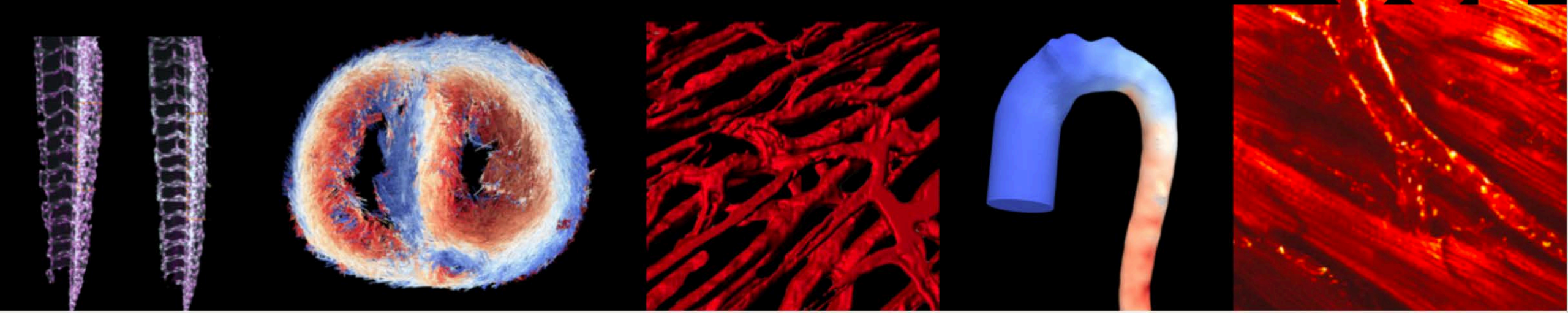
UCL INSTITUTE OF CARDIOVASCULAR SCIENCE



Precision Medicine in cardiology: our classification of cardiomyopathies

Cardiomyopathy UK the heart muscle charity

Barts Health NHS NHS Trust

Queen Mary University of London

British Heart Foundation

NHS National Institute for Health Research

wellcome

ACT

THE common cause of isolated myocardial disease is coronary disease; but there are many other causes, mostly obscure and relatively rare. When patients develop apparently causeless heart-failure, diagnosis of myocarditis is sometimes made, but usually the condition is attributed either to a previous hypertension or painless coronary disease. Often such patients die unexpectedly and pathological investigation may not reveal the cause and nature of the disease. The present study is concerned with these myocardial diseases which are either isolated or so nearly isolated that disease in other systems is of a minor degree and significant only as an aid to diagnosis. The term cardiomyopathy is used here to indicate isolated non-coronary myocardial disease.

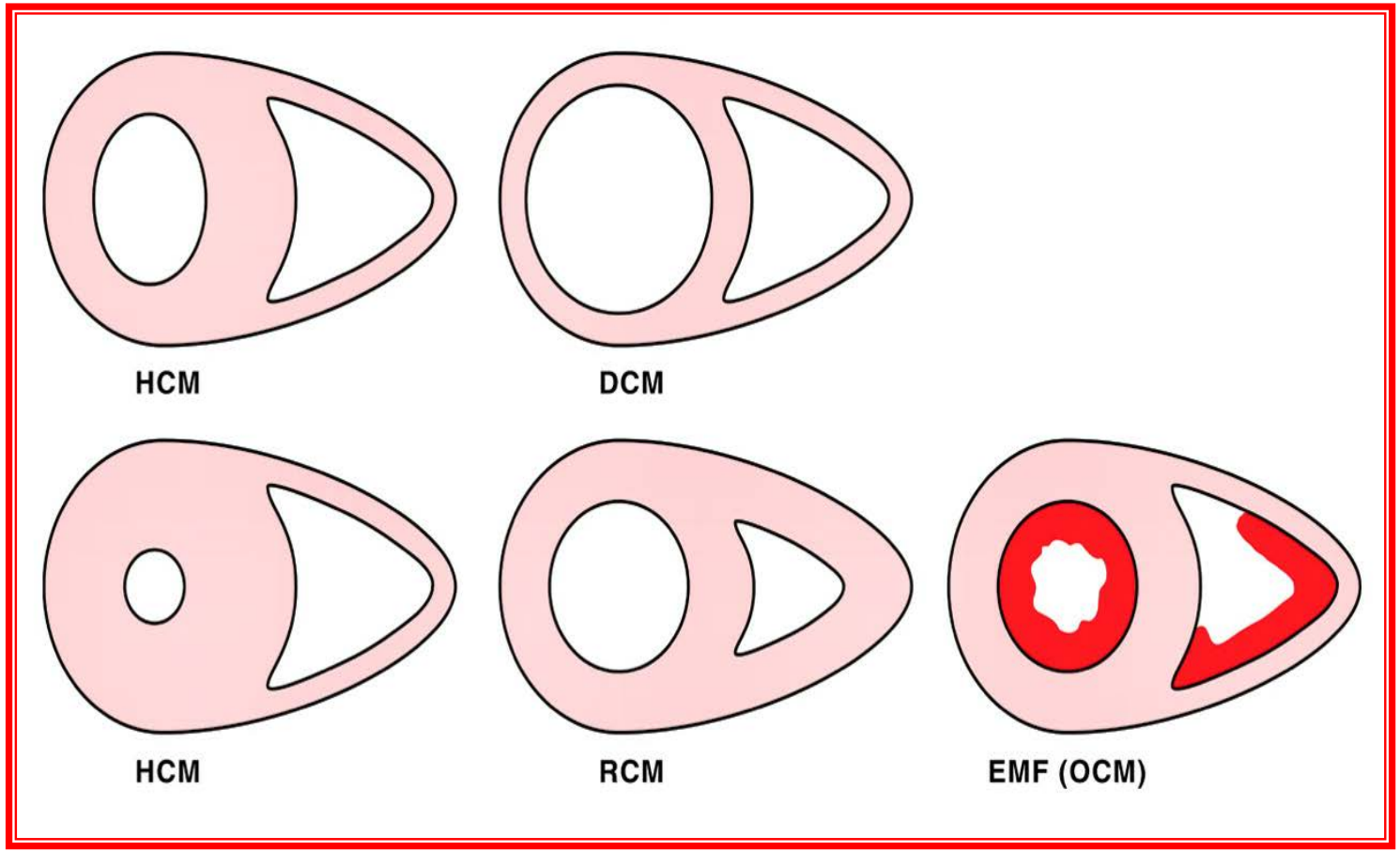
- The St.Cyres lecture, delivered in London on June 13, 1956.

Cardiomyopathies: The beginning.

- “primary myocardial disorders not caused by clearly identifiable structural abnormalities, such as valve disease and coronary artery stenoses, or systemic disorders.”
  - J. Goodwin

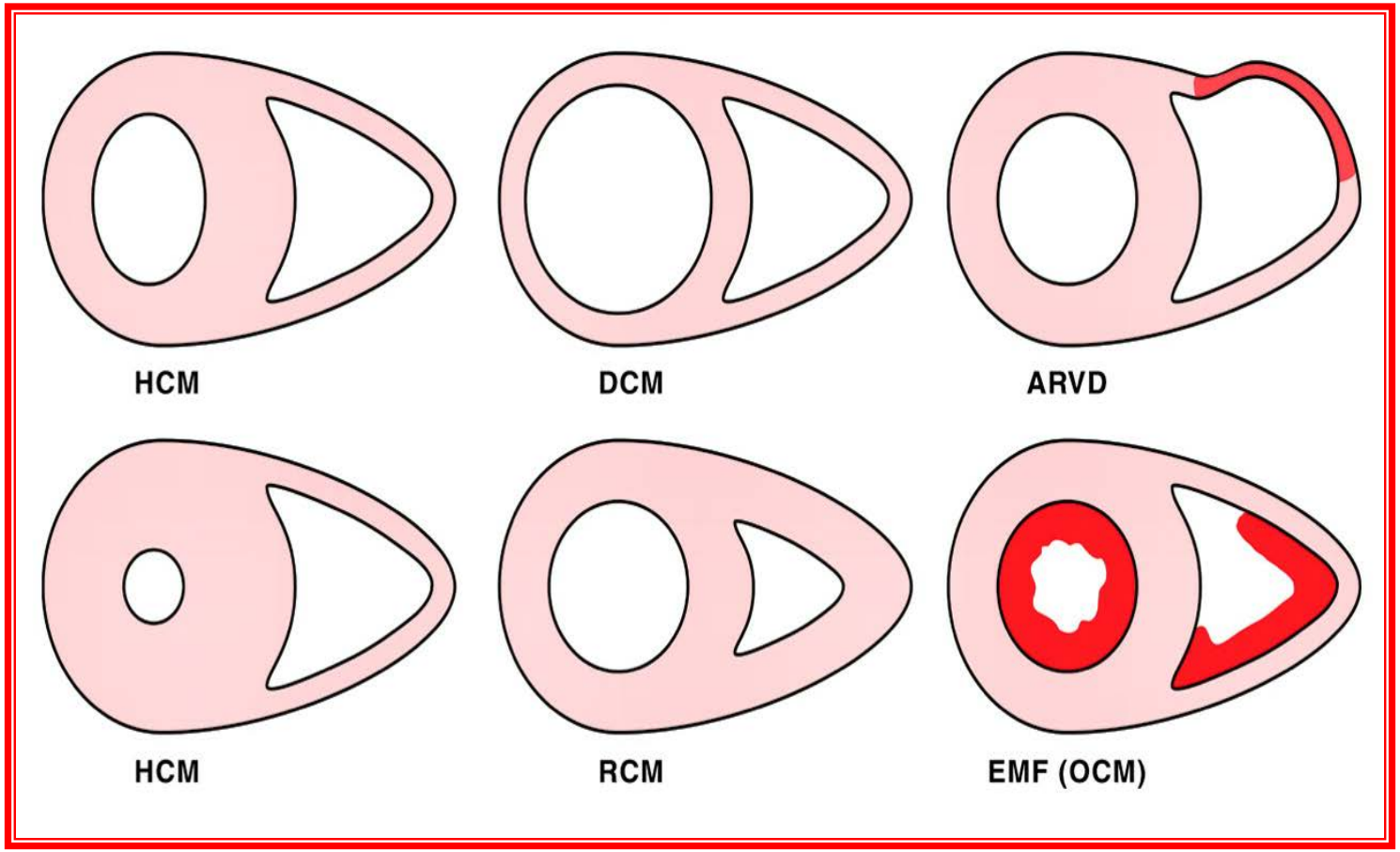
- “A disorder or heart muscle of unknown cause.”
  - C. Oakley

Classification of Cardiomyopathies



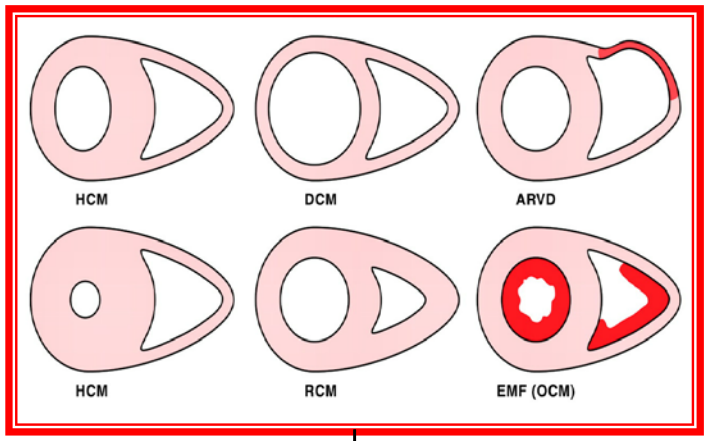
Adapted from Davies M. Heart 2000;83:469-474

Classification of Cardiomyopathies: 1995



Davies M. Heart 2000;83:469-474

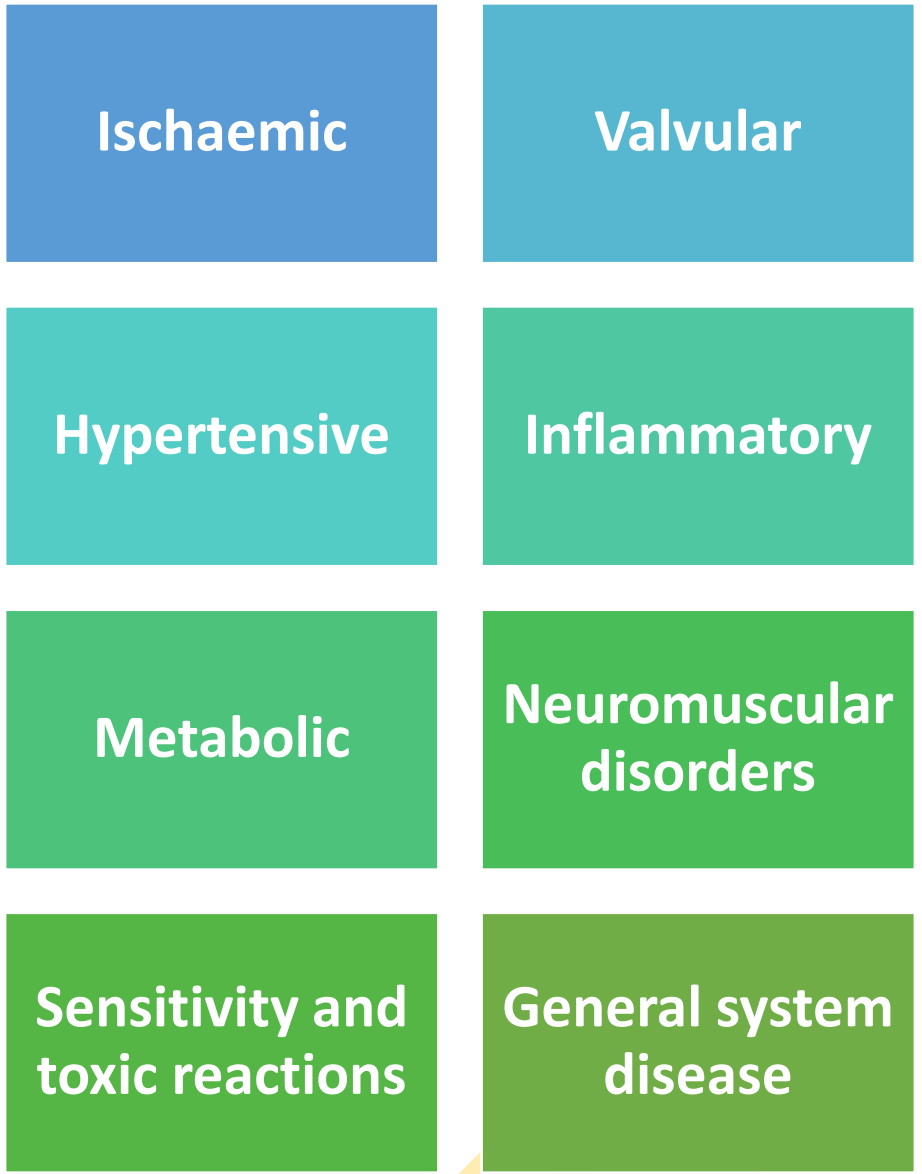
Classification of Cardiomyopathies: 1995



Primary (Cardiomyopathy)

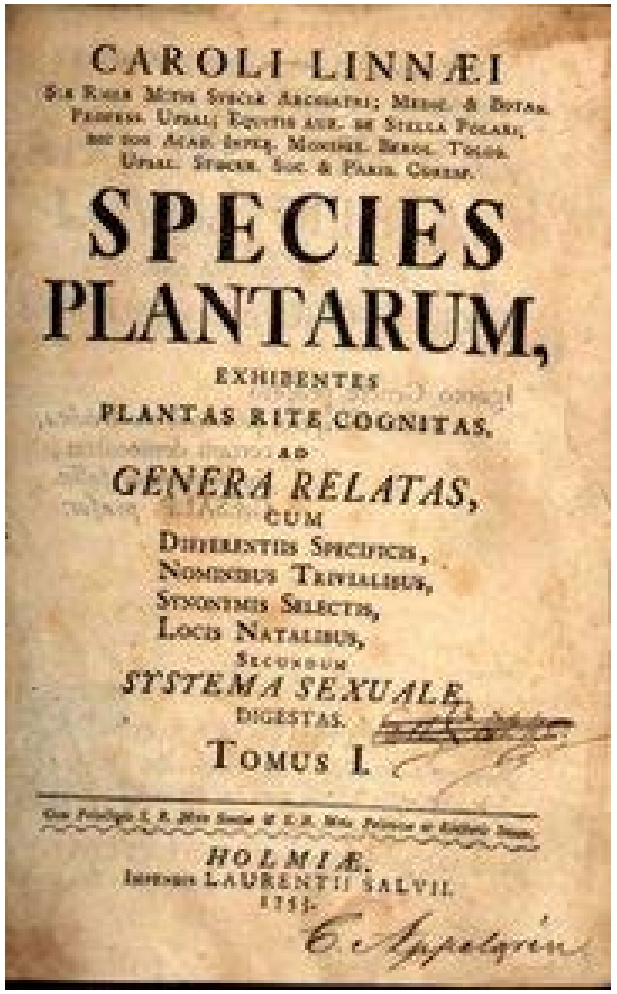
Secondary (Specific Cardiomyopathies)

Specific Heart Muscle Disease



Limitations

- Historical legacy
- Contradictory, confusing terminology, many situations (rare and common).
- Evolving or early phenotypes
- Emerging complexity (aetiology and phenotypes, overlapping diseases)
- Aetiology specific treatments



CAROLI LINNÆI

SPECIES PLANTARUM,

EXHIBENTES

PLANTAS RITE COGNITAS,

AD

GENERA RELATAS,

CUM

DIFFERENTIIS SPECIFICIS,

NOMINIBUS TRIVIALIBUS,

SYNONYMIS SELECTIS,

LOCIS NATALIBUS,

SECUNDUM

SYSTEMA SEXUALE

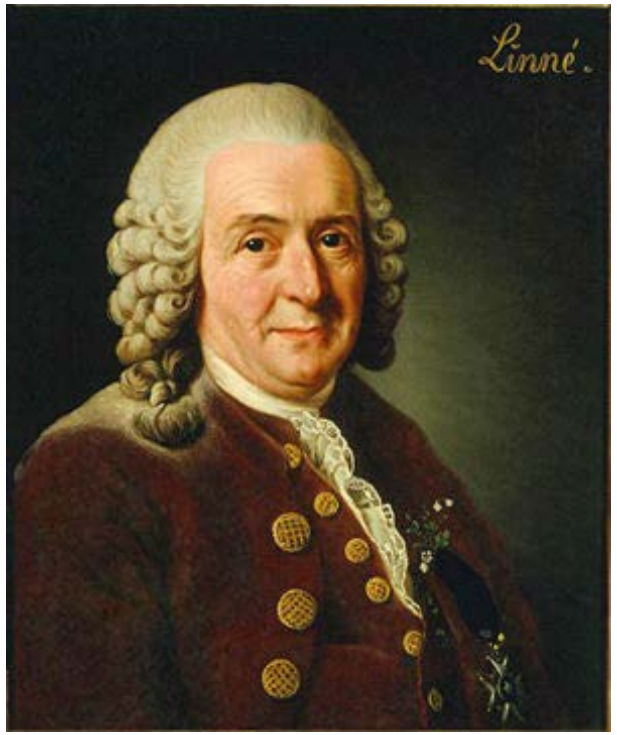
DIGESTAS.

