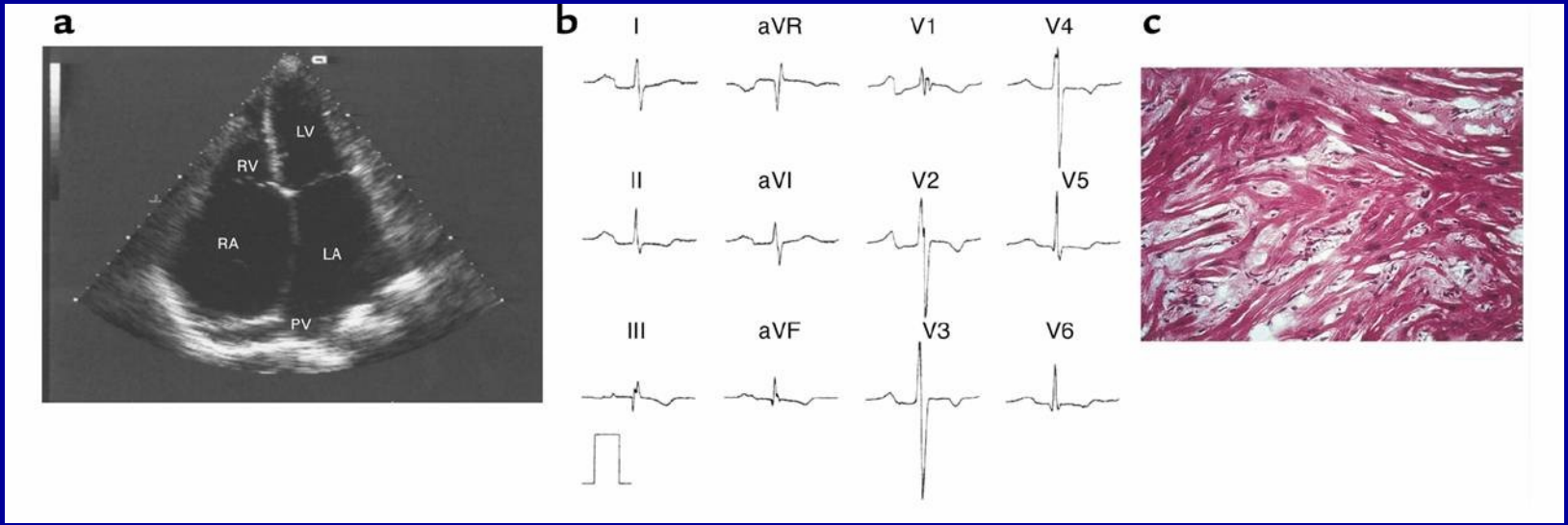
Types of RCM

RCM : Restrictive physiology
Nondilated ventricle
No LVH (<1.3 cm)
With/without disarray

Restrictive HCM: Restrictive physiology
Nondilated ventricle
LVH (≥ 1.3 /≥1.5)
With Disarray

Am J Cardiol 1997;80:1046-1050

TNNI3 Mutations found in 6/9 pts with RCM



Idiopathic RCM is part of the clinical expression of cardiac Troponin I mutations -

Mogensen J et al. J Clin Invest 2003;111:209-216

Troponin I Mutations in HCM

- prevalence 3%,

-extreme inter and intrafamilial heterogeneity

- **the same Troponin I mutation can express as either HCM or RCM**

.Mogensen J et al

JACC 2004:44:2315025

Prevalence, Clinical Significance, and Genetic Basis of Hypertrophic Cardiomyopathy With Restrictive Phenotype

Toru Kubo, MD,*† Juan R. Gimeno, MD,* Ajay Bahl, MD,* Ulla Steffensen,* Morten Steffensen,* Eyman Osman, BSc,* Rajesh Thaman, MD,* Jens Mogensen, MD, PhD,*‡ Perry M. Elliott, MD, FACC,* Yoshinori Doi, MD, FACC,† William J. McKenna, MD, FACC*

London, United Kingdom; Kochi, Japan; and Aarhus, Denmark

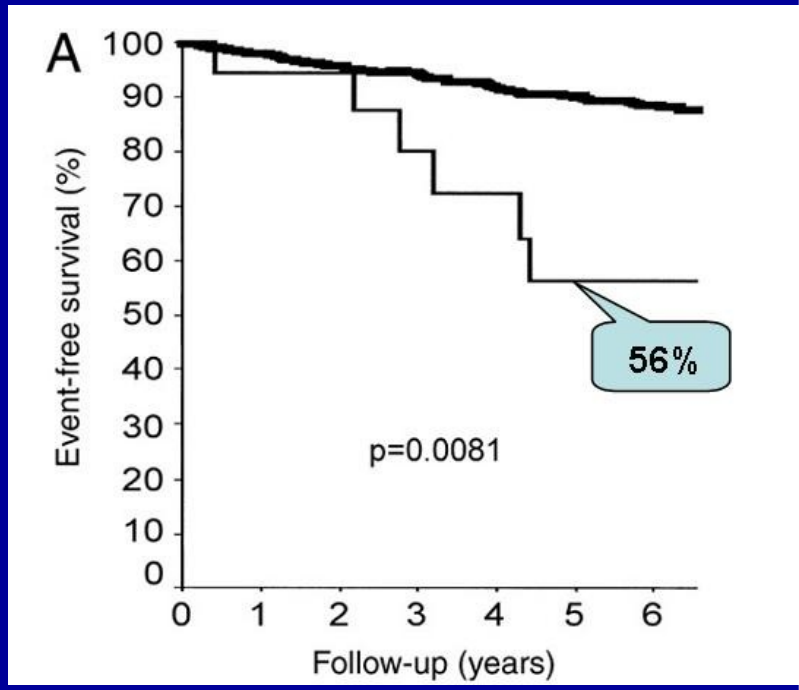
-Prevalence:

1.5% of HCM cases

2.3% of families

- BMHC&TnI mutations

- Severe course and poor prognosis



J Am Coll Cardiol 2007;49:2419-26

RESTRICTIVE CM

- **Current knowledge**

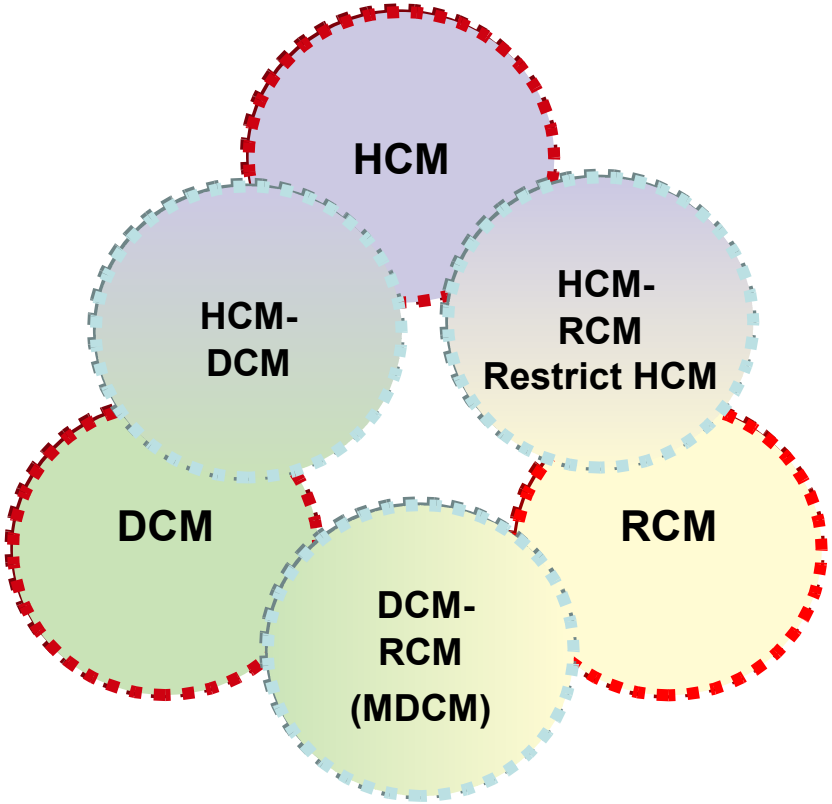
  - RCM can be part of the spectrum of HCM

  - RCM can be caused by mutations in sarcomeric proteins associated with HCM (BMHC &TnI)

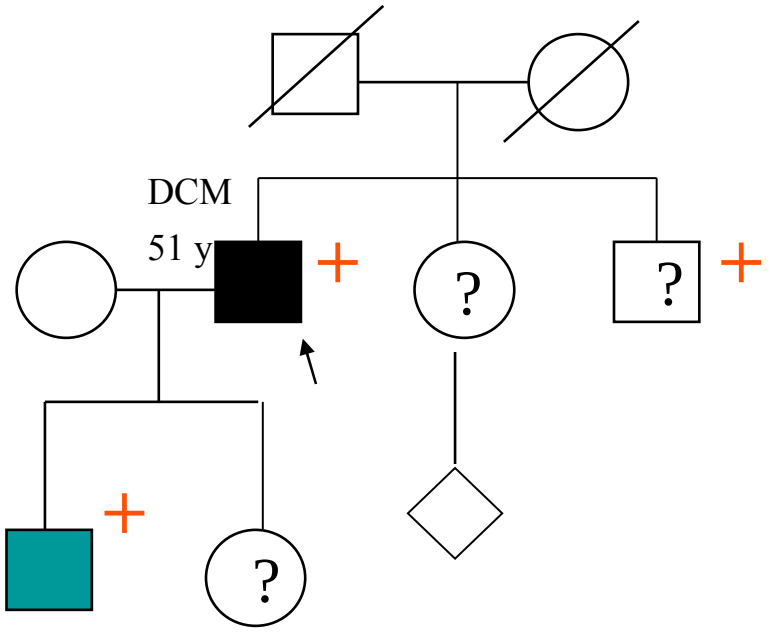
  - Myocardial disarray can be present in RCM

  - Restrictive physiology can occur in HCM and carries severe prognosis

HCM EVOLVING to DCM



Remodeling With Age of HCM



25 y.
No symptom
But HCM on Echo !