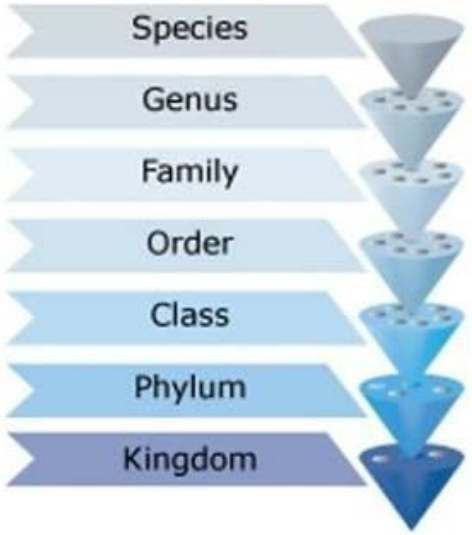
TOMUS I.

HOLMIÆ,

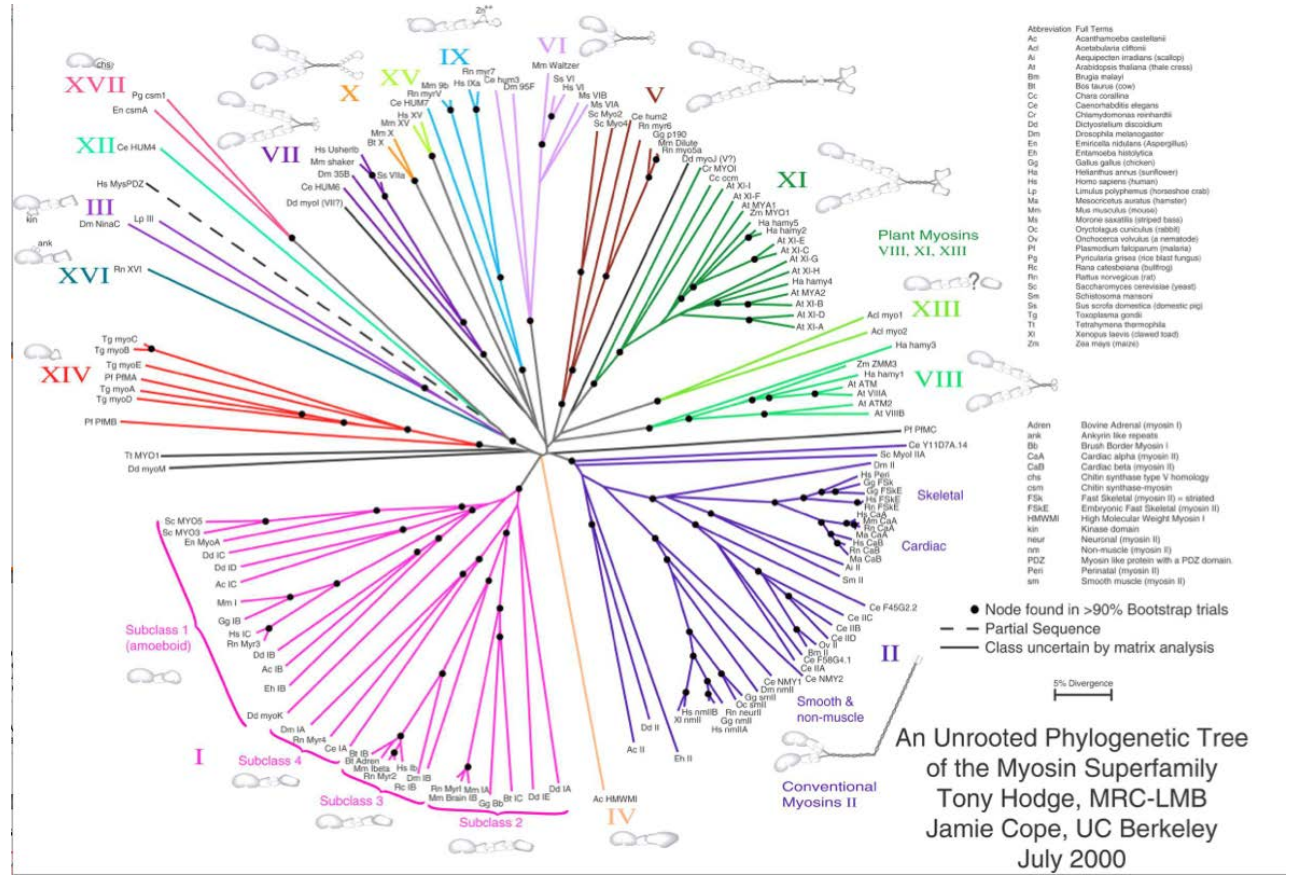
IMPENSIS LAURENTII SALVII.

1753.

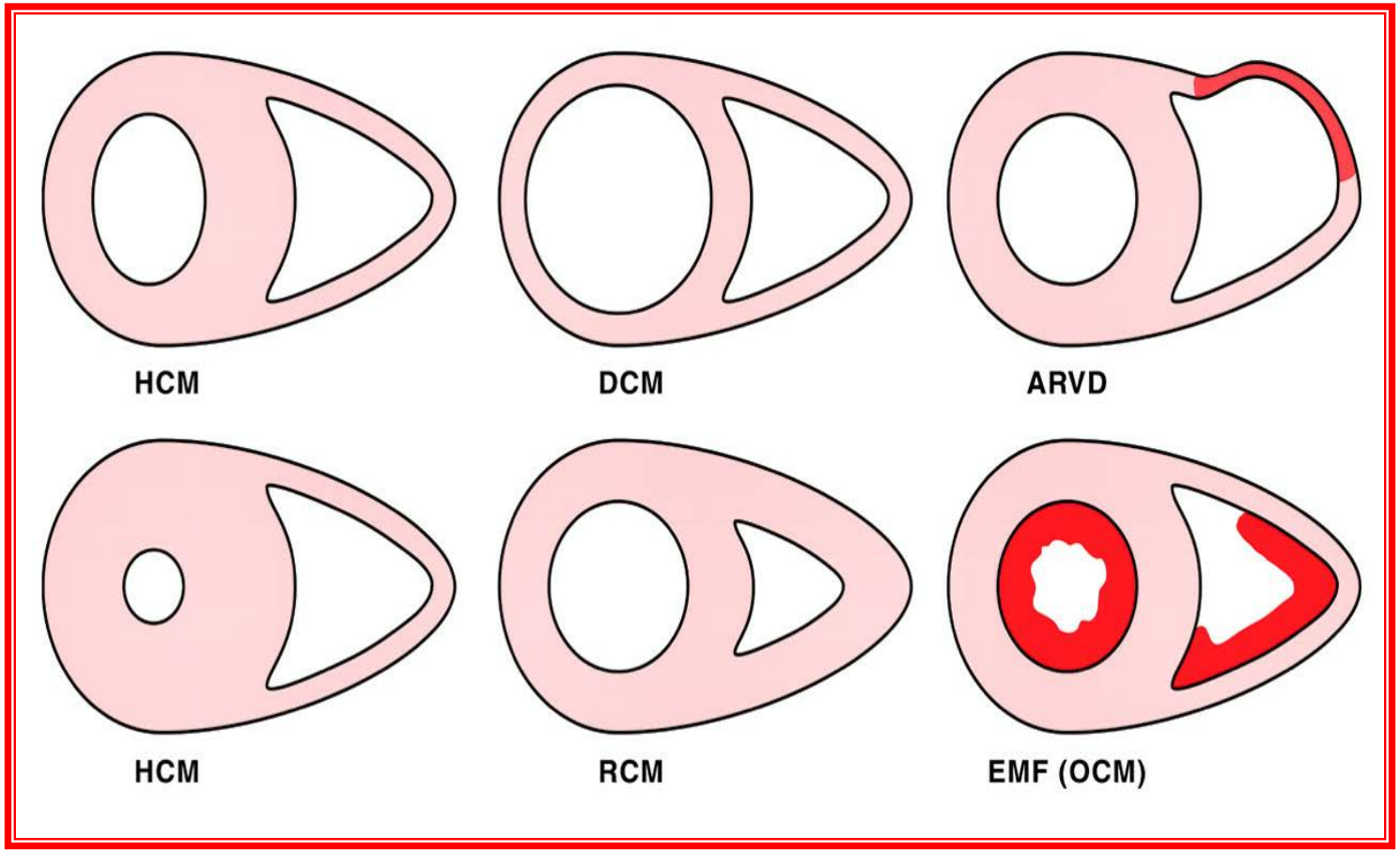





Ferns S.L.
Cycadales
Ginkgoales
Pinales
Gnetales
Amborellales
Nymphaeales
Austrobaileyales
Ceratophyllales
Chloranthales
Magnoliales
Laurales
Canellales
Piperales
magnoliids
Acorales
Alismatales
Petrosaviales
Dioscoreales
Pandanales
Liliales
Asparagales
Unplaced
Arecales
Poales
Commelinales
Zingiberales
commelinids
Ranunculales
Sabiales
Proteales
monocots
Trochodendrales
Buxales
Gunnerales
Berberidopsidales
Dilleniales
Caryophyllales
Santalales
Saxifragales
Vitales
Unplaced
Crossosomatales
Geraniales
Myrtales
Unplaced
Zygophyllales
Celastrales
Malpighiales
Oxalidales
Fabales
Rosales
Cucurbitales
Fagales
rosids
eurosid I
eurosid II
eudicots
Huerteales
Brassicales
Malvales
Sapindales
core eudicots
Cornales
Ericales
Unplaced
Garryales
Unplaced
Gentianales
Lamiales
Solanales
asterids
euasterid I
euasterid II
Aquifoliales
Unplaced
Apiales
Asterales
Dipsacales


XVII
XII
III
XVI
XIV
X
XV
IX
VI
VII
V
XI
XIII
VIII
Plant Myosins
VIII, XI, XIII
Skeletal
Cardiac
Smooth &
non-muscle
Conventional
Myosins II
Subclass 1
(amoeboid)
Subclass 4
Subclass 3
Subclass 2
I
II
IV
● Node found in >90% Bootstrap trials
– – Partial Sequence
—— Class uncertain by matrix analysis
5% Divergence
An Unrooted Phylogenetic Tree
of the Myosin Superfamily
Tony Hodge, MRC-LMB
Jamie Cope, UC Berkeley
July 2000

Classification of Cardiomyopathies: 1995



Davies M. Heart 2000;83:469-474

AHA Scientific Statement

Contemporary Definitions and Classification of the Cardiomyopathies

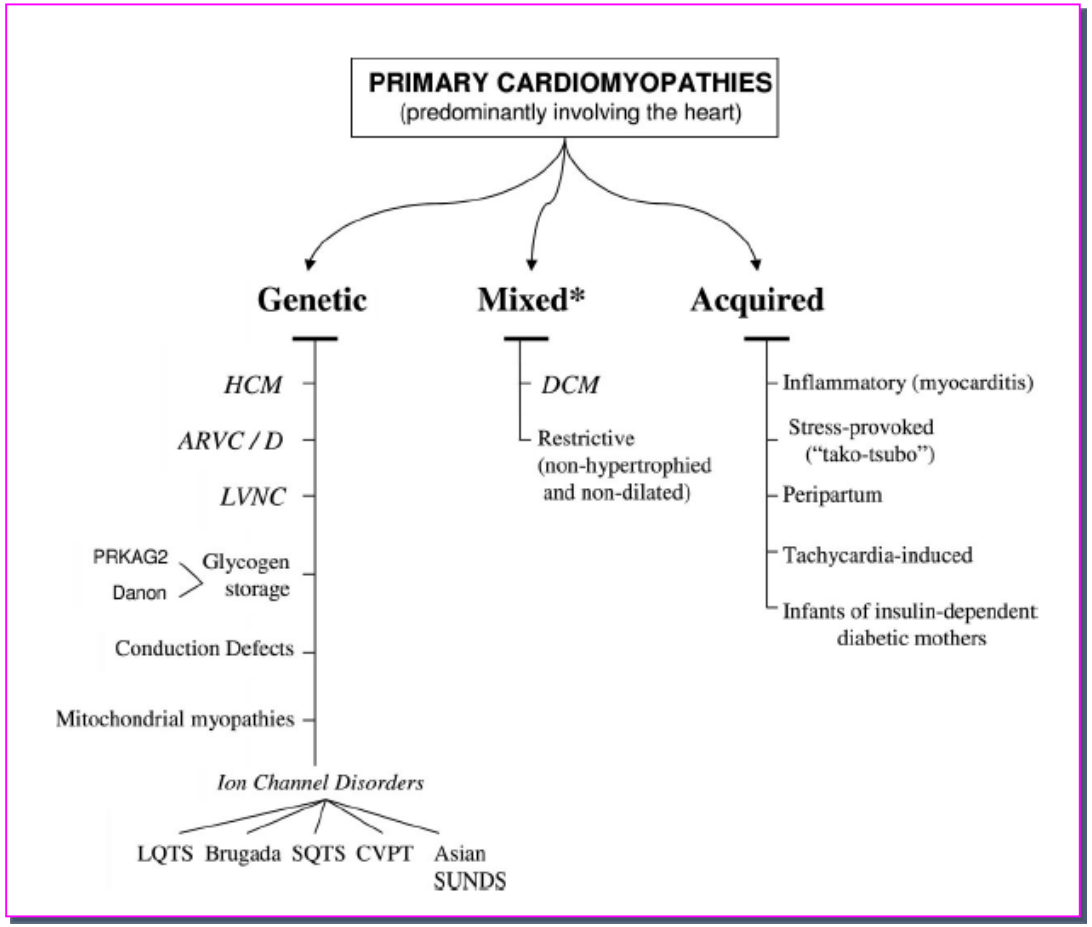
An American Heart Association Scientific Statement From the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention

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

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
- Drugs, heavy metals, chemical agents

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

Endomyocardial
Endomyocardial fibrosis
Hypereosinophilic syndrome (Löeffler's endocarditis)

- 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), pellagra, 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).

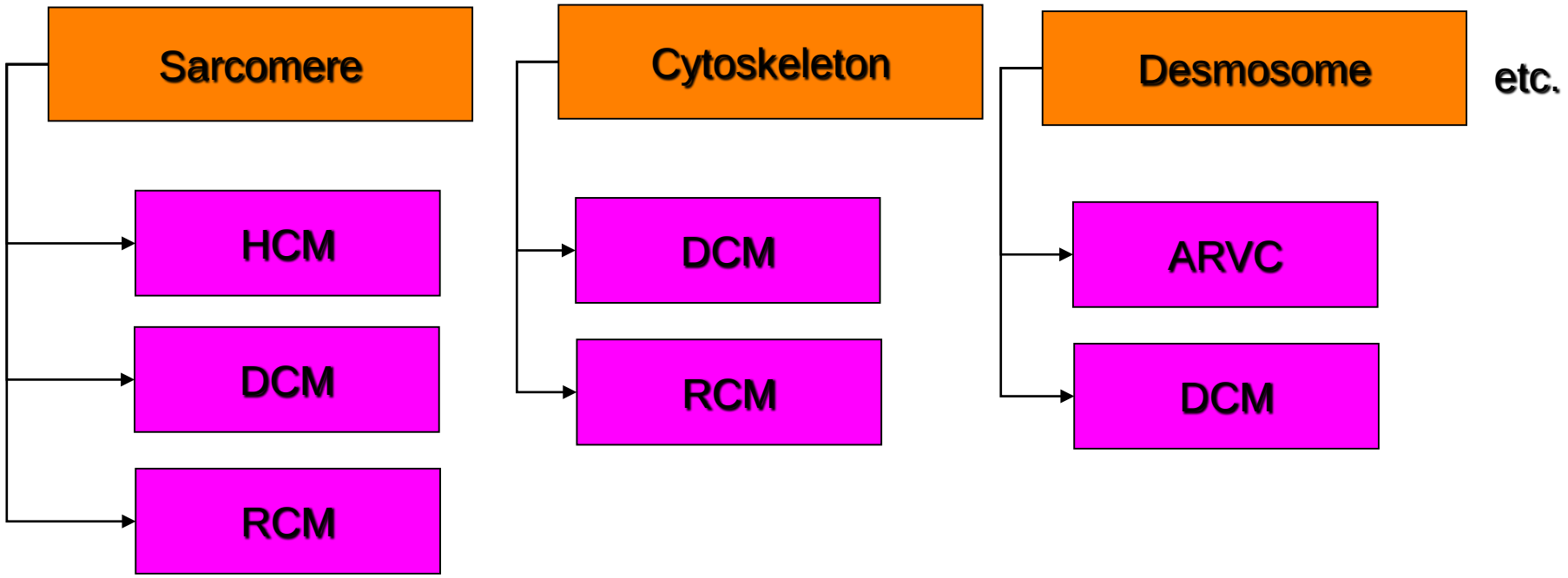
Maron BJ et al. Circulation 2006;113:1807-16

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*

European Heart Journal (2008) 29, 270–276

“Molecular” classification



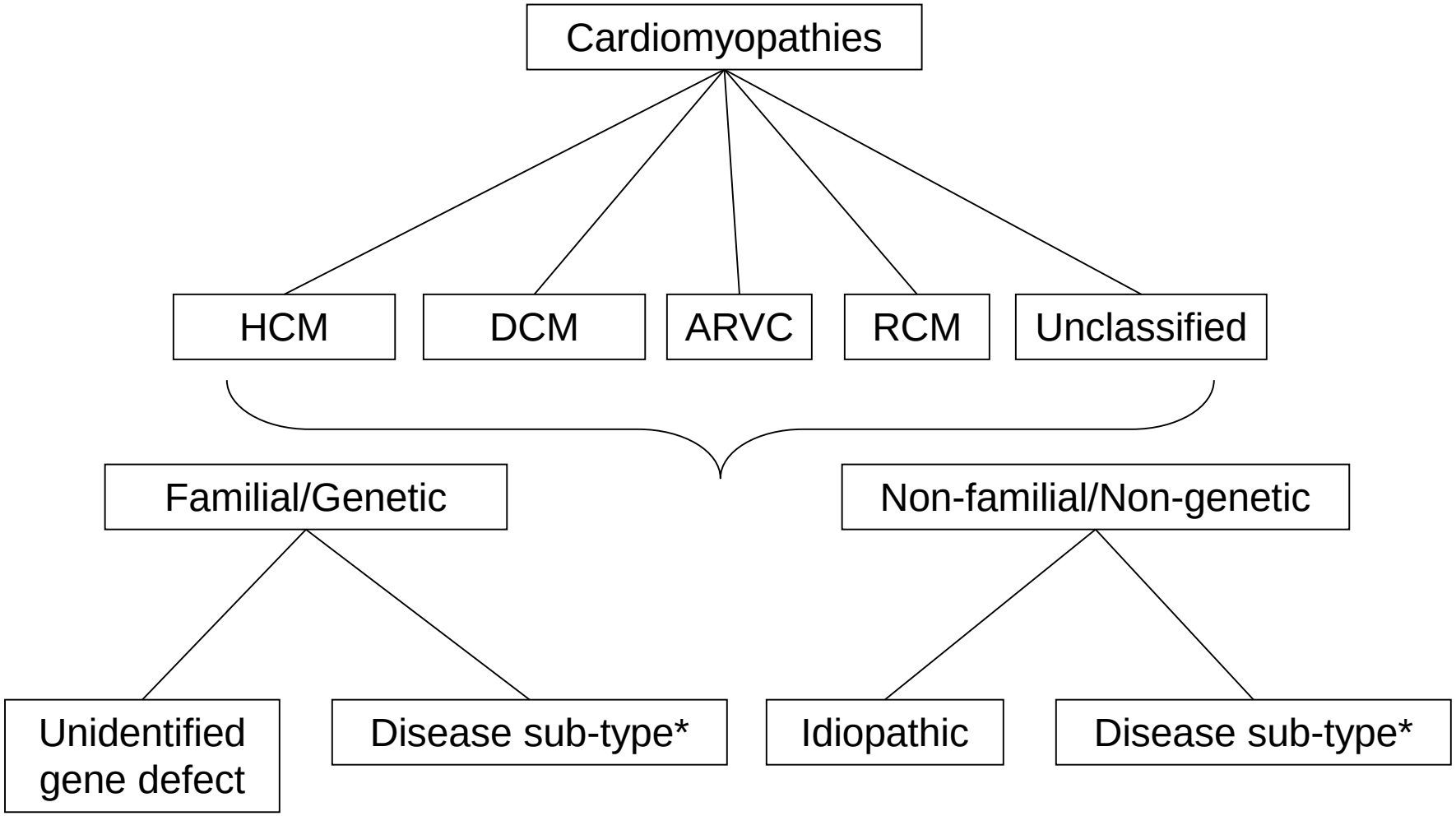
The clinical pathway

The patient is complaining of sarcomere protein disease.