→ Genetic testing: β–myosin mutation

Charron P, 2007

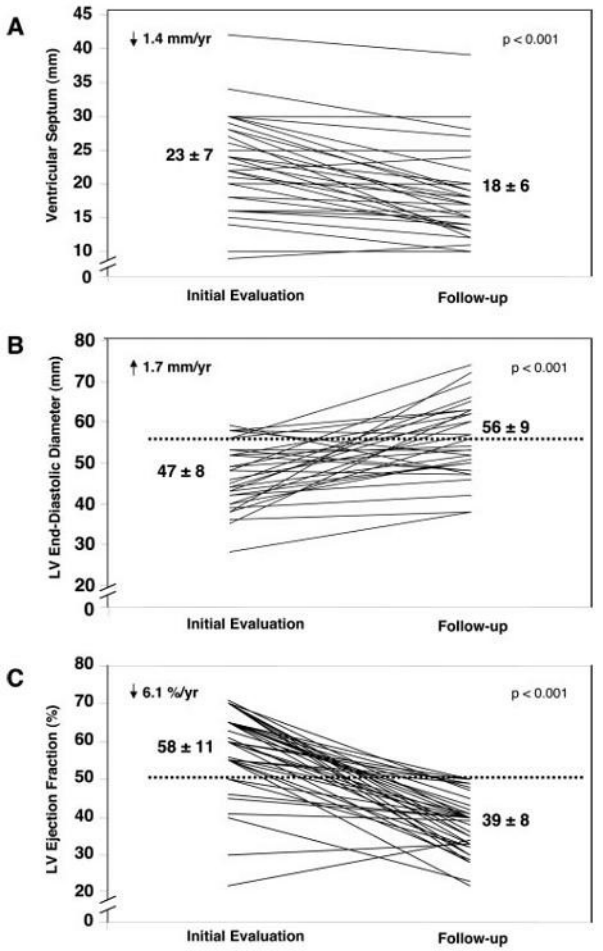
HCM and remodeling LV – End-stage phase

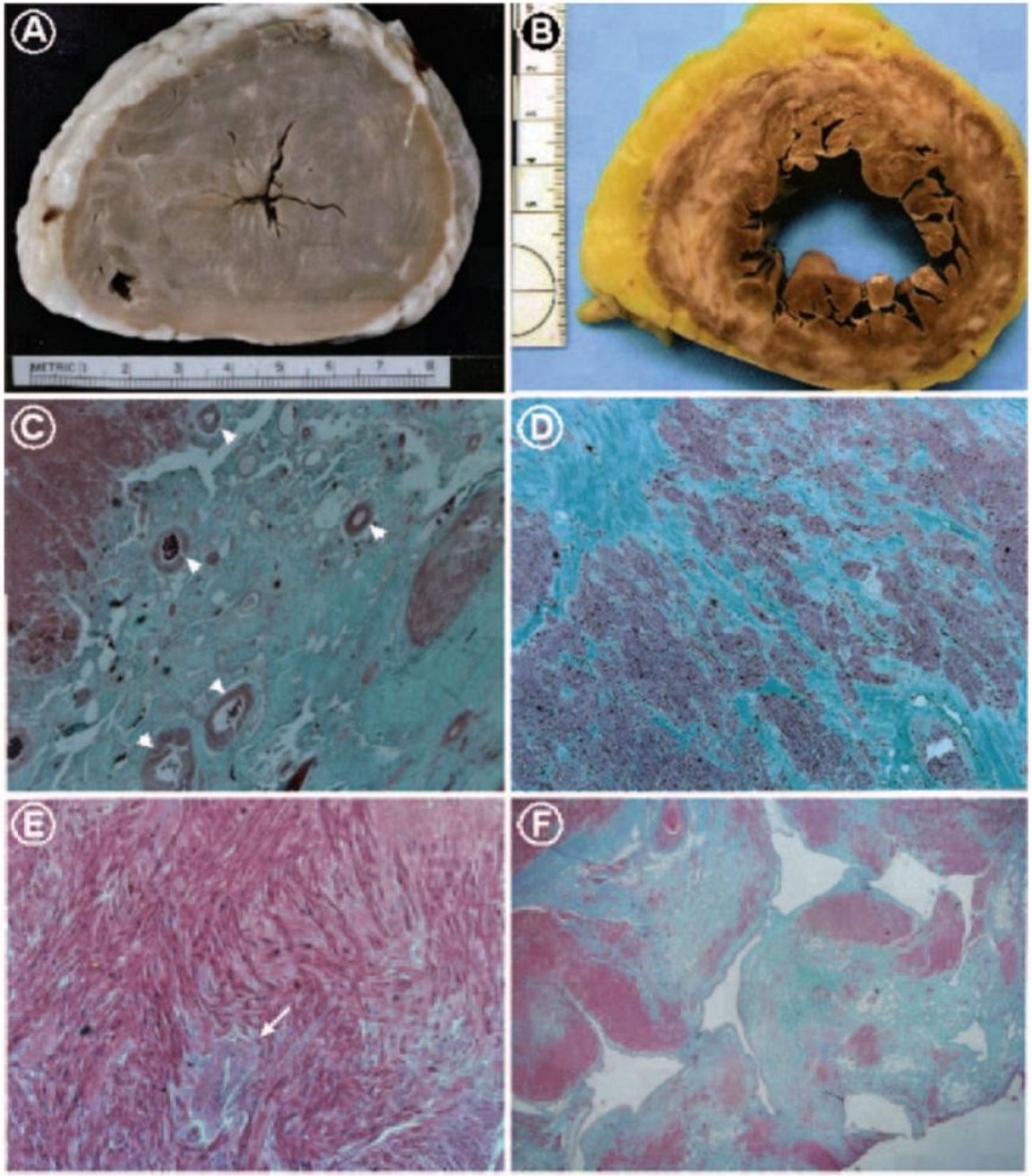
- **LV remodeling**
  - in ~10% of HCM patients

  (Spirito et al, AJC 1987)

- End-stage phase (EF<50%)
  - 3.5% of 1259 HCM pts
  - 52% with LV remodeling-dilation, 48% without

  (Harris et al, Circulation 2006)





END STAGE HCM

With:

Decrease in LVEF

:Without

LV Enlargement -

Wall thinning -

Mortality/year 11%

.Harris KM, Maron BJ et al

Circulation 2006;114:216-225

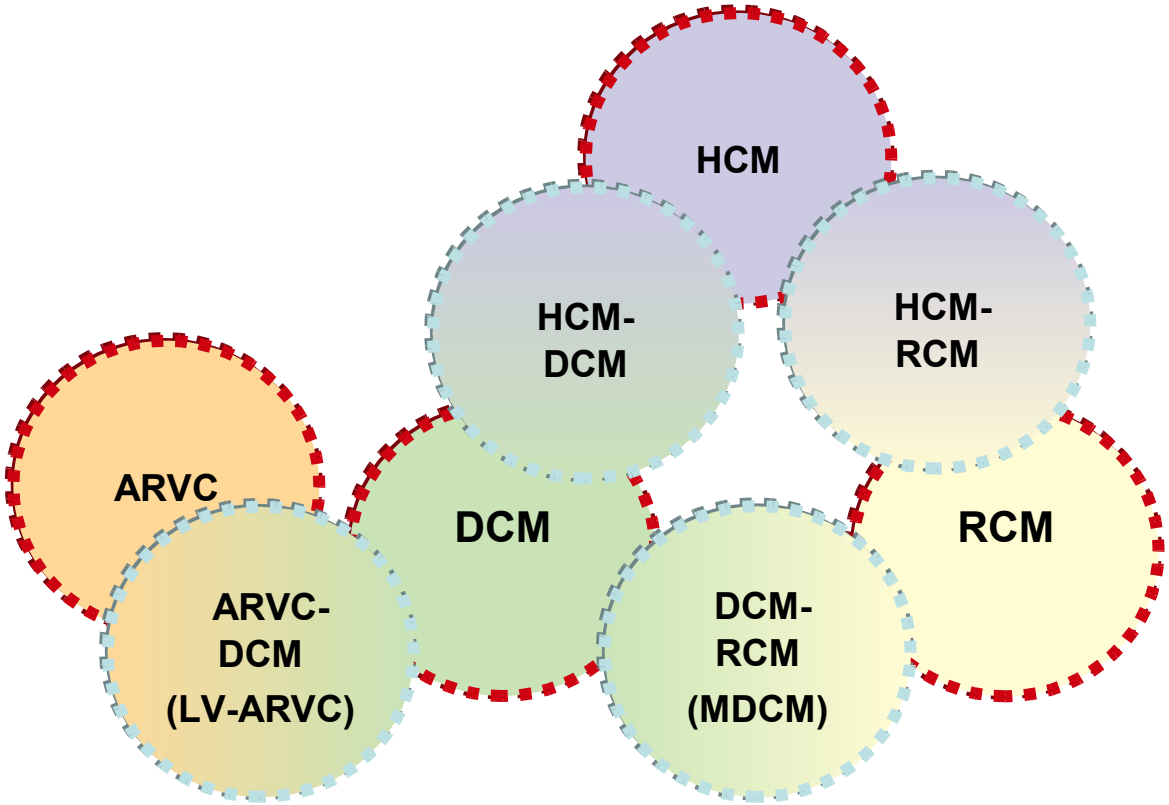
Conclusions
End Stage HCM

- In sporadic DCM cases, family screening might reveal familial HCM

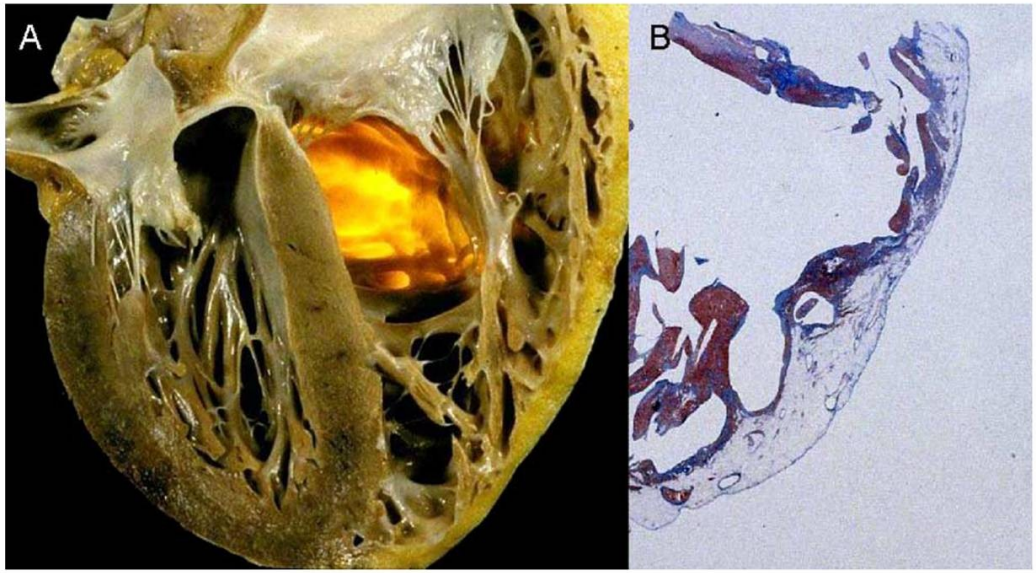
- End stage HCM is not always associated with ventricular dilatation and wall thinning

- Is associated with poor prognosis

Overlapping ARVC-DCM



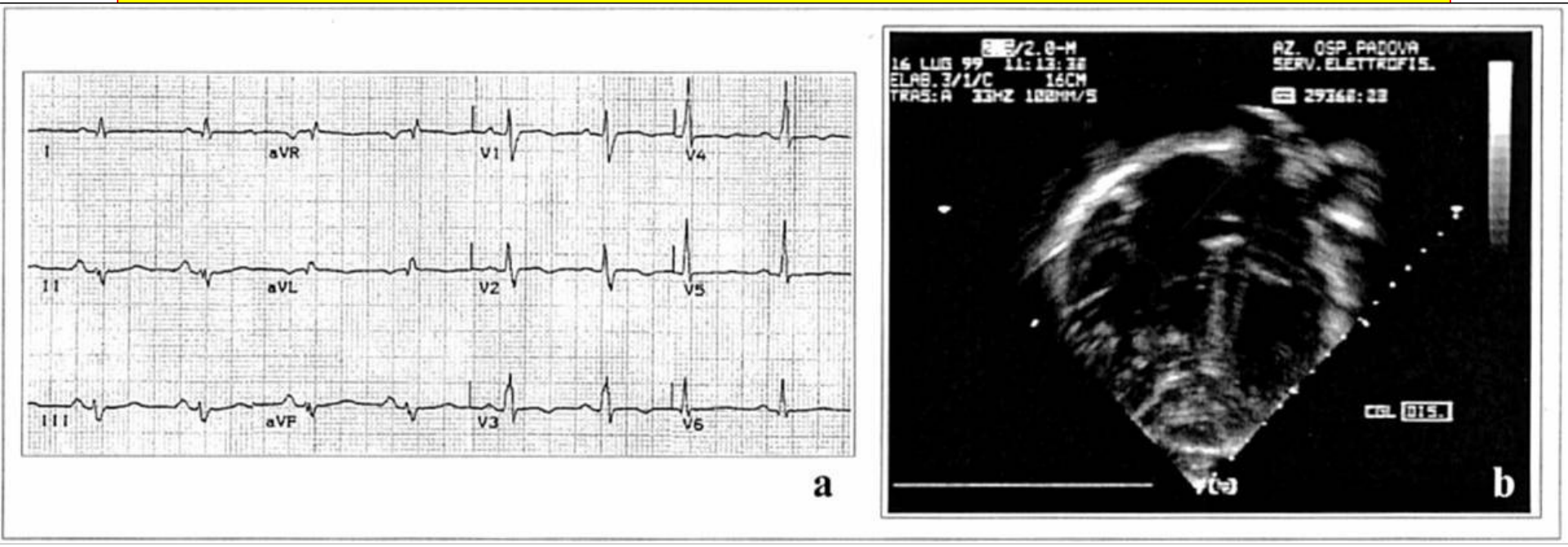
ARVC



Thiene G et al. Cardiovasc Path 2005;14:165

UCLH London, UK

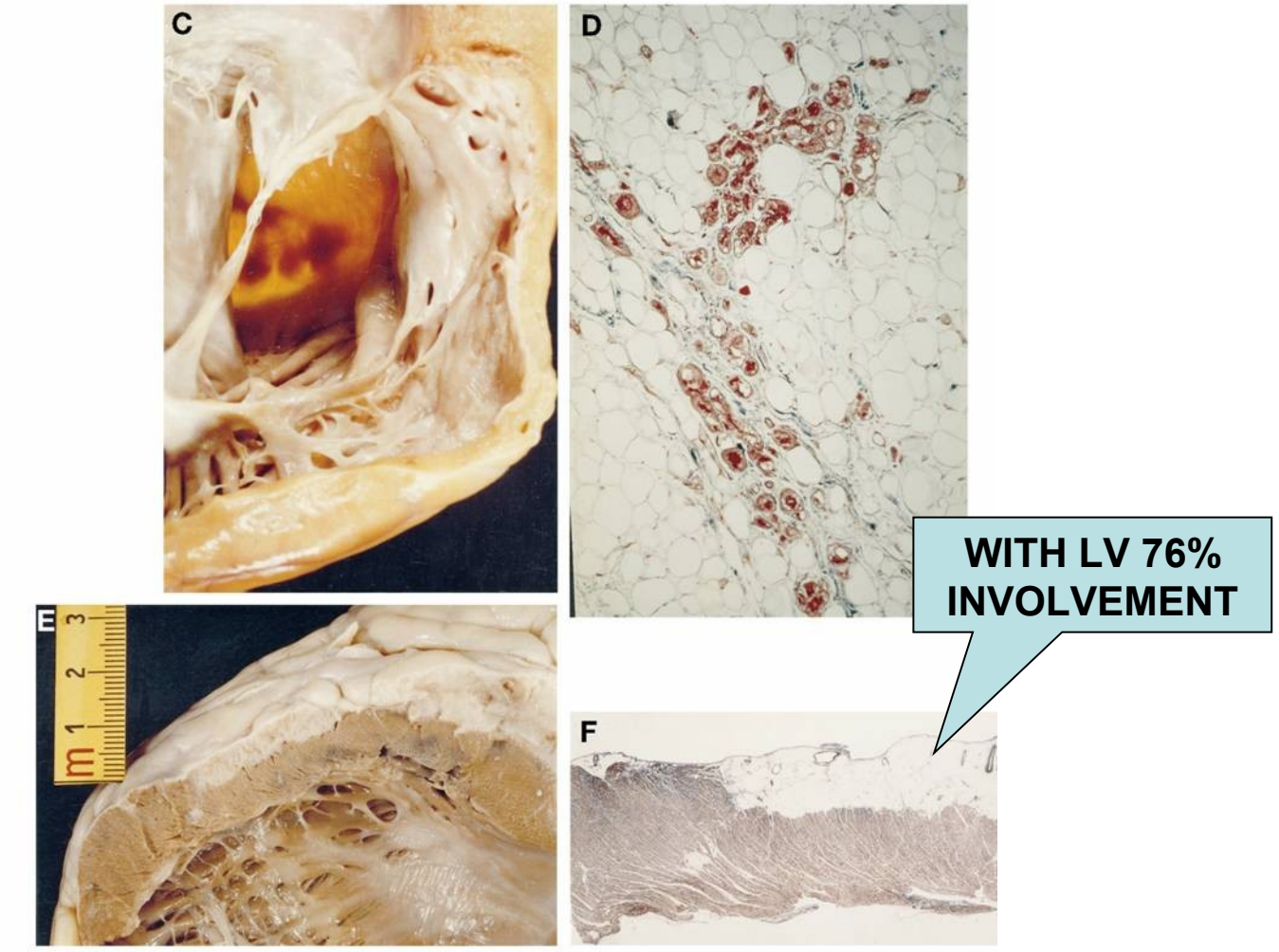
Mutation in Desmoplakin Domain Binding to Plakoglobin Causes Autosomal Dominant ARVC