Symptoms/ Signs

Phenotype (HCM/DCM…)

Diagnosis

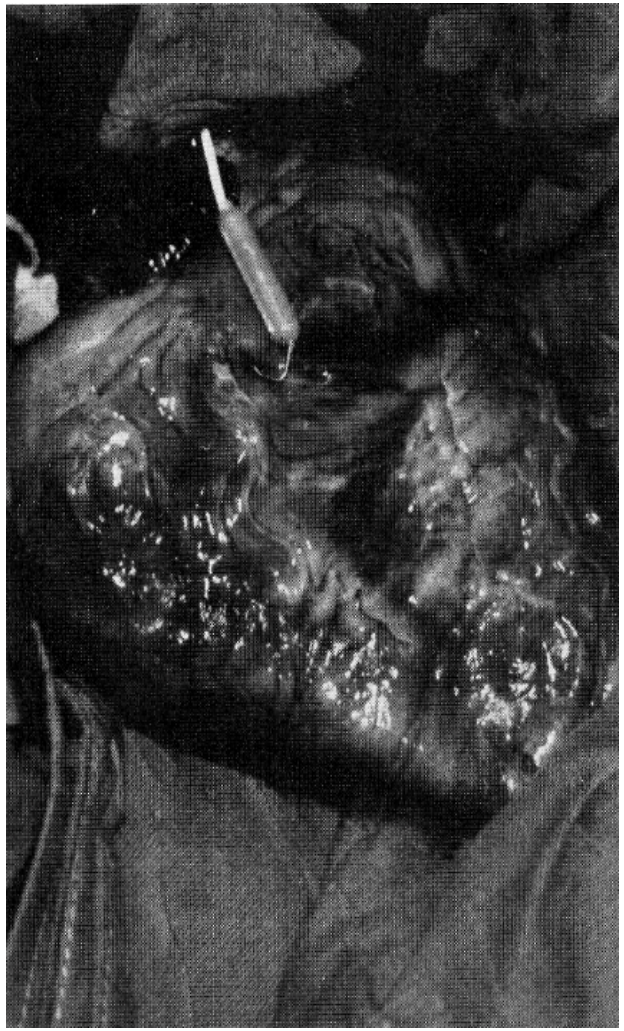


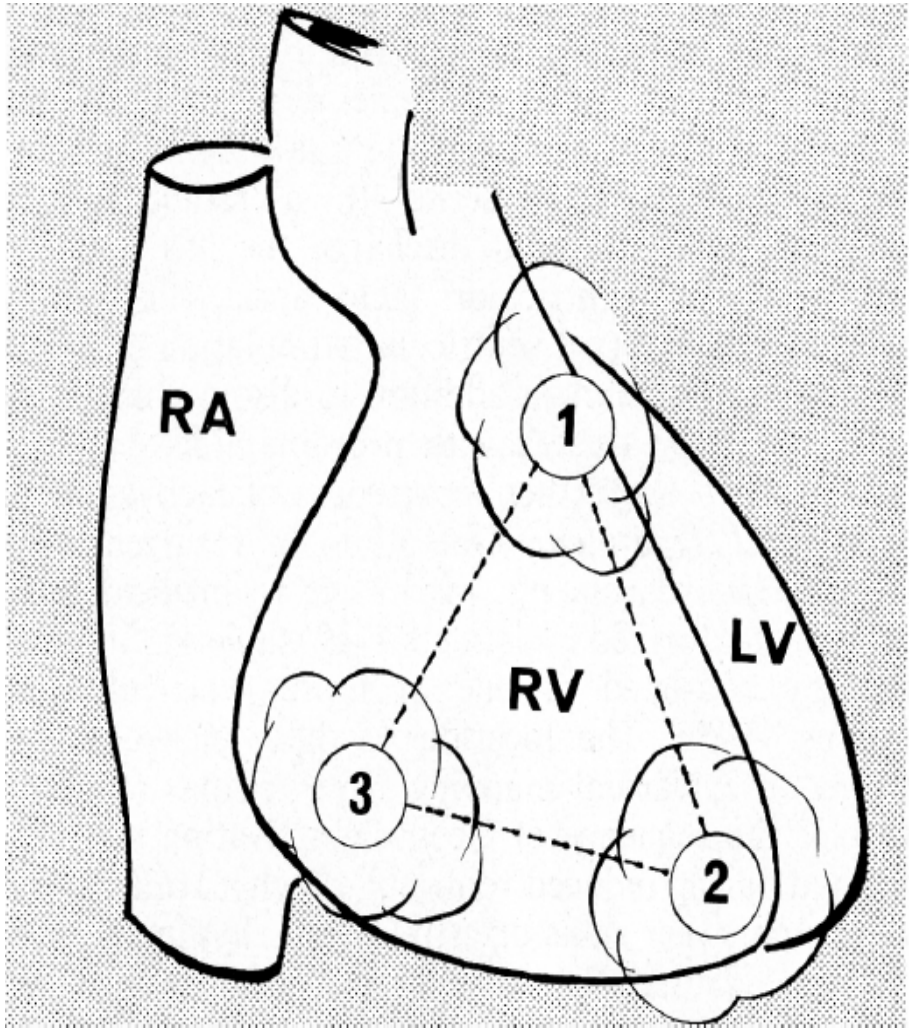
European WG on Myocardial and Pericardial Diseases (EHJ 2007)

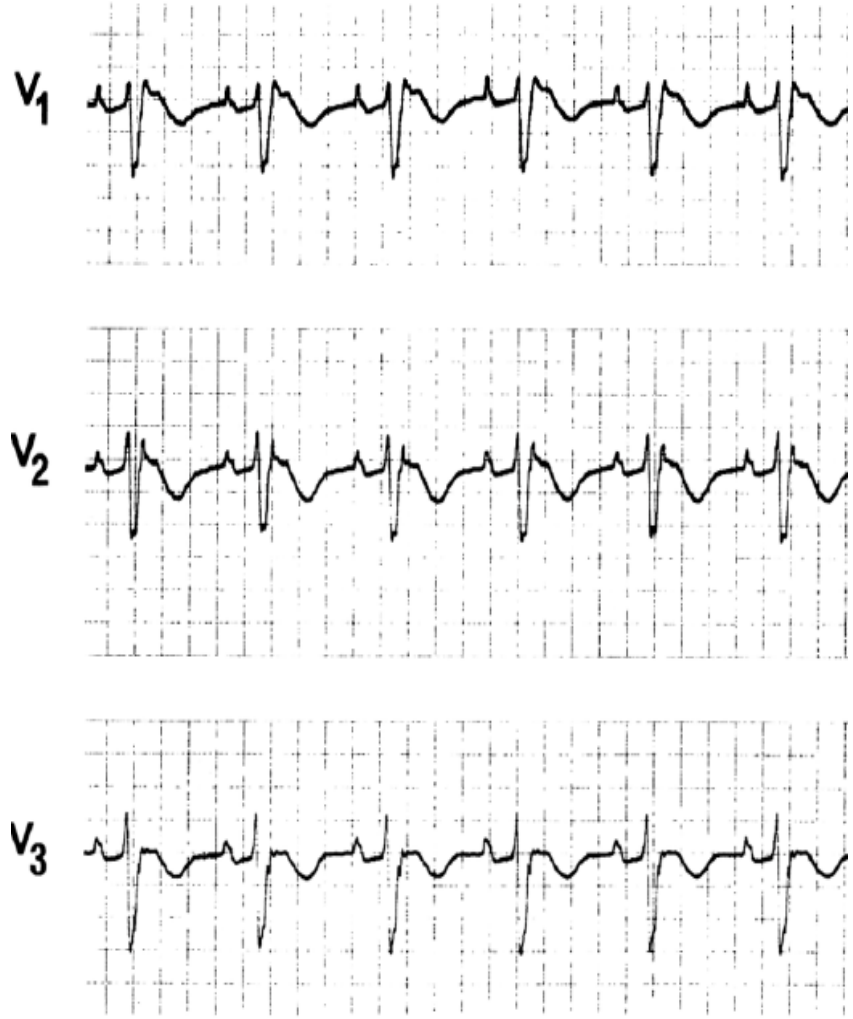
Limitations: 2021

- Cardiomyopathies no longer “idiopathic”
- Overlapping phenotypes (“one gene many diseases, one disease many genes”)
- New phenotypes (LVNC, TTS)
- No consideration of advances in molecular biology

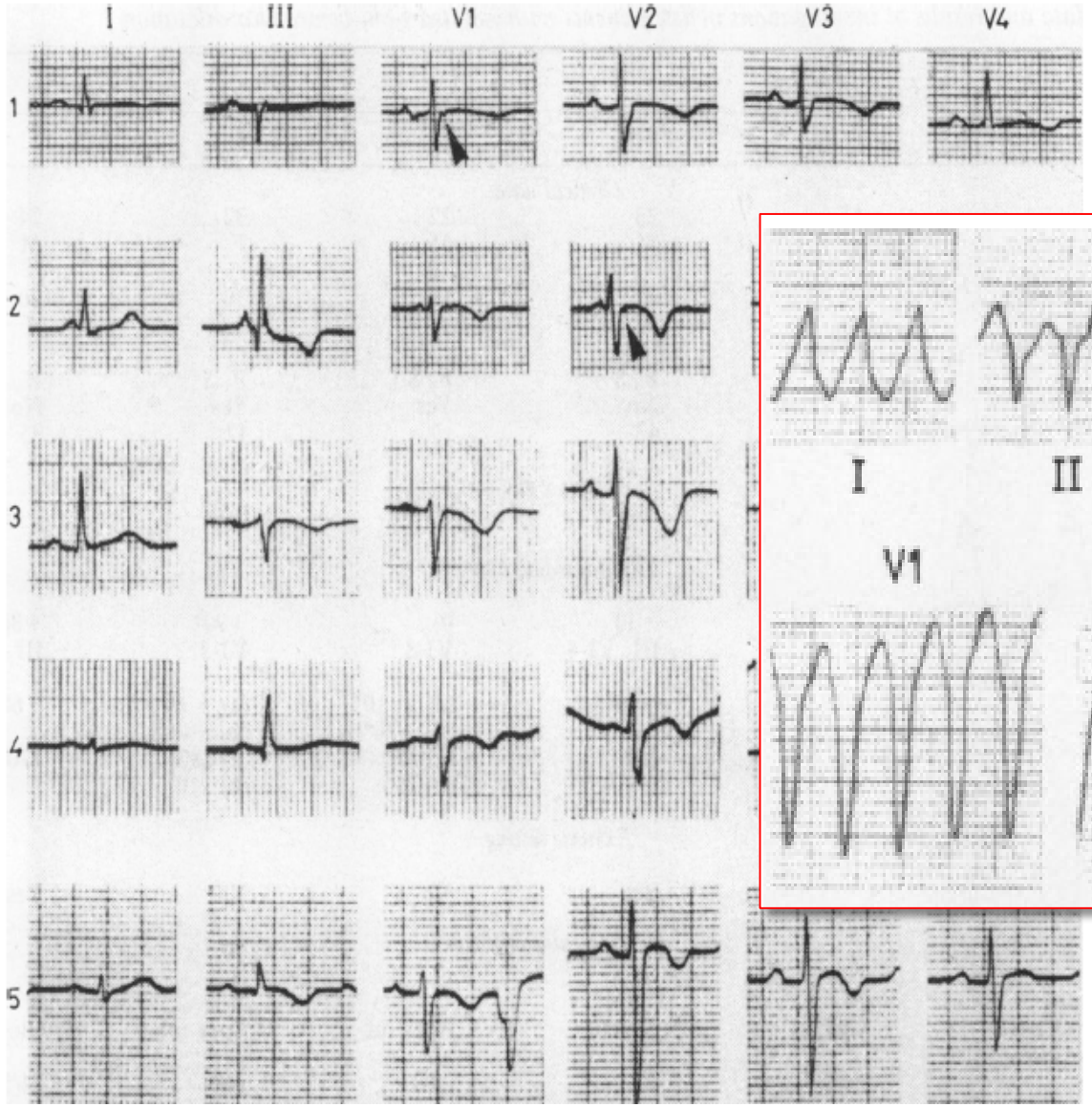
Arrhythmogenic Right Ventricular Cardiomyopathy