Rampazzo et al 2002

LEFT VENTRICULAR INVOLVEMENT IN ARVC

JACC Vol. 30, No. 6
November 15, 1997:1512–20



Cardiocutaneous syndromes

(“(“Naxos disease

Reports on Naxos disease and Carvajal syndrome

	First report, country (first author, year)						
	Greece (Protonotarios, 1986)	Italy (Tosti, 1994)	India (Rao, 1996)	Ecuador (Carvajal, 1998)	Israel (Djabali, 2002)	Israel (Alcalai, 2003)	Turkey (Narin, 2003)
No. of families	12	1	1	4	2	1	1
Inheritance	AR	AD	AR	AR	AR	AR	AR
Molecular genetics, gene	Plakoglobin	Not done	Not done	Desmoplakin	In progress	Desmoplakin	Plakoglobin
No. of patients/ gender	14M, 14F	2M	4M	7M, 5F	8F	6M, 3F	2M
Cutaneous phenotype	WH, PPK	WH, PPK	WH, PPK	WH, PPK	WH, PPK	WH, Pemphigous	WH, PPK
Cardiomyopathy							
Diagnosis	ARVC	Suspected ARVC	DCM	DCM	ARVC	ARVC	ARVC
Earliest diagnosis, age	13 years	20 years	7 years	8 years	18 years	16 years	13 years
RV involvement	Yes	Yes	Yes	Yes	Yes	Yes	Yes
LV involvement	Yes	No	Yes	Yes	Yes	No	No
Arrhythmias	VES, VT	No	Not reported	VES, VT	VES, VT	VT	VT
Outcome	HF, SD	Not reported	HF	HF, SD	SD	SD	Alive

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; F, female; HF, heart failure; M, male; PPK, palmoplantar keratoderma; SD, sudden death; VES, ventricular extrasystoles; VT, ventricular tachycardia; WH, wooly hair.