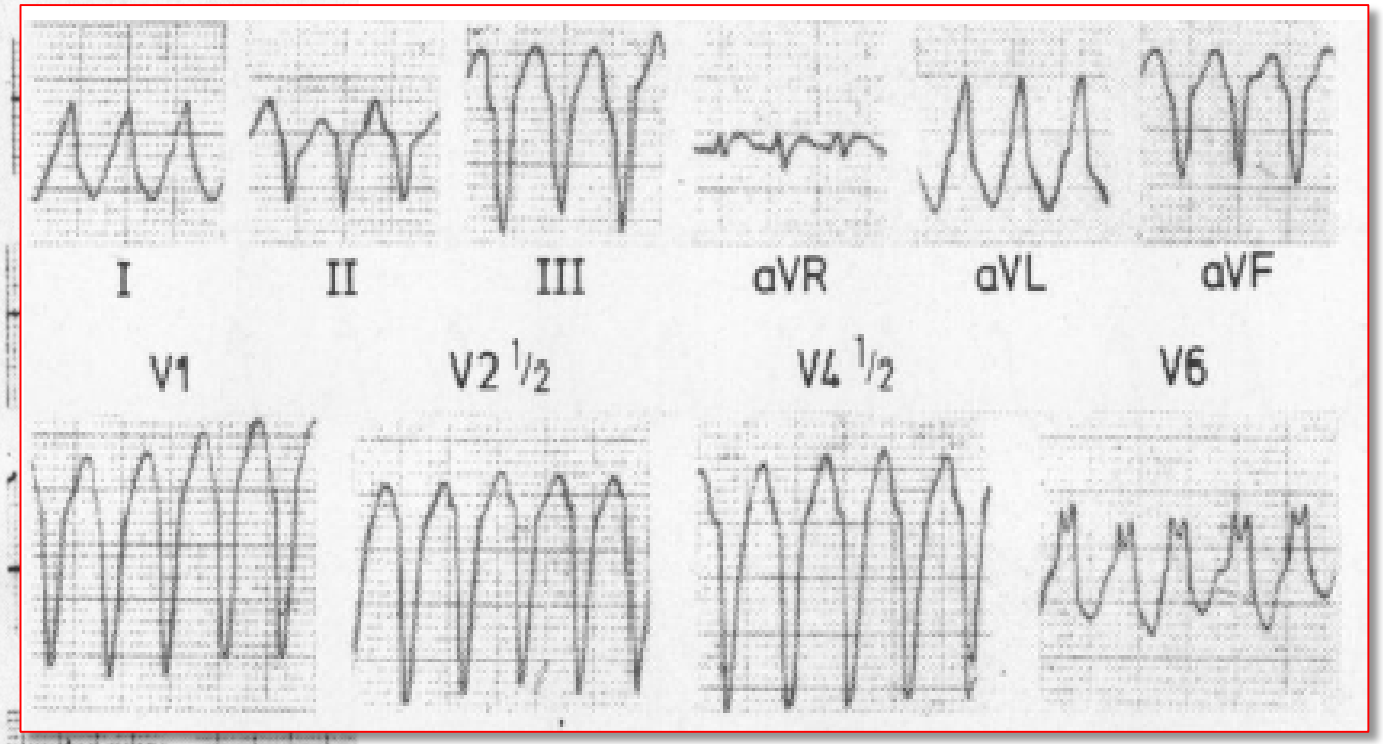






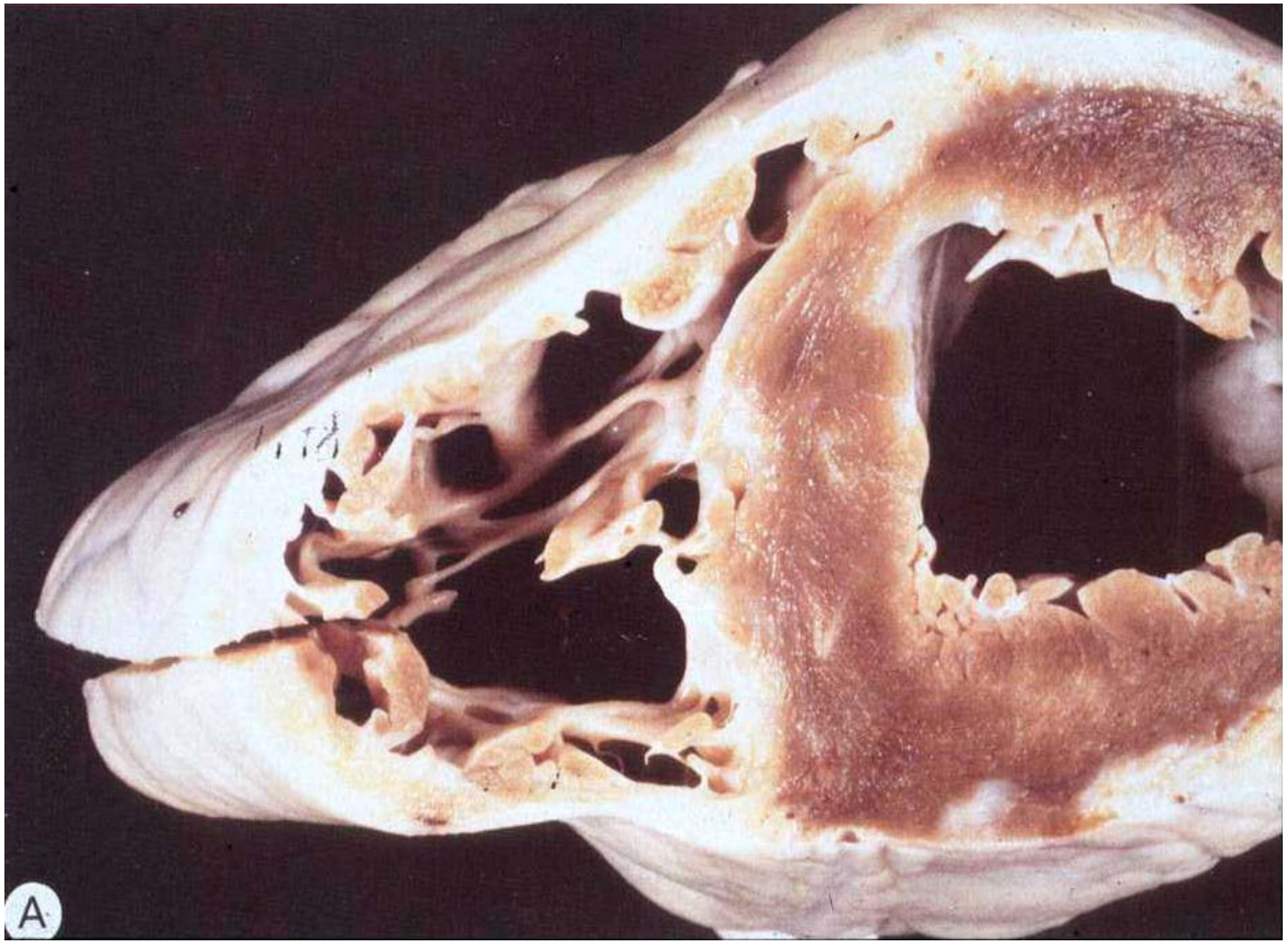
Circulation 1982; 2: 65



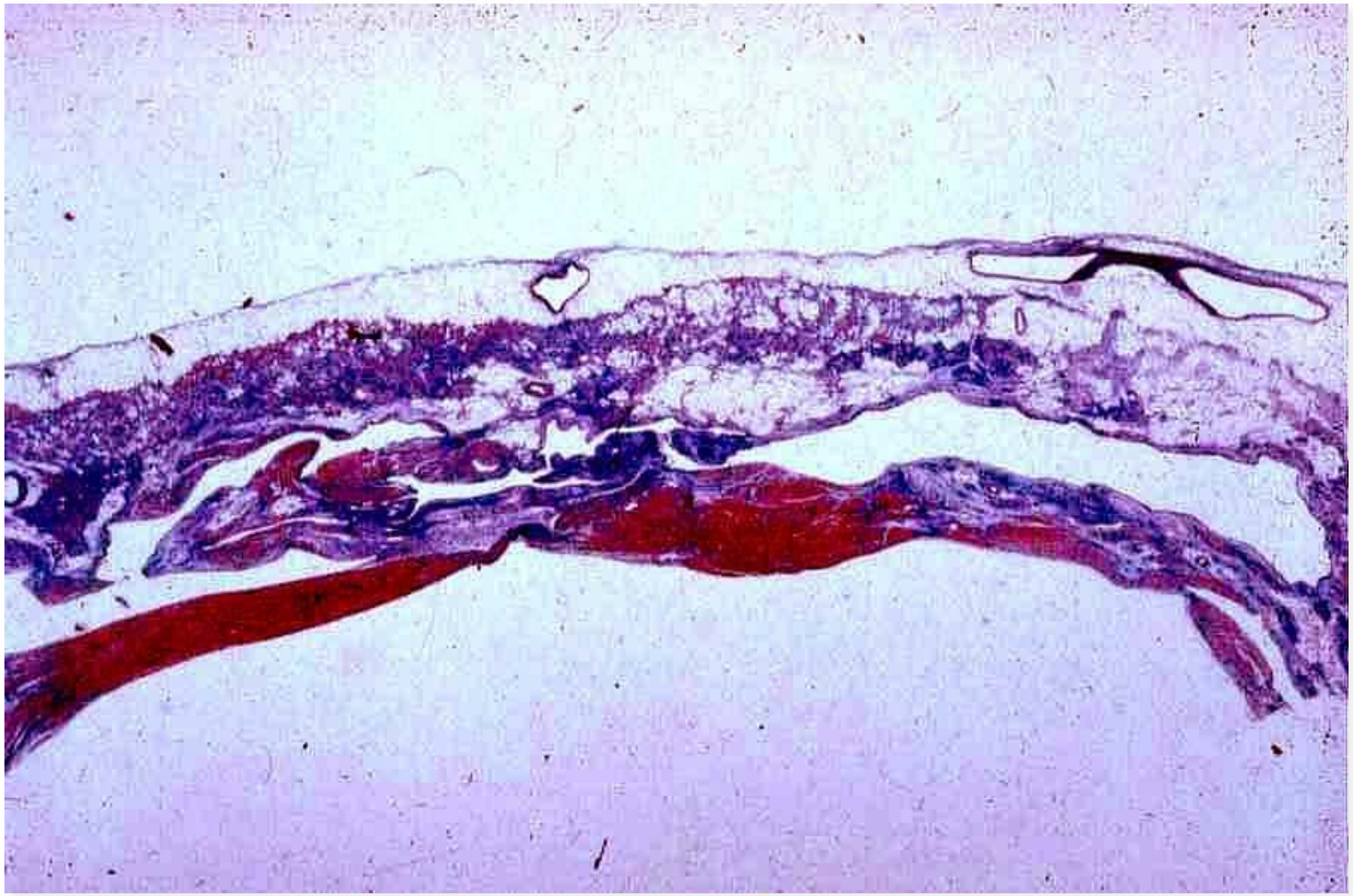


Br Heart J 1984 51: 15-24

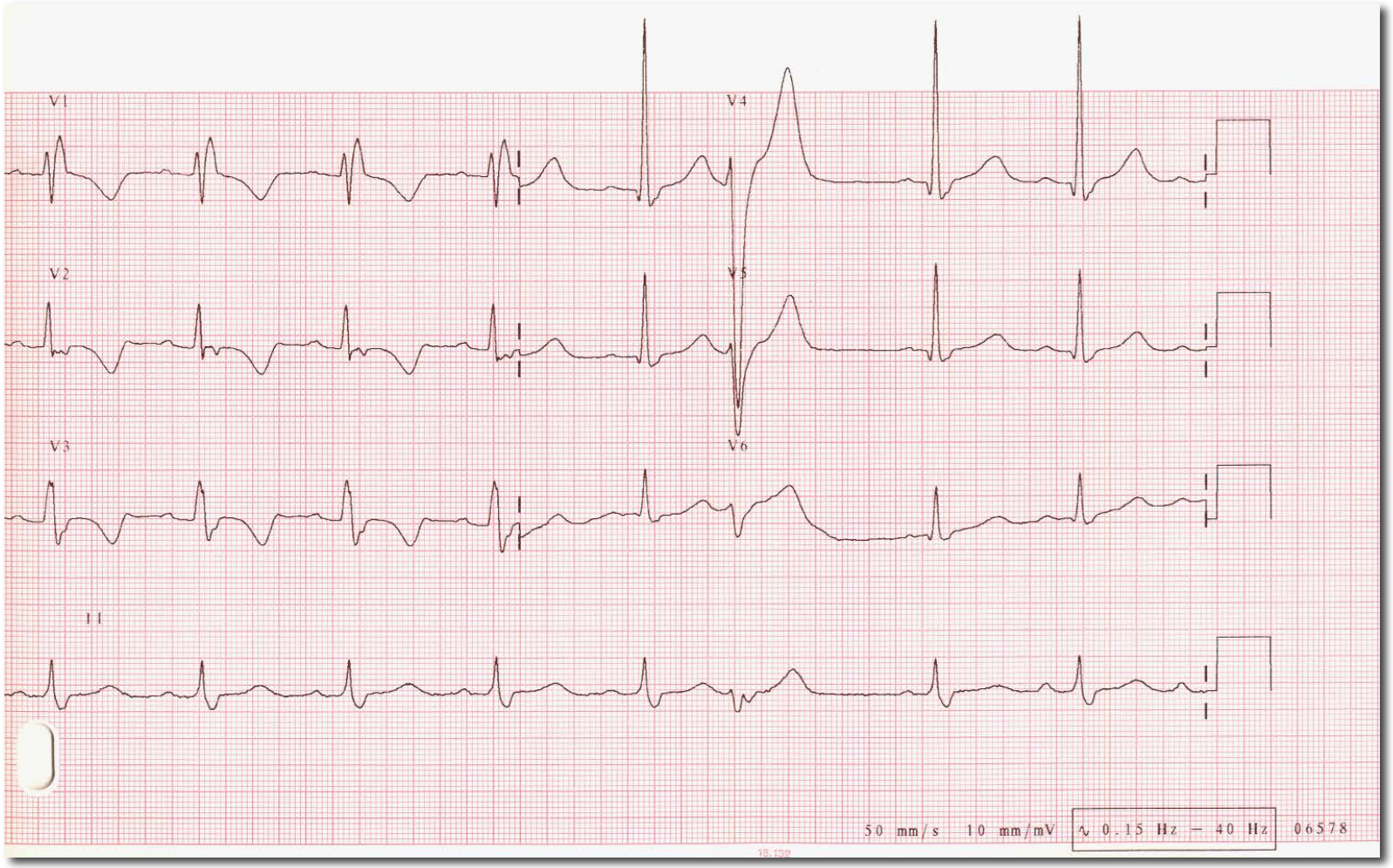
Arrhythmogenic Right Ventricular Cardiomyopathy

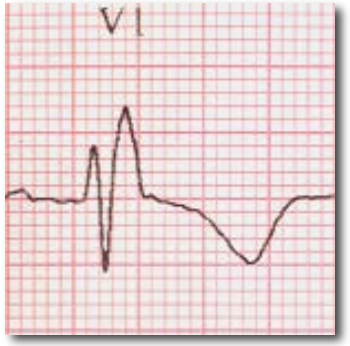


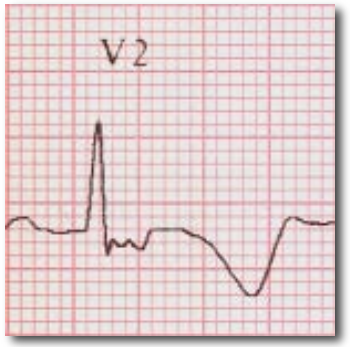
Arrhythmogenic Right Ventricular Cardiomyopathy

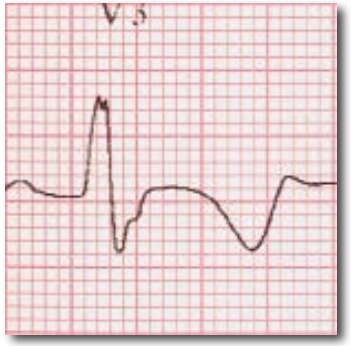


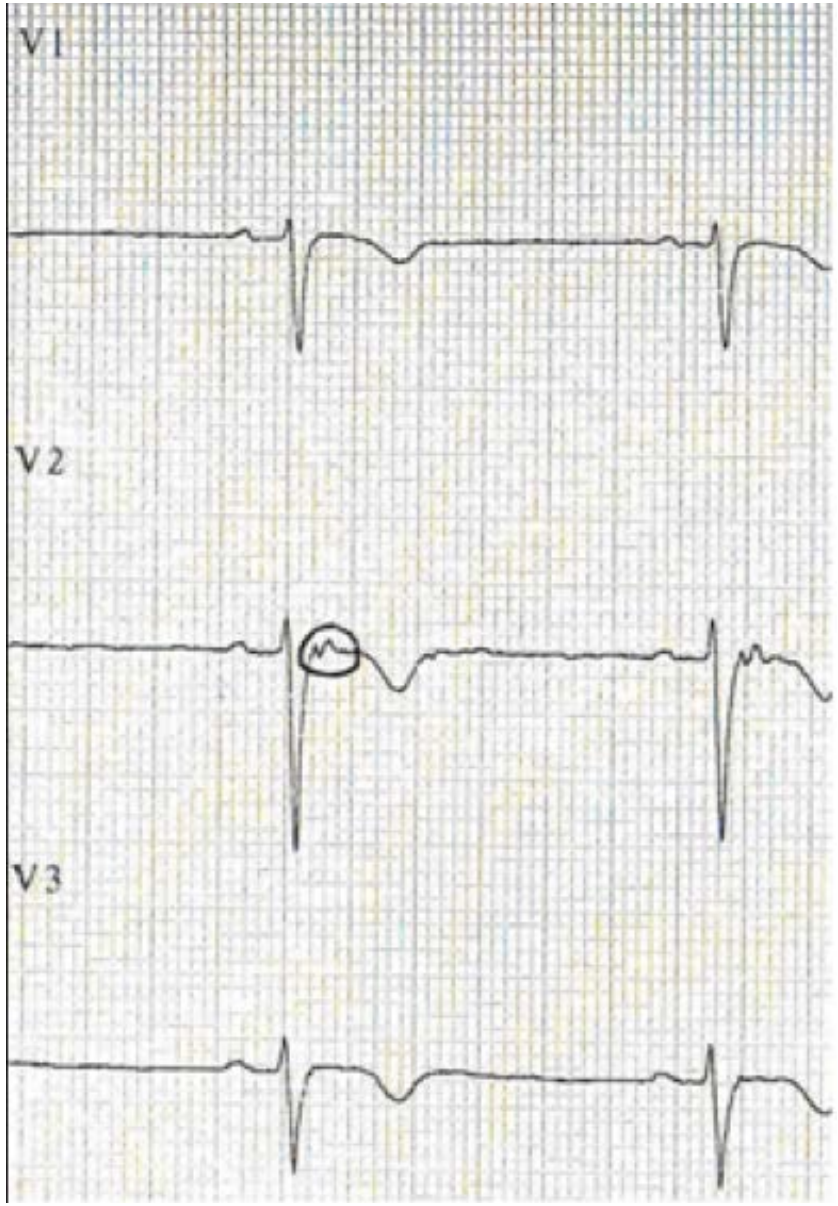
ARVC: Electrocardiography

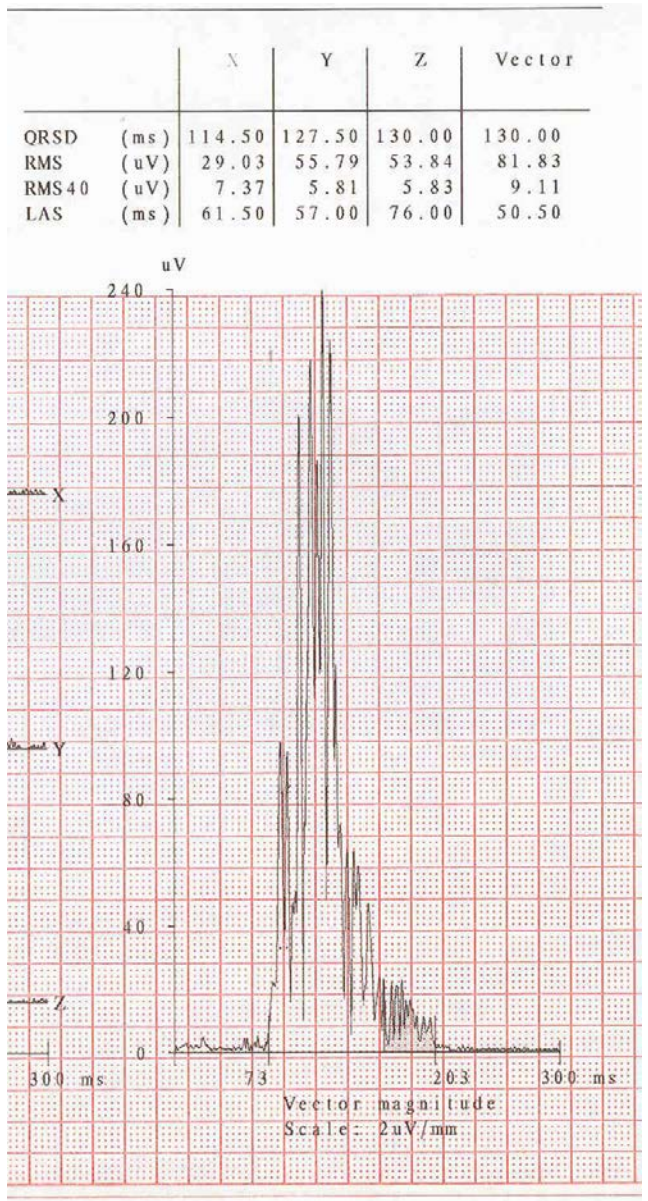








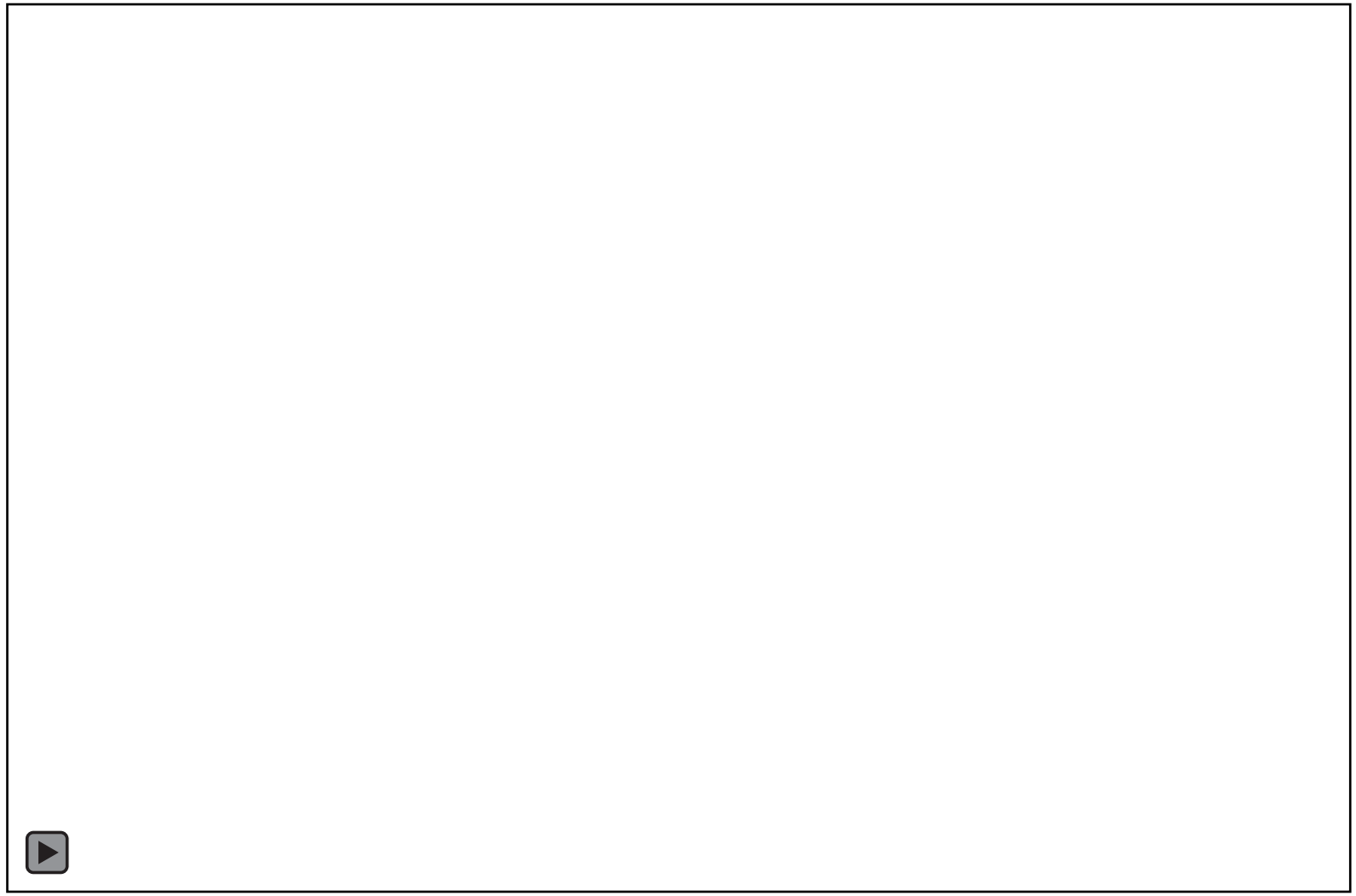




>114 ms

< 20 uV

>38 msec



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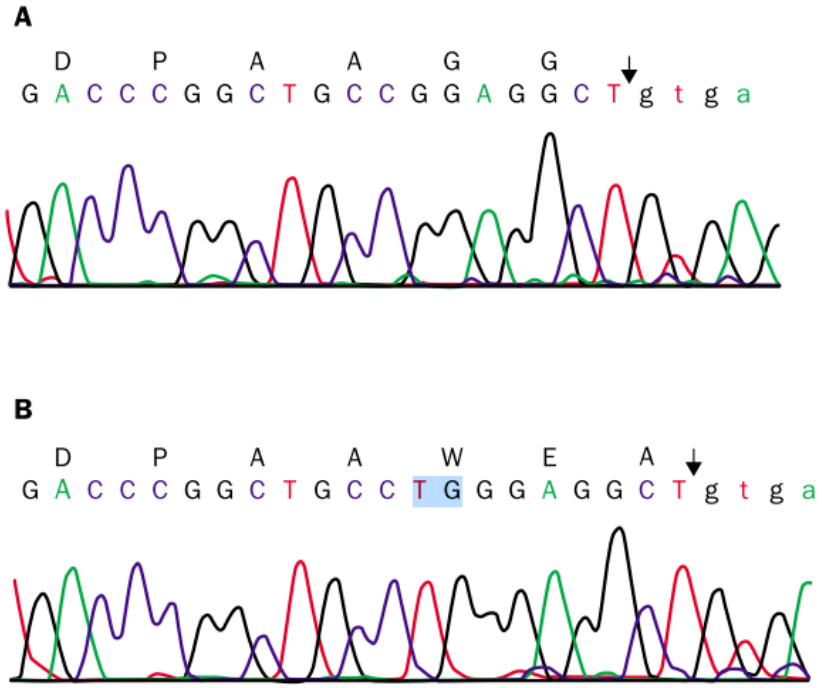
< Previous Article Volume 355, No. 9221, p2119–2124, 17 June 2000 Next Article >

Articles

Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease)

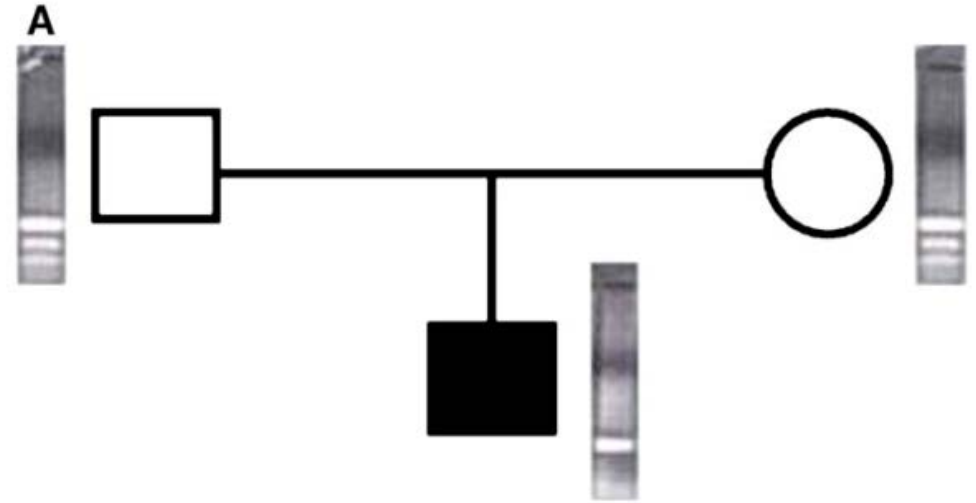
Godfrina McKoy, PhD, Nikos Protonotarios, MD, Andrew Crosby, PhD, Adalena Tsatsopoulou, MD, Aris Anastasakis, MD, Aman Coonar, MB, Mark Norman, MD, Christina Baboonian, PhD, Steve Jeffery, PhD, Prof William J McKenna, MD

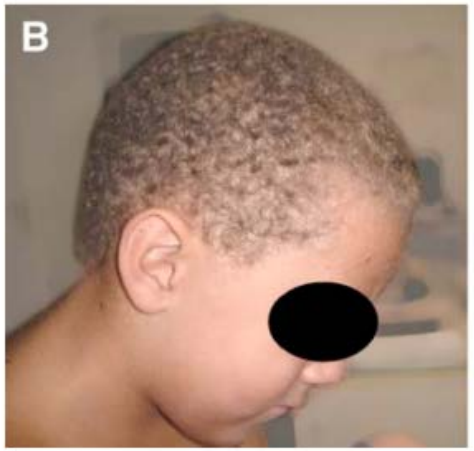
Published: 17 June 2000

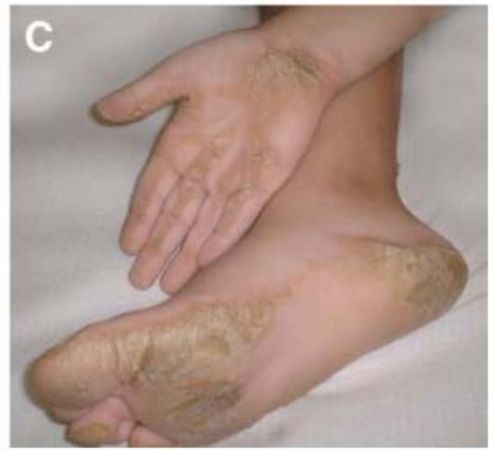


Pk2157del2

frameshift and premature termination of translation







+ ARVC

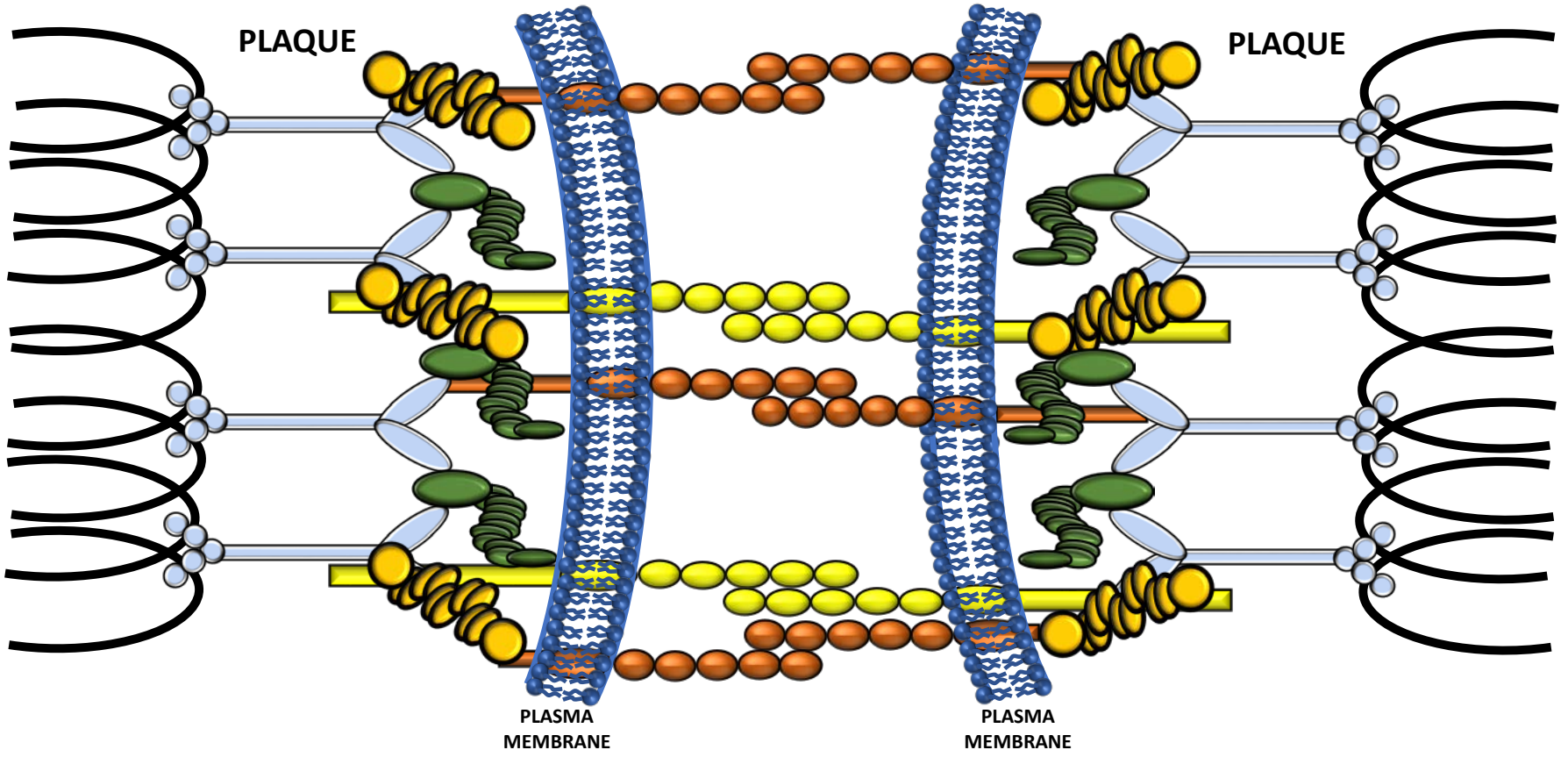
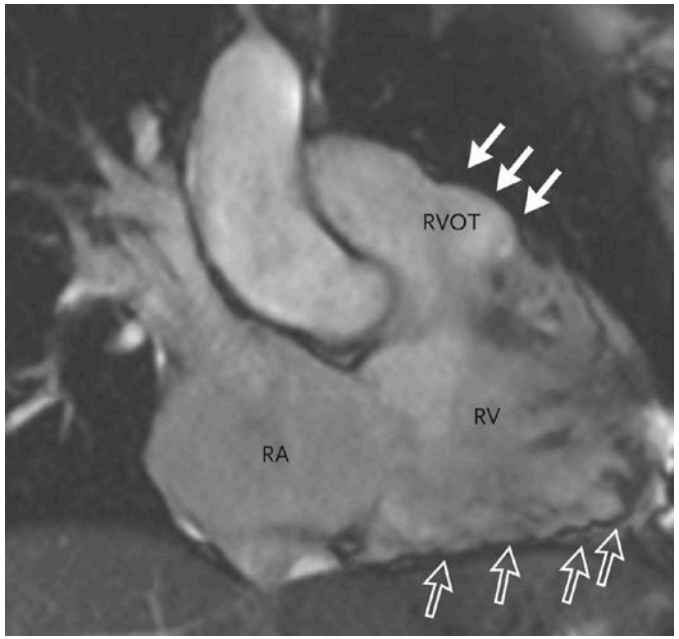
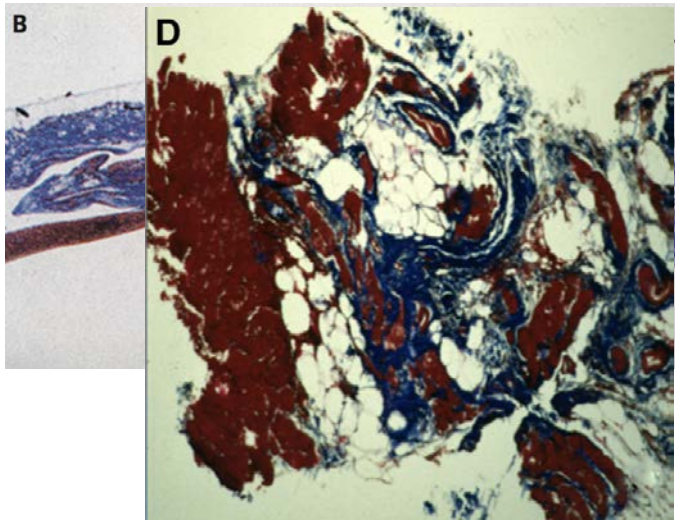


Figure 1. Schematic model of a desmosome.

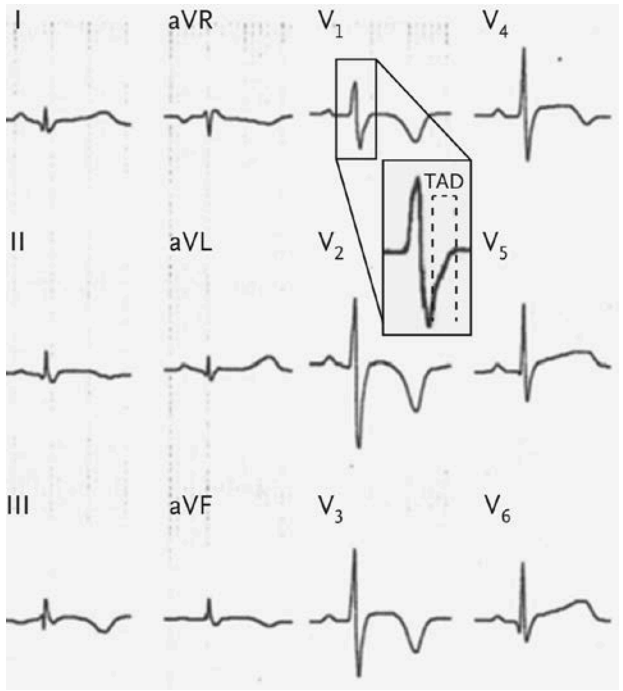
Desmoplakin
Desmoglein
Plakoglobin
Desmocollin
Plakophilin
Intermediate filaments

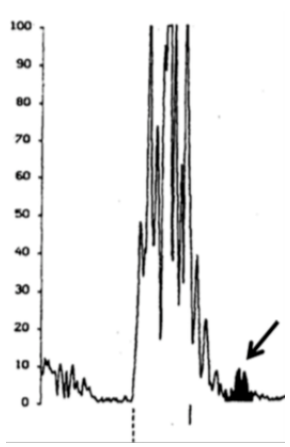
Structural

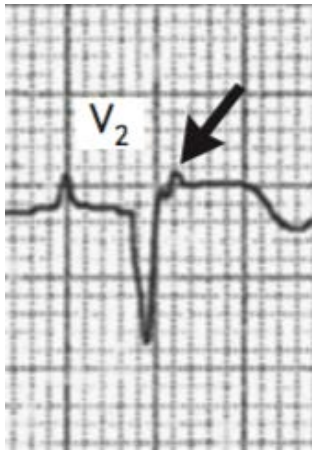




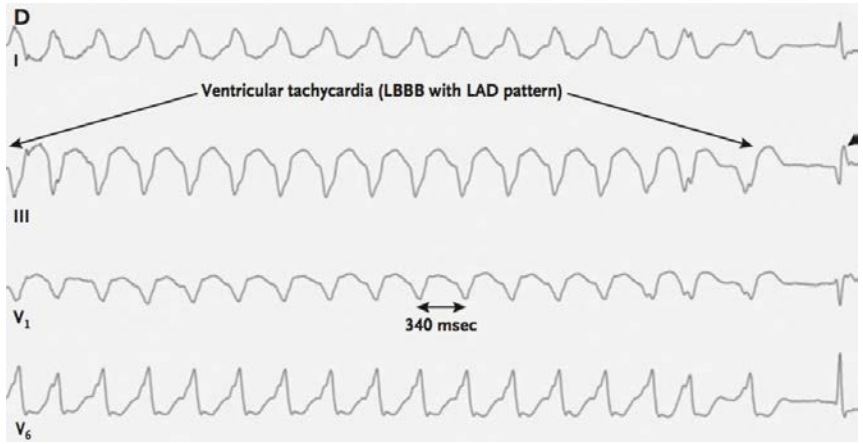
Electrical

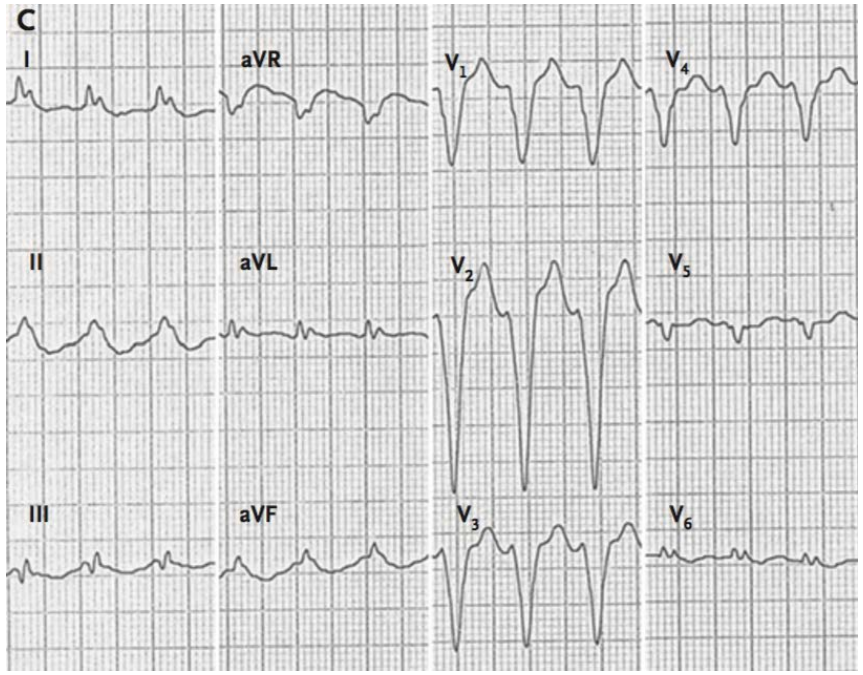






Arrhythmic





Corrado et al. NEJM 2017

Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Proposed Modification of the Task Force Criteria

Frank I. Marcus[1]* Chair, William J. McKenna[2] Co-Chair, Duane Sherrill[1], Cristina Basso[3], Barbara Bauce[3], David A. Bluemke[4], Hugh Calkins[5], Domenico Corrado[3], Moniek G.P.J. Cox[6], James P. Daubert[7], Guy Fontaine[10], Kathleen Gear[1], Richard Hauer[6], Andrea Nava[3], Michael H. Picard[11], Nikos Protonotarios[13], Jeffrey E. Saffitz[12], Danita M. Yoerger Sanborn[11], Jonathan S. Steinberg[9], Harikrishna Tandri[5], Gaetano Thiene[3], Jeffrey A. Towbin[14], Adalena Tsatsopoulou[13], Thomas Wichter[15], and Wojciech Zareba[8]

Marcus et al. European Heart Journal (2010) vol. 31 (7) pp. 806-14

Table 1 Comparison of original and revised task force criteria

Original task force criteria	Revised task force criteria
I. Global or regional dysfunction and structural alterations*	
Major	
	By 2D echo:
• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment • Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) • Severe segmental dilatation of the RV	• Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): — PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) — PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) — *or* fractional area change ≤33%
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) — *or* RV ejection fraction ≤40%
	By RV angiography:
	• Regional RV akinesia, dyskinesia, or aneurysm
Minor	
	By 2D echo:
• Mild global RV dilatation and/or ejection fraction reduction with normal LV • Mild segmental dilatation of the RV • Regional RV hypokinesia	• Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): — PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) — PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) — *or* fractional area change >33% to ≤40%
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) — *or* RV ejection fraction >40% to ≤45%
II. Tissue characterization of wall	
Major	
• Fibrofatty replacement of myocardium on endomyocardial biopsy	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor	
• Inverted T waves in right precordial leads (V_2 and V_3) (people age >12 years, in absence of right bundle-branch block)	• Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block

Continued

Table 1 *Continued*

Original task force criteria	Revised task force criteria
IV. Depolarization/conduction abnormalities	
Major	
• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)
Minor	
• Late potentials (SAECG)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms • Root-mean-square voltage of terminal 40 ms ≤20 μV • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
V. Arrhythmias	
Major	
	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	
• Left bundle-branch block-type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) • Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • > 500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
Major	
• Familial disease confirmed at necropsy or surgery	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	
• Family history of premature sudden death (<35 years of age) due to suspected ARVC/D • Familial history (clinical diagnosis based on present criteria)	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