Mutation in Desmoplakin Domain Binding to Desmin Causes - LV ARVC

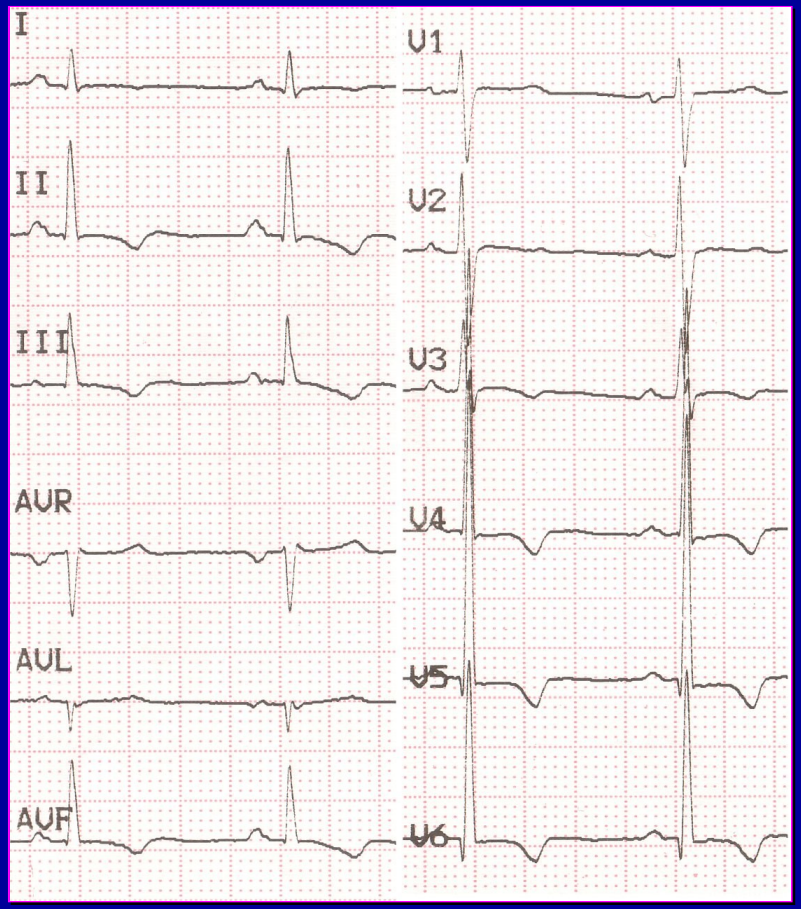
2034insA mutation

10 individuals: ARVC+LV involvement

7 Inf/Lat T wave changes

8 RBBB ventricular arrhythmia

3 exercise syncope

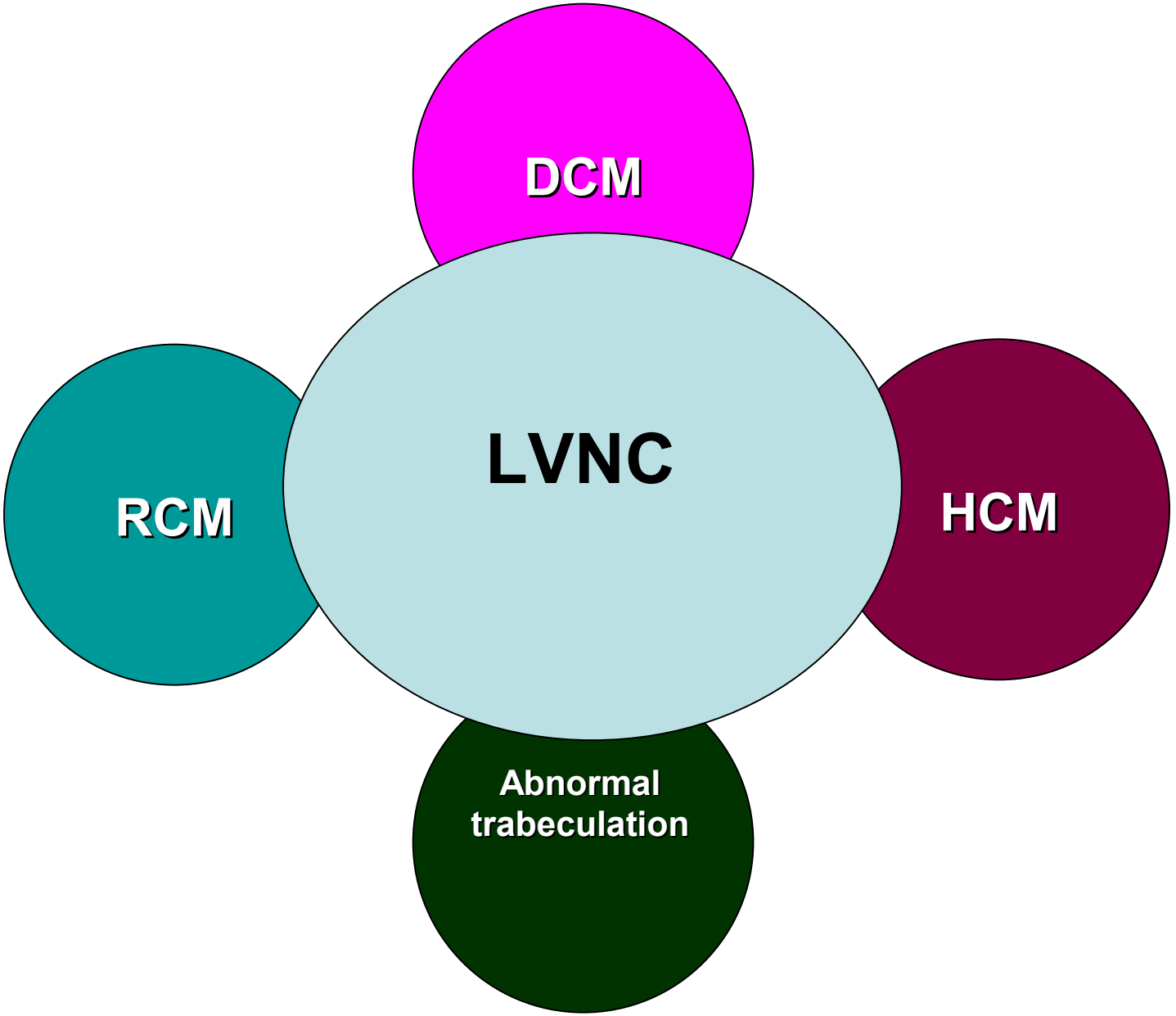


Norman M et al. Circulation 2005;112:636-642

LV Involvement in ARVC

- Can occur with both the AR and the AD inheritance of the disease
- The pathologic process can predominantly involve the LV
- LV involvement negatively influences prognosis and is a risk factor for SCD

LVNC CAN BE ASSOCIATED WITH MOST FORMS OF CARDIOMYOPATY



Overlapping Phenotypes

- MDCM:- DCM / RCM
  Some cases related to LMNA
- HCM: -Troponin T mutation
  -Restrictive HCM or Hypertrophic RCM?
  -End stage HCM– DCM
- ARVC: LV – ARVC
- LVNC

CONCLUSION

Mixed phenotypes are associated with more severe manifestations of the disease and more severe prognosis than the classical CM categories they overlap

Therefore, their recognition is important for proper management sometimes including life saving procedures (like heart Tx despite preserved heart size in DCM, ICD implant (despite lack of hypertrophy in HCM, etc

FACTORS WHICH MIGHT INFLUENCE THE PHENOTYPIC EXPRESSION OF DISEASE

1. Single gene mutations have variable severity
2. Influences from polymorphic “modifier genes“
3. Influences from “non-coding RNAs“
4. Modulation by environmental factors

HISTORICAL NOTES

- 1850 Virchow RLK: ***"Chronic myocarditis"***
- 1891 Krehl I : ***"Idiopathic heart muscle disease"***
- 1901 Josserand E, Gallavardin I: ***"Primary myocardial diseases"***
- 1957 Brigden W : ***"Cardiomyopathy"***

Abelmann WH, Progr Cardiovasc Dis 1984;27:73

Official Classifications of CM

- **1968 WHO:** ***Primary/Secondary**
- **1980 WHO/ISFC:*** ***Primary/Specific HM Dis***
- **1995 WHO/ISFC:** ***Primary/Specific CM***
- **2006 AHA:** ***Primary/Secondary**
- **2008 EHS:** ***No distinction**

Excluded HT, CAD, Valvular, Congenital heart disease *

BROADER INTERPRETATION OF THE PATHOLOGIC PROCESSS

- Early, less typical and new forms of the disease
- Evolving process with loss of classical features
- Unusual, overlapping features – do not belong to any conventional disease categories