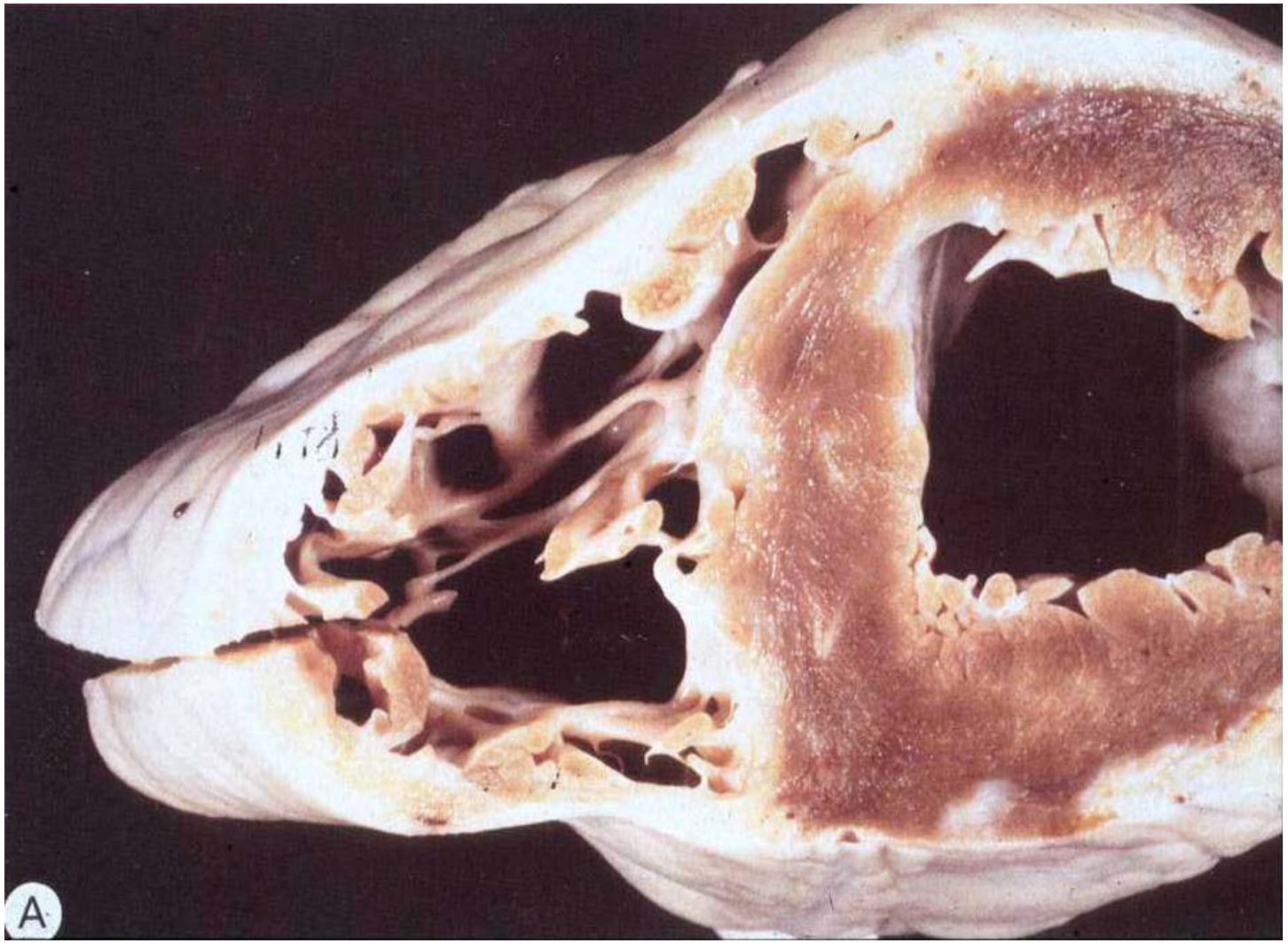
Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups.

Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

Arrhythmogenic Right Ventricular Cardiomyopathy



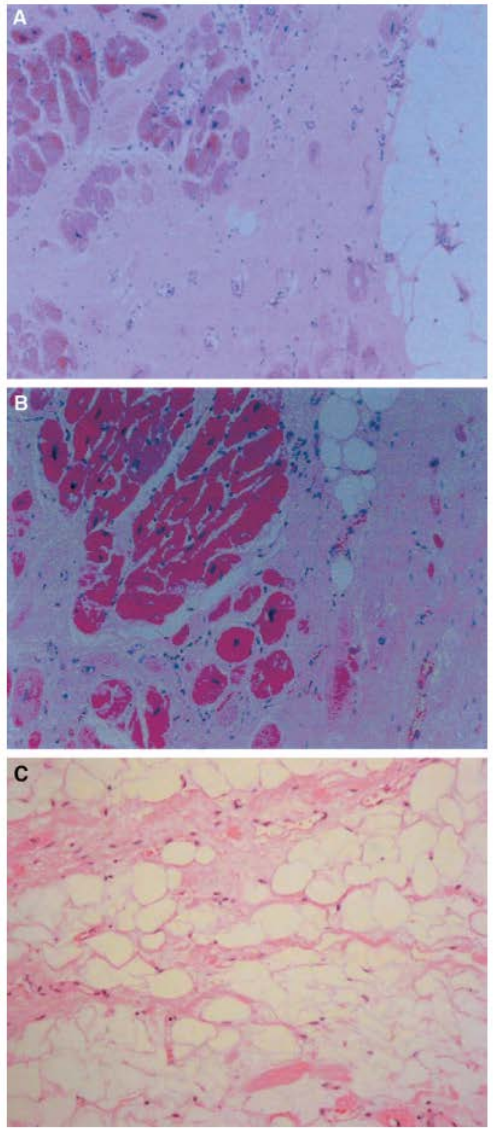


Figure 2. Histological example of LV myocardium from proband IV:1, showing myocyte loss with fibrofatty replacement (Hematoxylin and eosin staining). A, Low-power (×4) view; B, slightly higher low-power (×10) view; C, high-power view (×20).

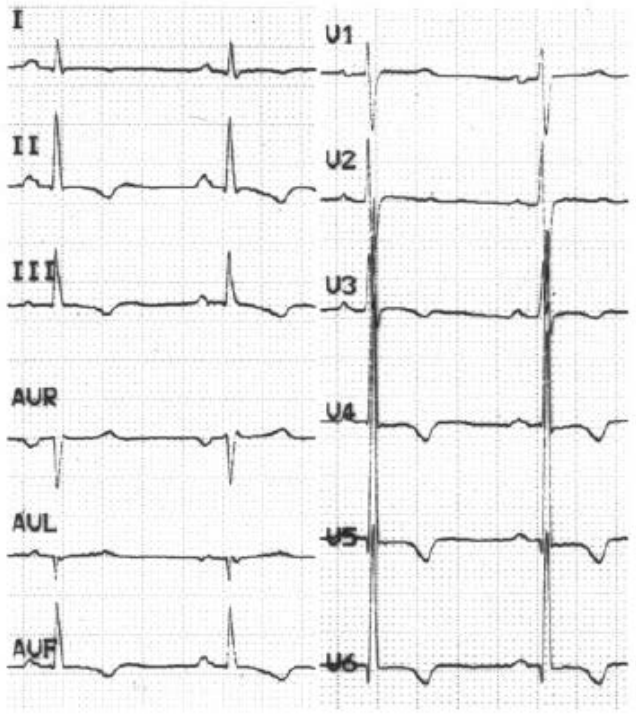


Figure 3. Typical resting 12-lead ECG findings with inferior and lateral T-wave inversion.

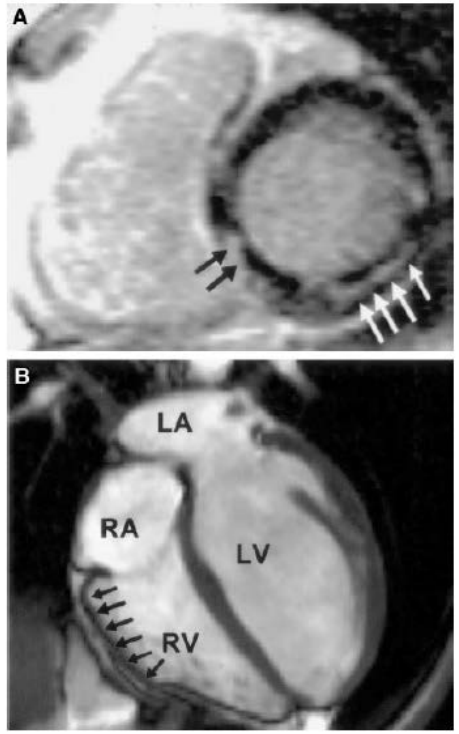
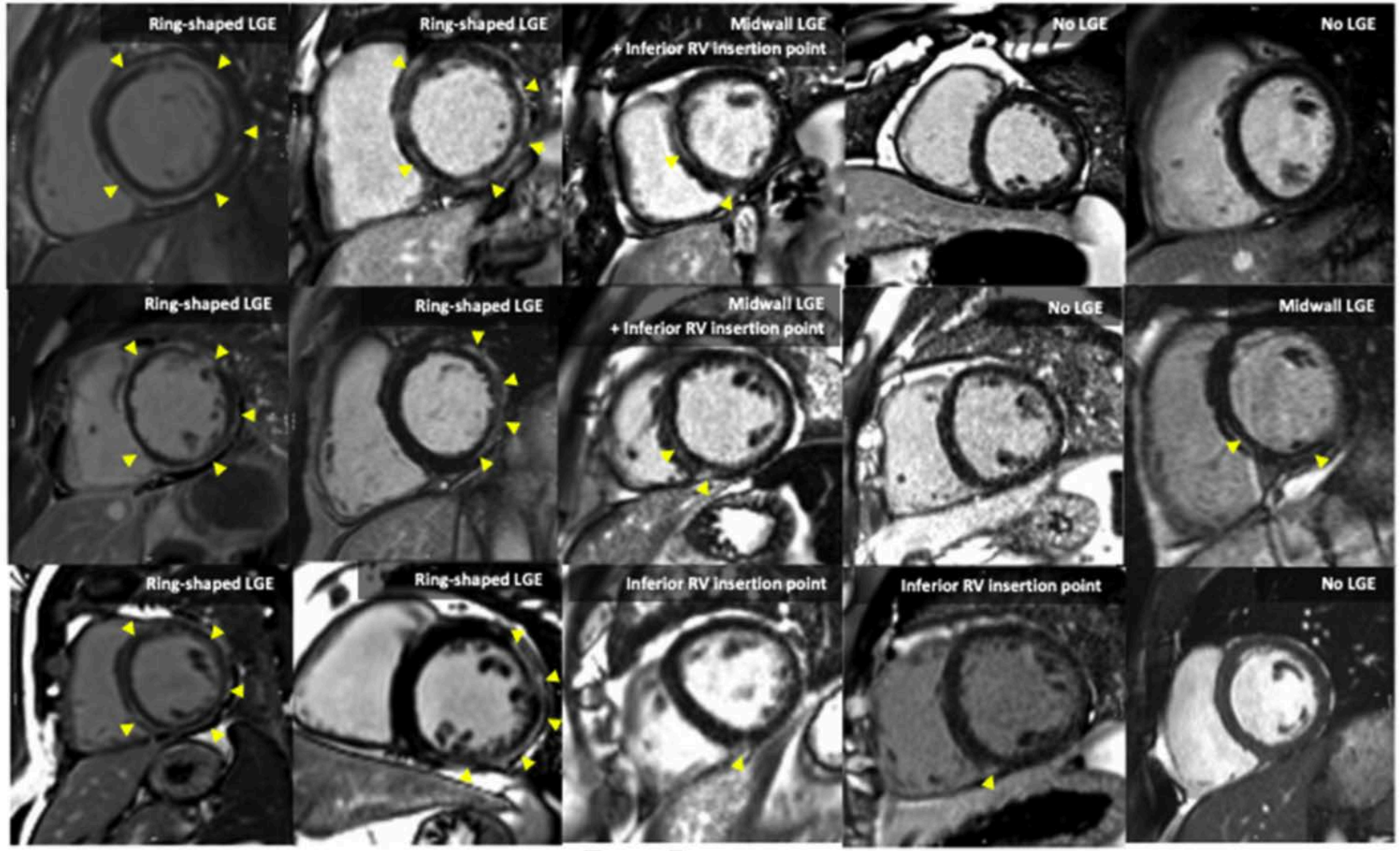
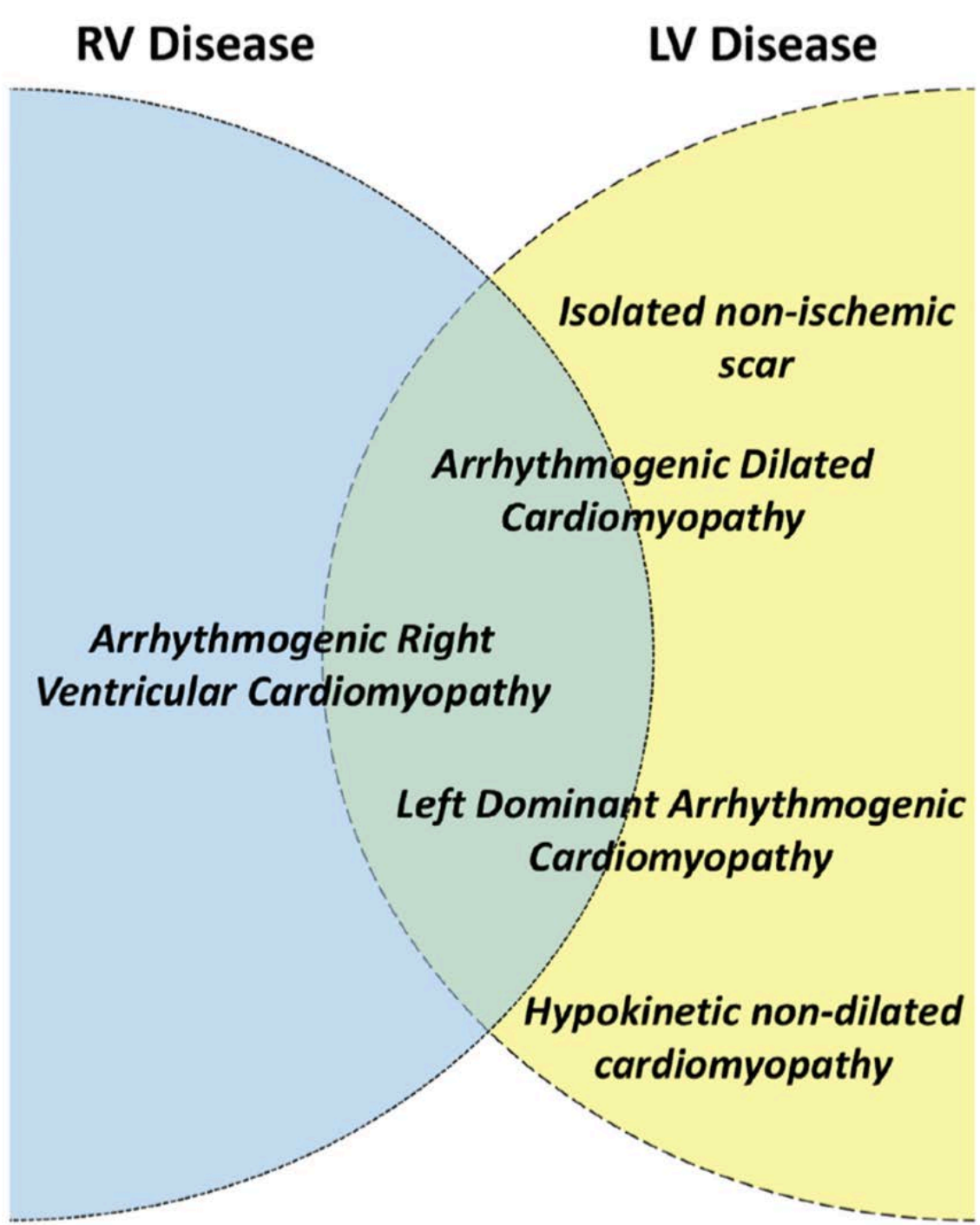
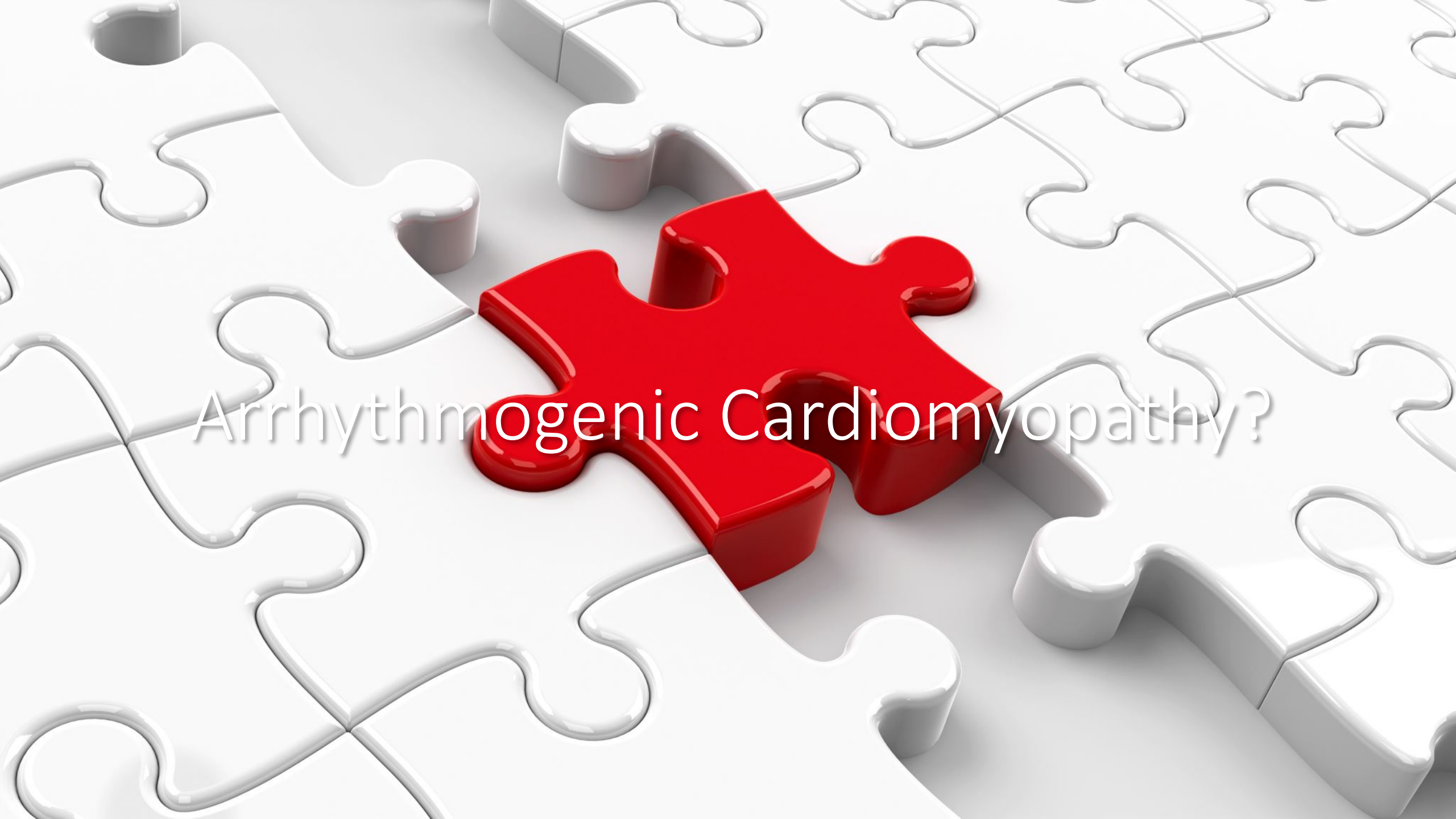


Figure 4. CMR images from 2 patients (III:7 and IV:9). A, Late gadolinium enhancement at inferolateral LV wall (white arrows) and septum (black arrows). B, Localized dilation in subtricuspid region (black arrows) of RV. This segment was markedly hypokinetic during systole. RA indicates right atrium; LA, left atrium.

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

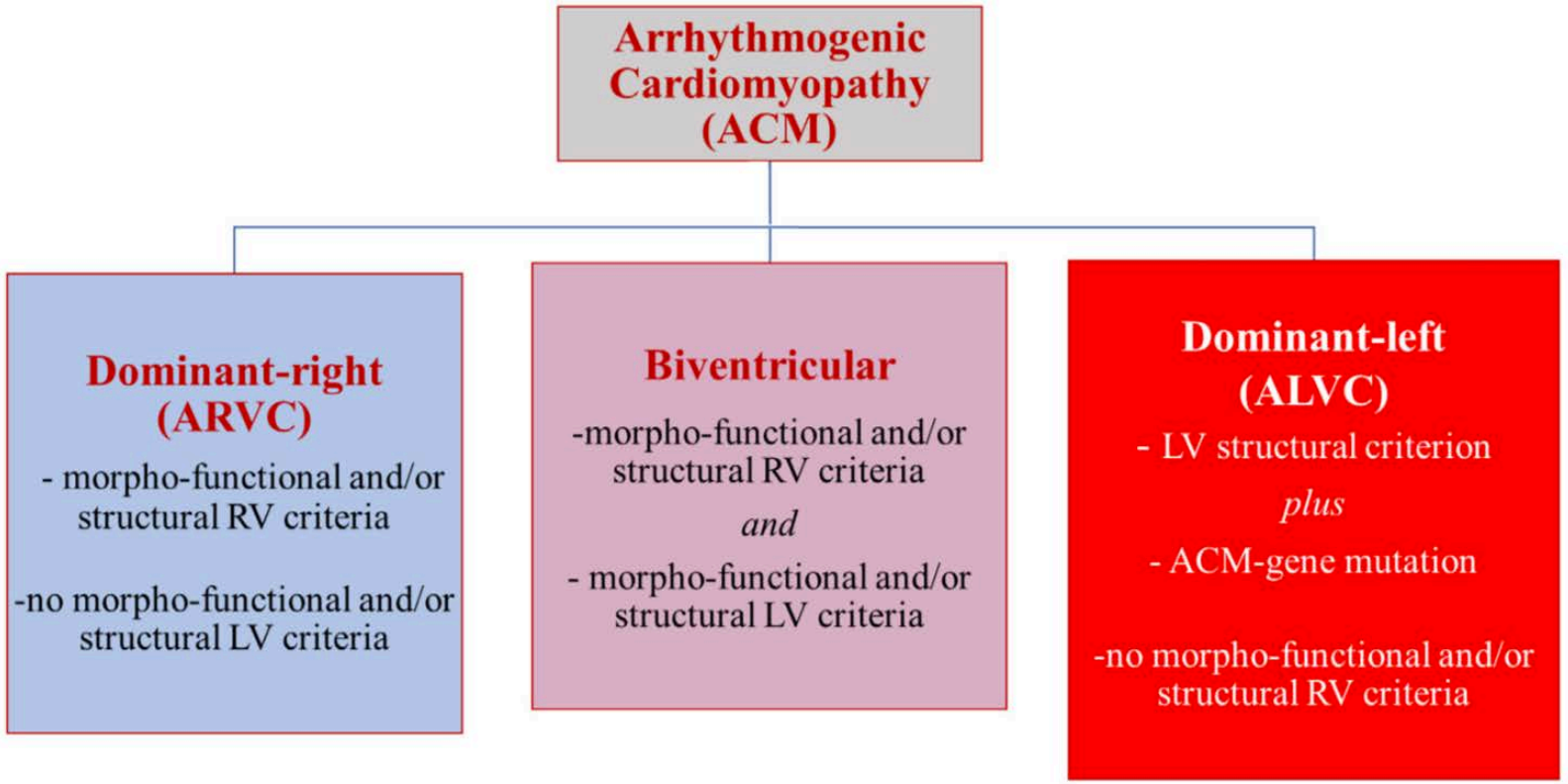

Ring-shaped LGE
Ring-shaped LGE
Midwall LGE
+ Inferior RV insertion point
No LGE
No LGE
Ring-shaped LGE
Ring-shaped LGE
Midwall LGE
+ Inferior RV insertion point
No LGE
Midwall LGE
Ring-shaped LGE
Ring-shaped LGE
Inferior RV insertion point
Inferior RV insertion point
No LGE


RV Disease
LV Disease
Isolated non-ischemic scar
Arrhythmogenic Dilated Cardiomyopathy
Arrhythmogenic Right Ventricular Cardiomyopathy
Left Dominant Arrhythmogenic Cardiomyopathy
Hypokinetic non-dilated cardiomyopathy


Arrhythmogenic Cardiomyopathy?

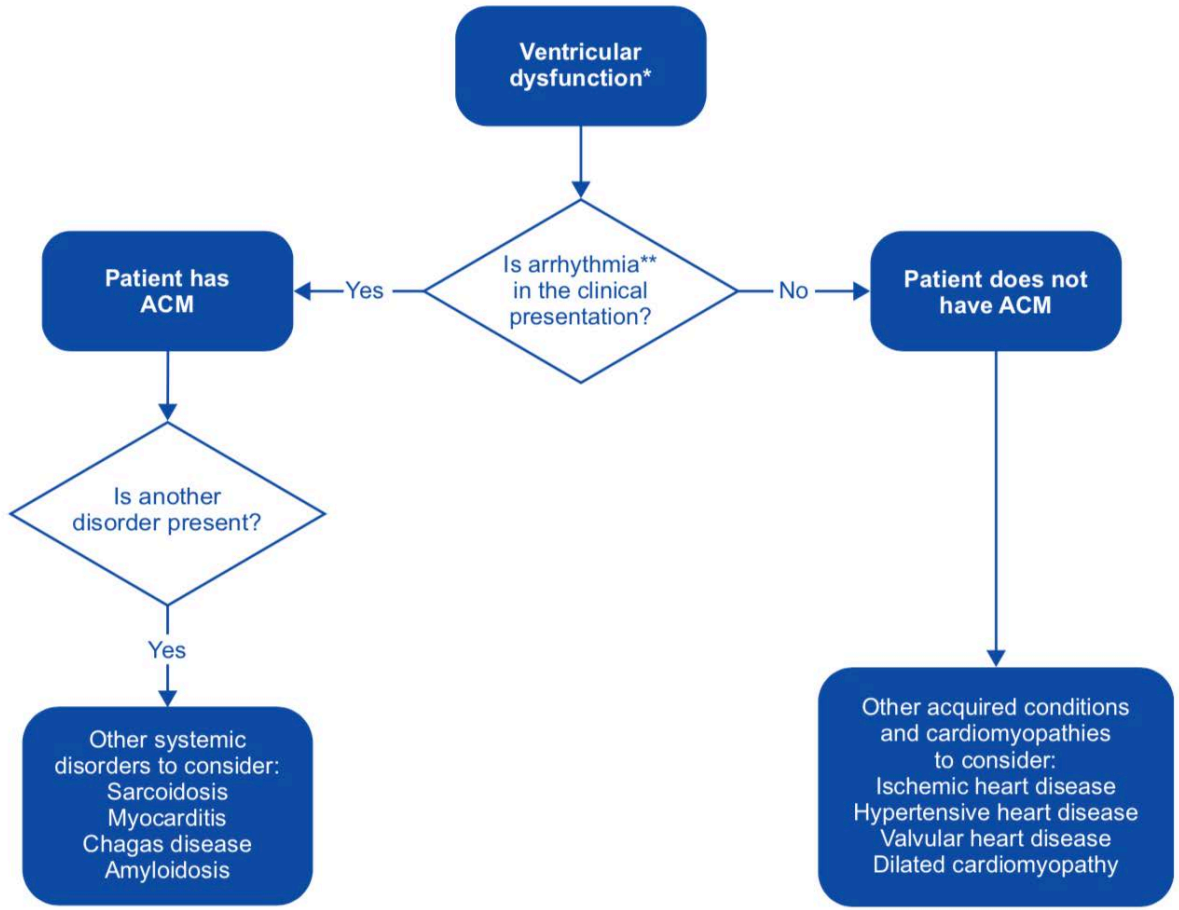
Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria

Domenico Corrado [a,*], Martina Perazzolo Marra [a], Alessandro Zorzi [a], Giorgia Beffagna [a], Alberto Cipriani [a], Manuel De Lazzari [a], Federico Migliore [a], Kalliopi Pilichou [a], Alessandra Rampazzo [b], Ilaria Rigato [a], Stefania Rizzo [a], Gaetano Thiene [a], Aris Anastasakis [c], Angeliki Asimaki [d], Chiara Bucciarelli-Ducci [e], Kristine H. Haugaa [f], Francis E. Marchlinski [g], Andrea Mazzanti [h], William J. McKenna [i], Antonis Pantazis [j], Antonio Pelliccia [k], Christian Schmied [l], Sanjay Sharma [m], Thomas Wichter [n], Barbara Bauce [a], Cristina Basso [a]



International Journal of Cardiology 319 (2020) 106–114

2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy



*Not explained by ischemic, hypertensive, or valvular heart disease
**Arrhythmia includes conduction disease, atrial arrhythmias, ventricular arrhythmias

If it doesn't fit, then do not force it

TALES FROM THE CLINIC (1)

Clinical History

42y, male

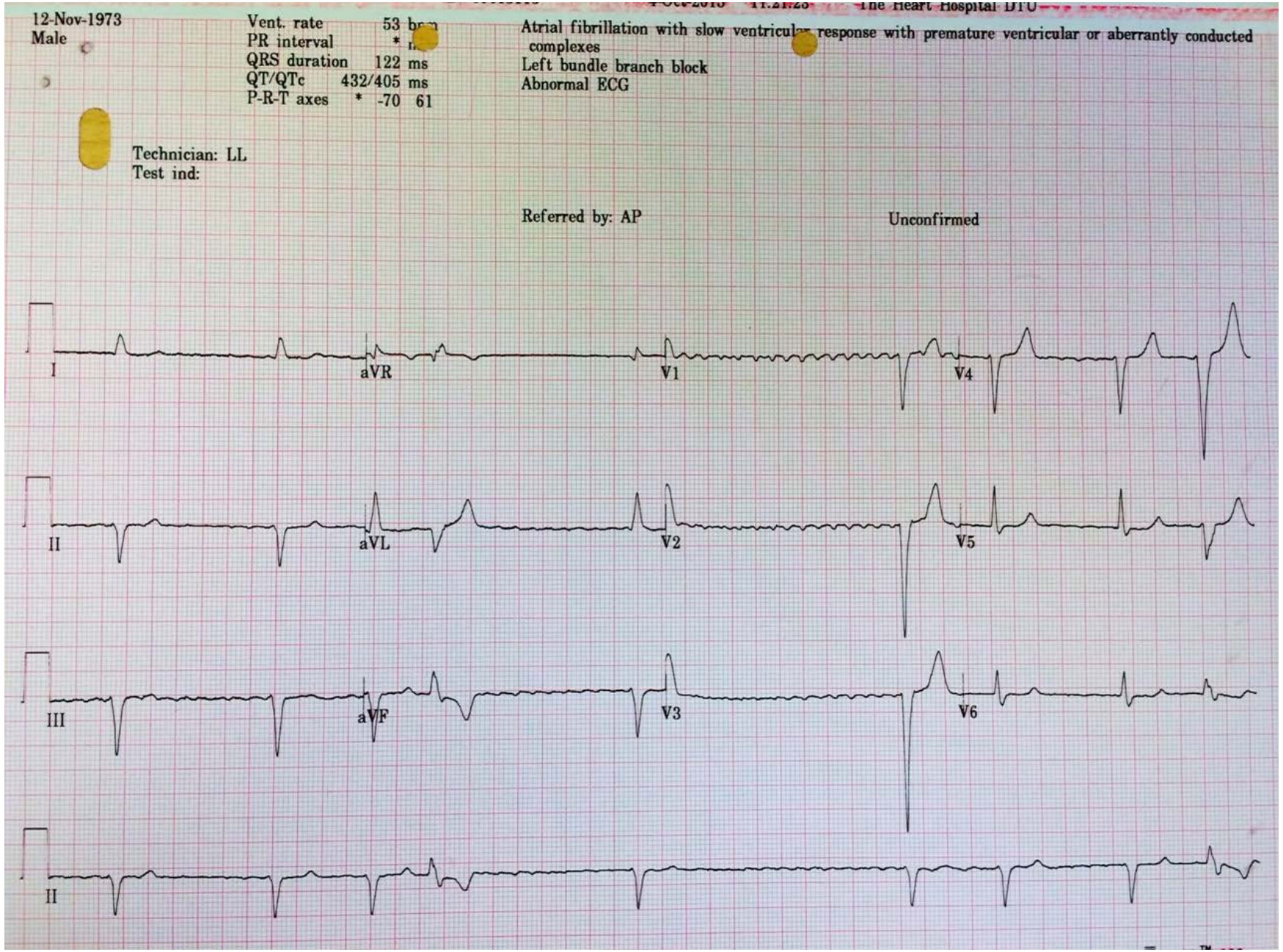
- AF 2007
  - Incidental finding
  - DCCV 2008
  - Medication: Aspirin 75mg
  - Holter: NSVT x 5 beats

- CMR: Mild impairment of LV function. Biatrial dilatation with LA diameter of 43mm.

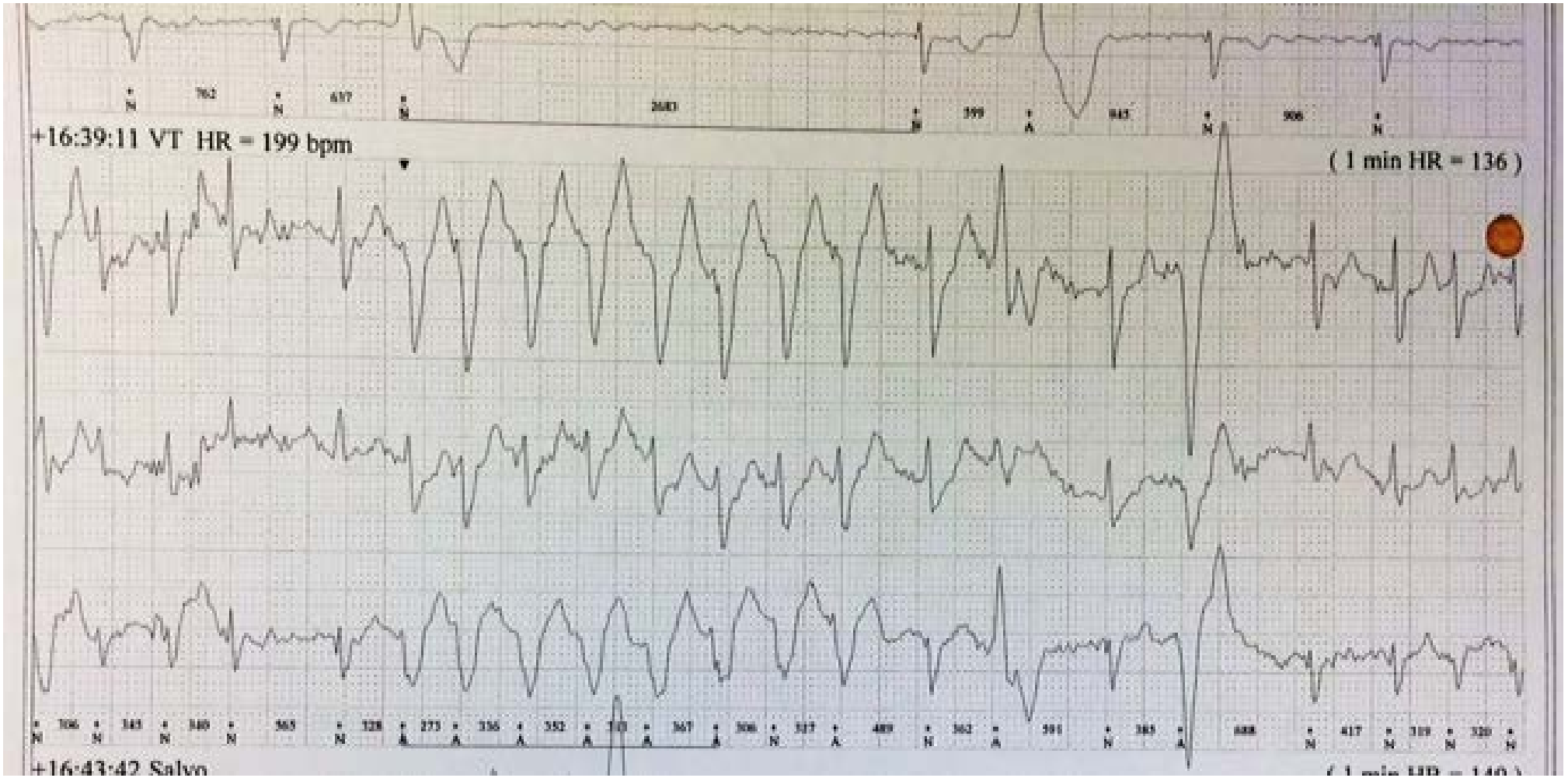
Clinical History

- Family History
  - Father:
    - AF
    - PPM – CHB
    - CRT-P 2011
    - RIP aged 63
  - Paternal grandfather:
    - AF and PPM
    - RIP aged 64 ?cause