BROADER INTERPRETATION OF THE PATHOLOGIC PROCESSS

- One gene - One disease
- Many genes - One disease
- One gene - Many diseases

Multifactorial disease etiologies

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

Maron B et al. Circulation 2006;113:1807-1816

AHA Scientific Statement 2006

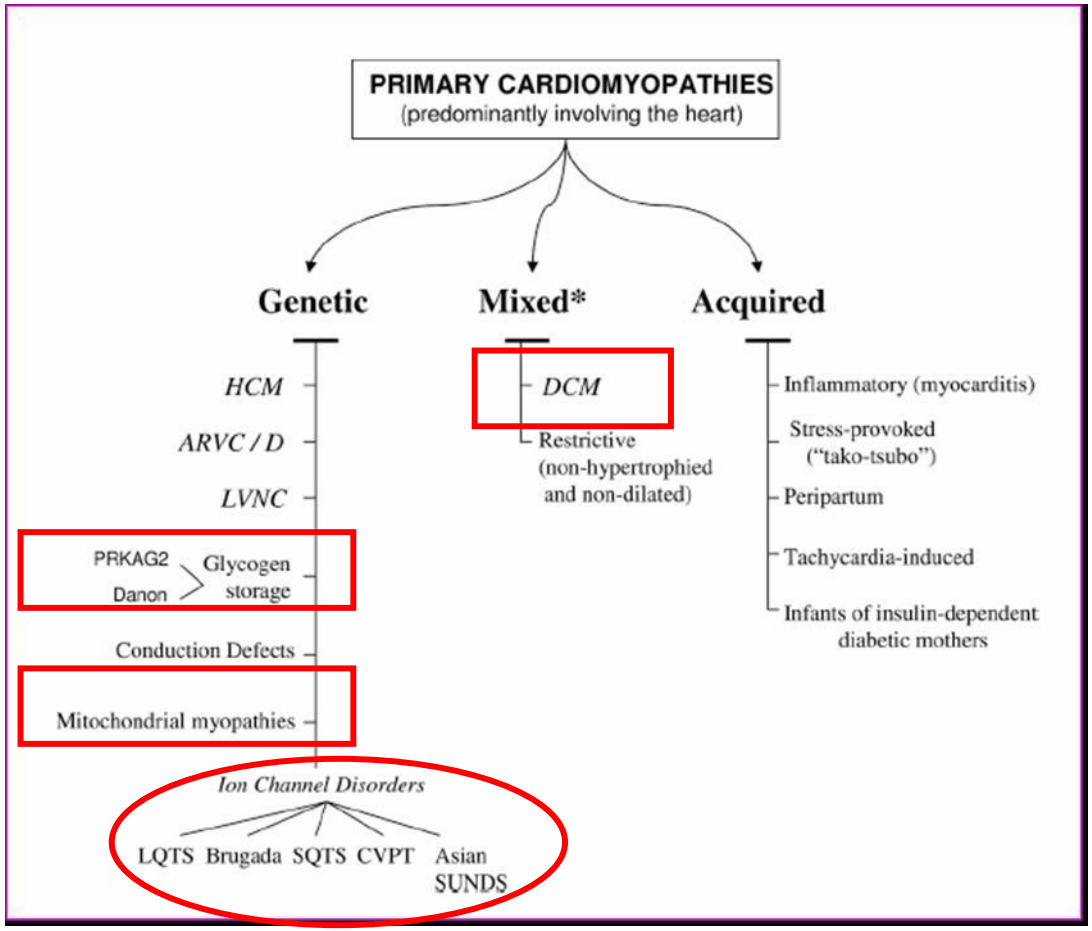
Cardiomyopathies are a heterogeneous group of diseases ” of the myocardium associated with mechanical *and/or electrical dysfunction* that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are *confined to the heart or are part of generalized systemic disorders,* often leading to cardiovascular death or progressive heart

“.failure–related disability

Maron B et al. Circulation 2006;113:1807-1816

AHA Scientific Statement

Contemporary Definitions and 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

Endomyocardial
- Endomyocardial fibrosis
- Hypereosinophilic syndrome (Löeffler's endocarditis)

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).

Maron BJ et al. Circulation 2006;113:1807-16

European Heart Journal
doi:10.1093/eurheartj/ehm342

Esc report

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*

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Received 6 March 2007; revised 27 June 2007; accepted 16 July 2007

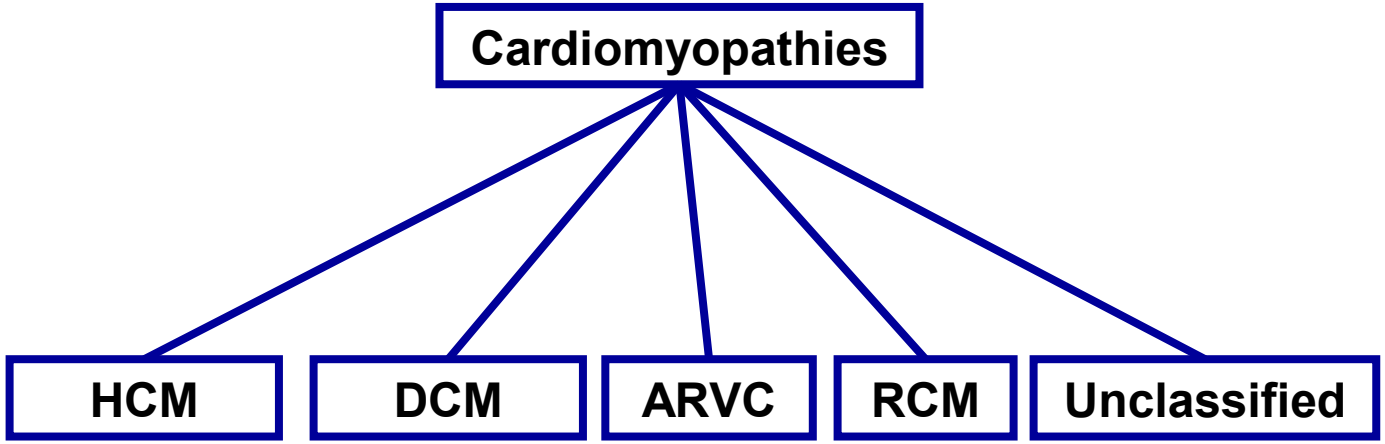
Eur Heart J 2008;29:270-276

Cardiomyopathy: Definition

"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."

ESC Working Group on Myocardial Pericardial Diseases

Eur Heart J 2008;29:270-276



European WG on Myocardial and Pericardial Diseases (EHJ 2008)

Key Point #1

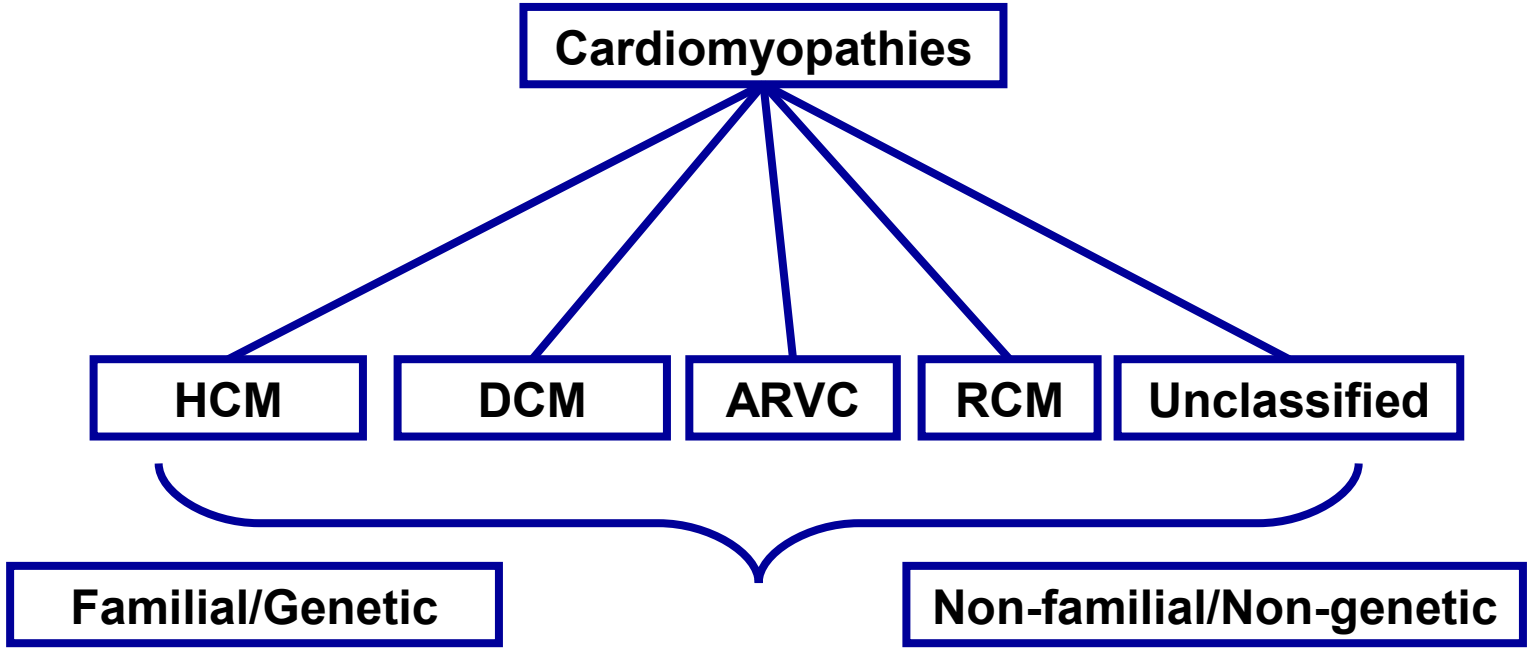
- **Primary versus secondary abandoned**

ESC Working Group on Myocardial Pericardial Diseases (EHJ 2008)

Key Point #2

- **Sub-classification into familial and non-familial forms so as to raise awareness of genetic determinants of and to orient diagnostic tests (including the search for specific mutations, when appropriate).**

ESC Working Group on Myocardial Pericardial Diseases (EHJ 2008)



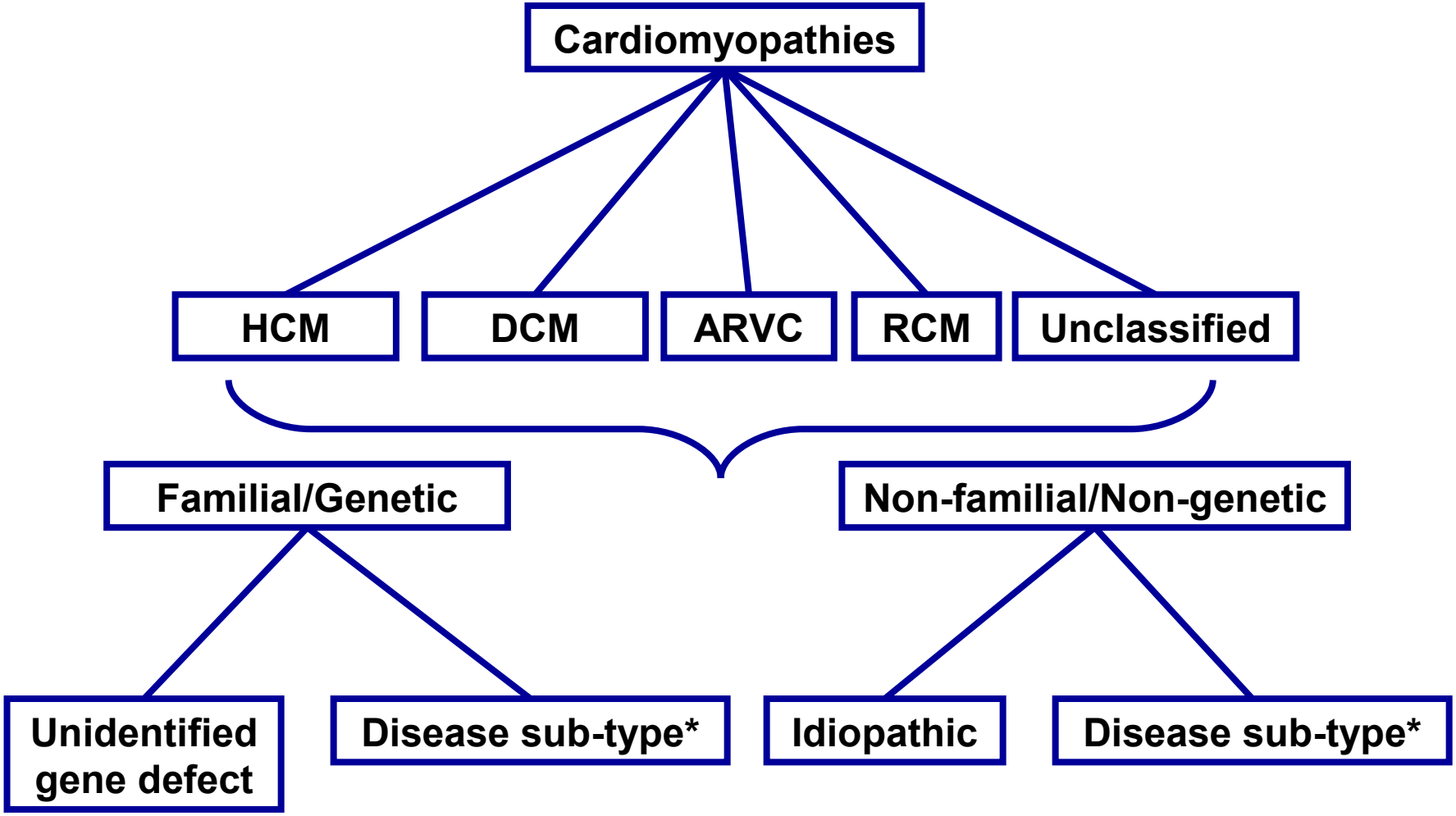
European WG on Myocardial and Pericardial Diseases (EHJ 2008)

Table 1 Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß 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, Hurler'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–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin 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-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma 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 (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional − thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

ESC Working Group on Myocardial Pericardial Diseases (EHJ 2008)



European WG on Myocardial and Pericardial Diseases (EHJ 2008)

Key Point #3

- **A move away from the predominantly exclusion-based diagnostic work-up towards a positive, logical search for diagnostic indicators.**

ESC Working Group on Myocardial Pericardial Diseases (EHJ 2008)

any classification is necesarily incomplete ... and acts as a bridge between complete

...ignarance and total understanding

Goodwin JF. The frontiers of cardiomyopathy. Br Heart J, 1982