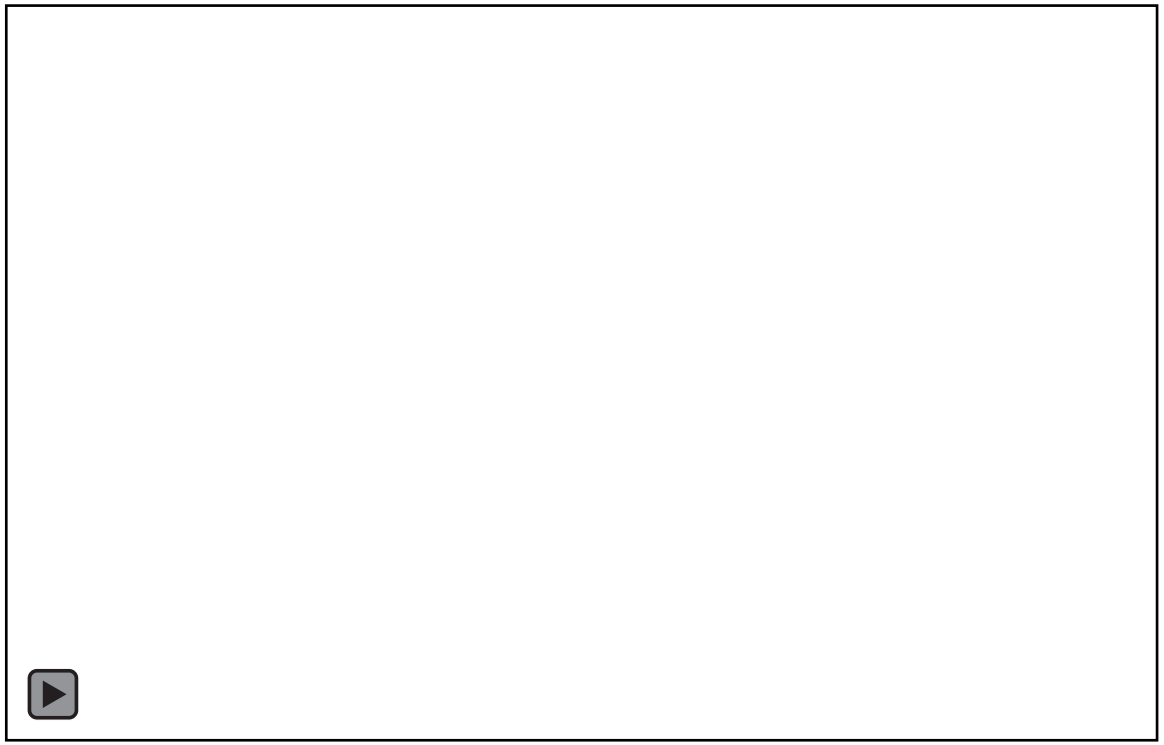
ECG

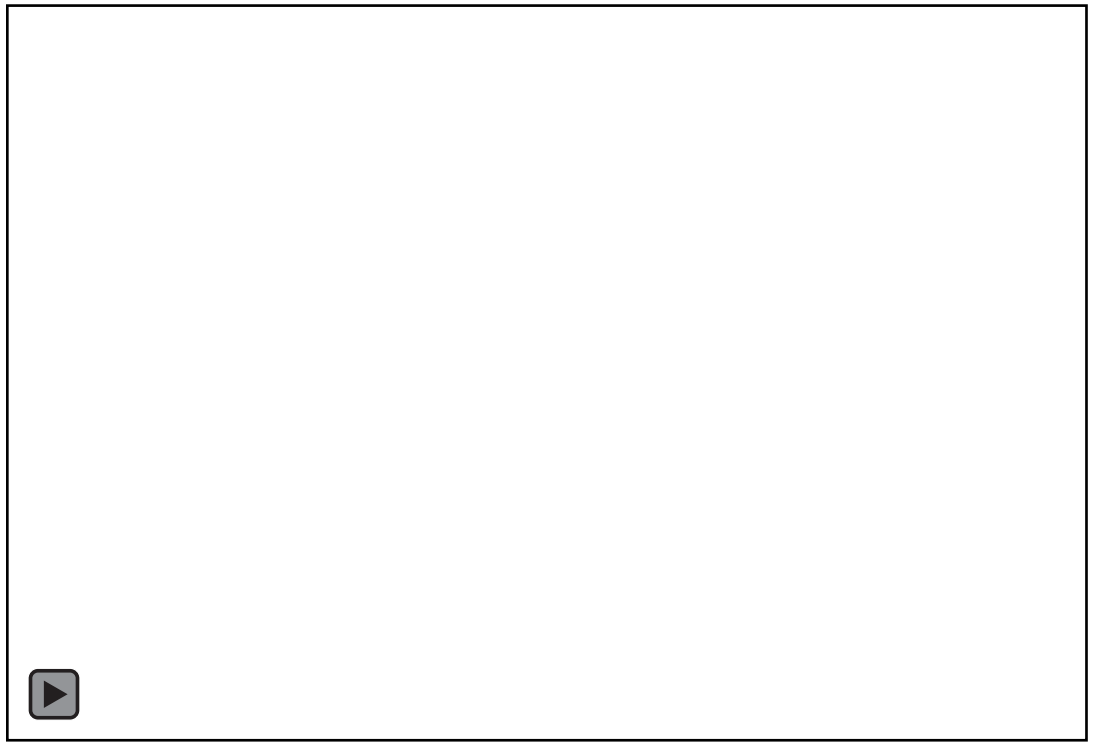

12-Nov-1973
Male
Vent. rate 53 bpm
PR interval * ms
QRS duration 122 ms
QT/QTc 432/405 ms
P-R-T axes * -70 61
Atrial fibrillation with slow ventricular response with premature ventricular or aberrantly conducted complexes
Left bundle branch block
Abnormal ECG
Technician: LL
Test ind:
Referred by: AP
Unconfirmed
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

24 hour Holter

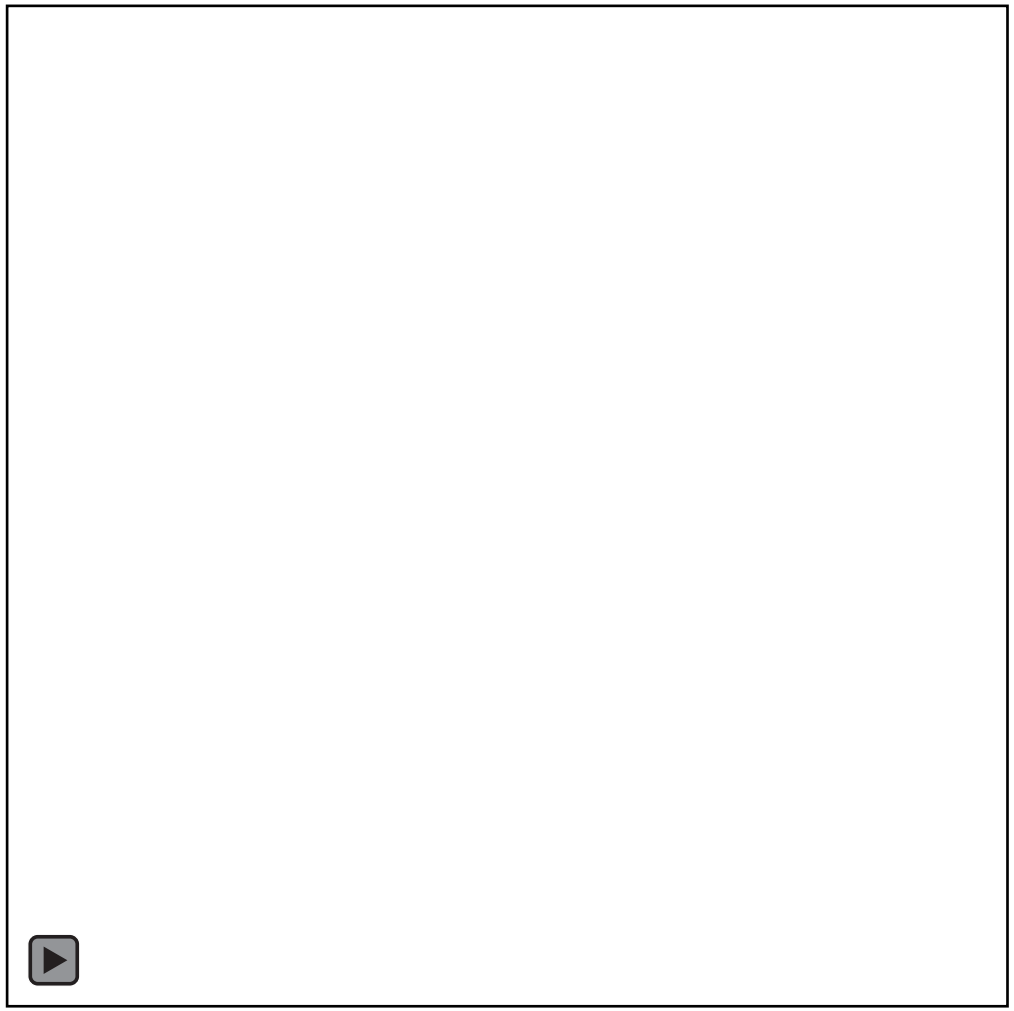


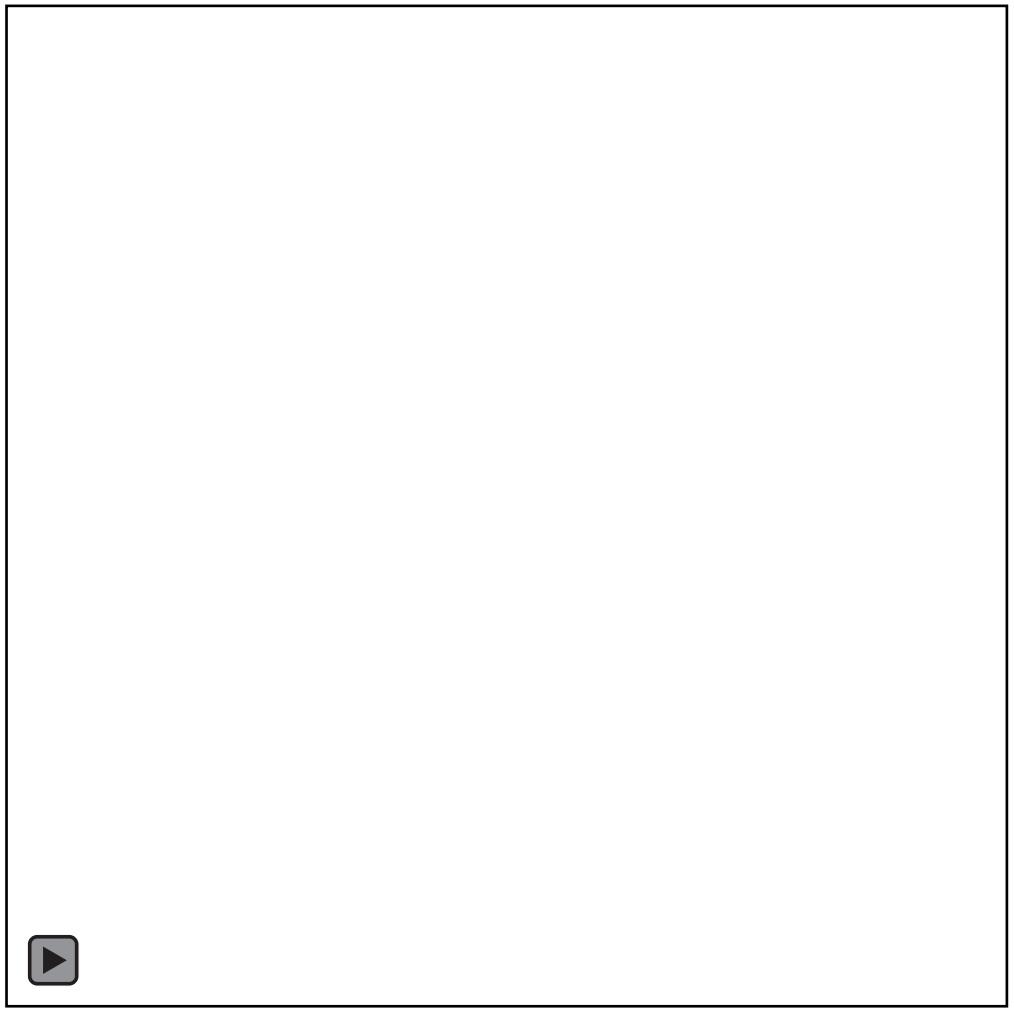
Echocardiogram





CMR





The Phenotype

- Young
- Family History of AF, PM
- NSVT
- Mild LV impairment

- WHY?

Diagnosis

- **Genetic Testing**
  - **Lamin A/C : c.**1489-1 G>A

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

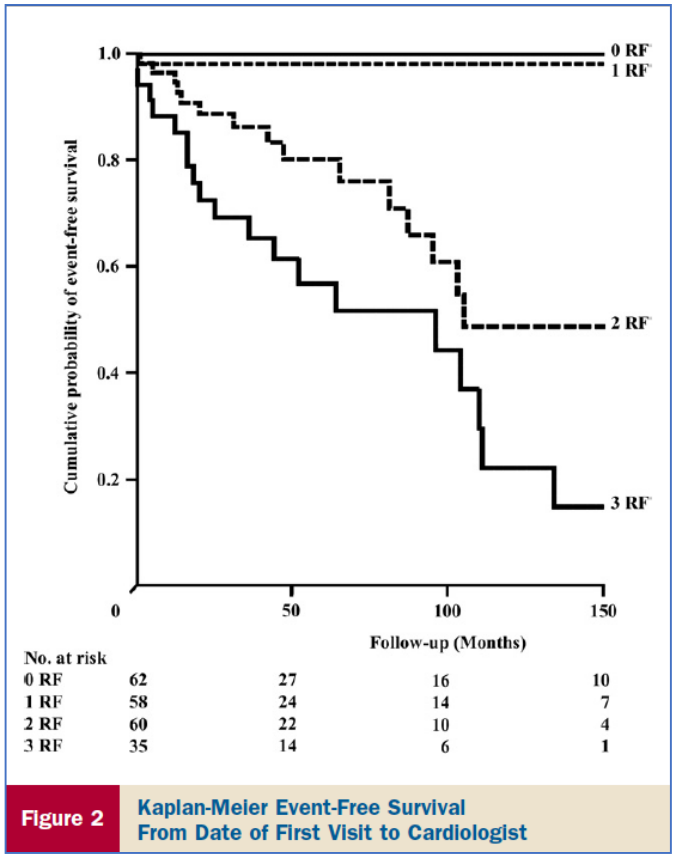


Figure 2 Kaplan-Meier Event-Free Survival From Date of First Visit to Cardiologist

NSVT, LVEF 45%, male

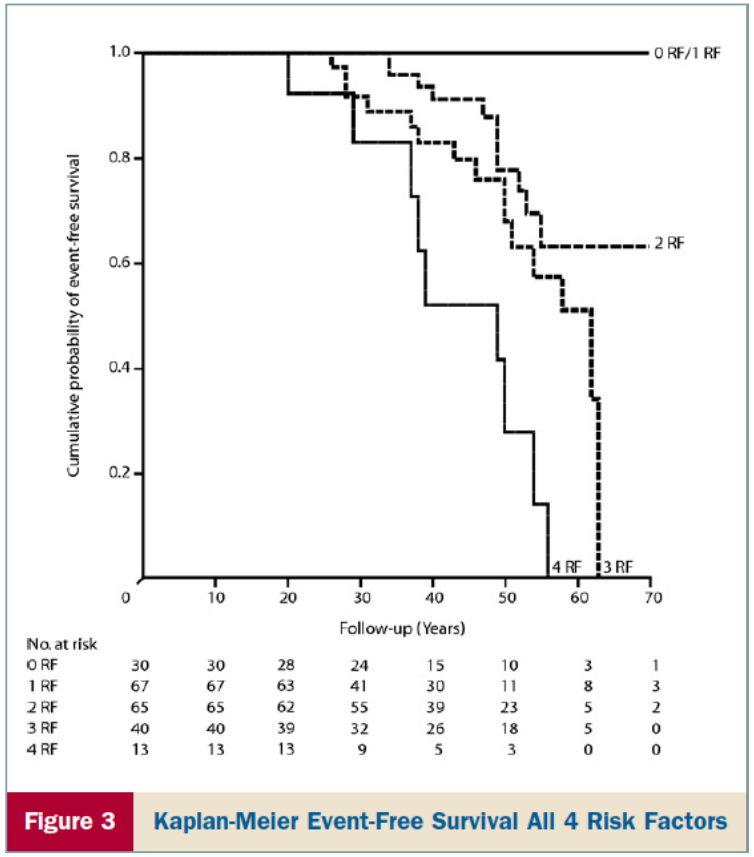


Figure 3 Kaplan-Meier Event-Free Survival All 4 Risk Factors

+ non-missense mutations (ins-del/truncating or mutations affecting splicing)

(J Am Coll Cardiol 2012;59:493–500)

TALES FROM THE CLINIC (2)

Background - 71y Male

Asymptomatic: tennis 3/week

Family history of DCM

- Nephew RIP 27 SCD – PM DCM, enlarged LV with uniform fine fibrosis
- Brother RIP 71 – Chemo for hairy cell leukaemia
- Niece – DCM and ICD

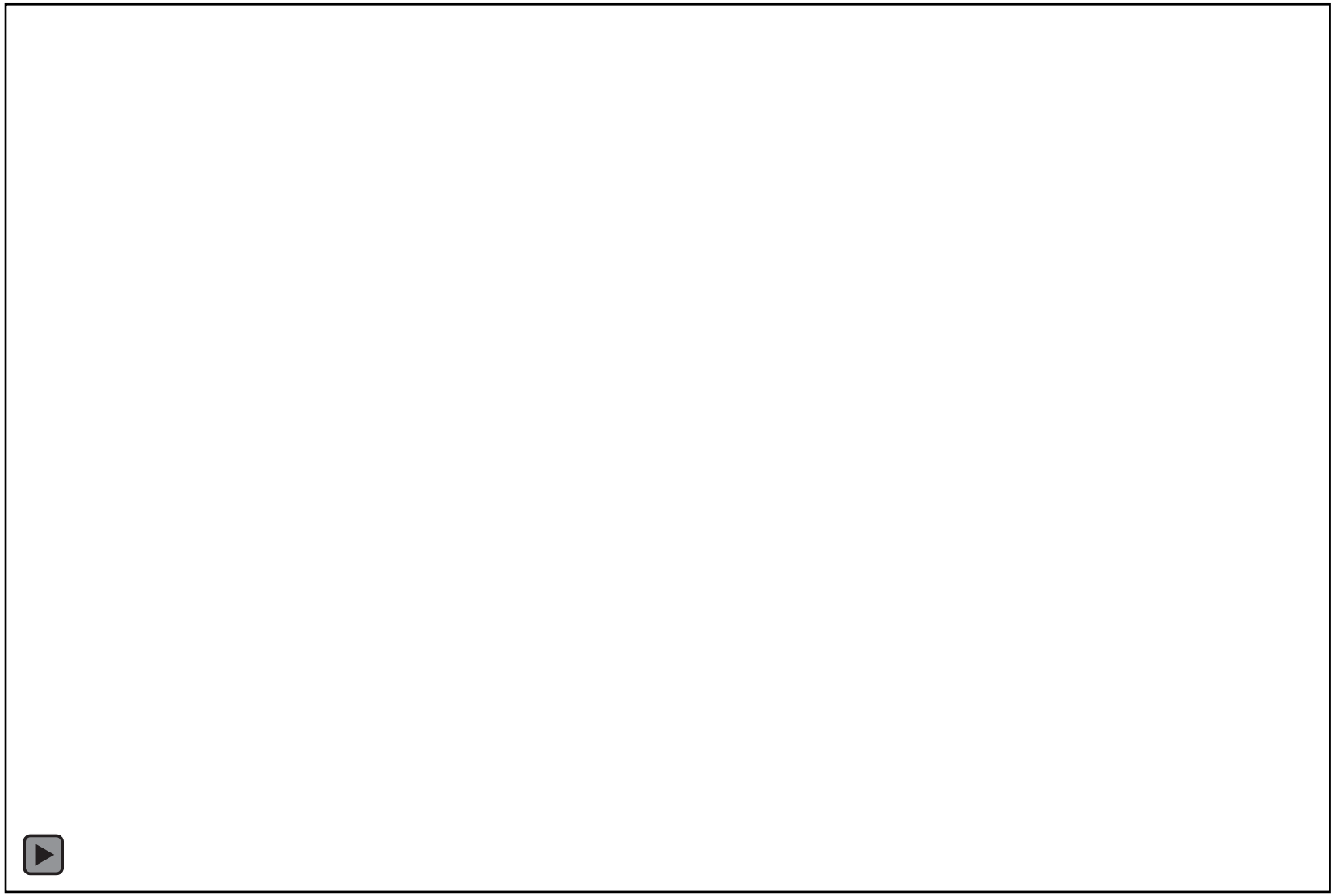
Holter 4-5% VE, no NSVT

Echo 2011

- EF 45%

Medications

- Ramipril 2.5mg



Test(s) requested: Dilated cardiomyopathy - Familial "screening"

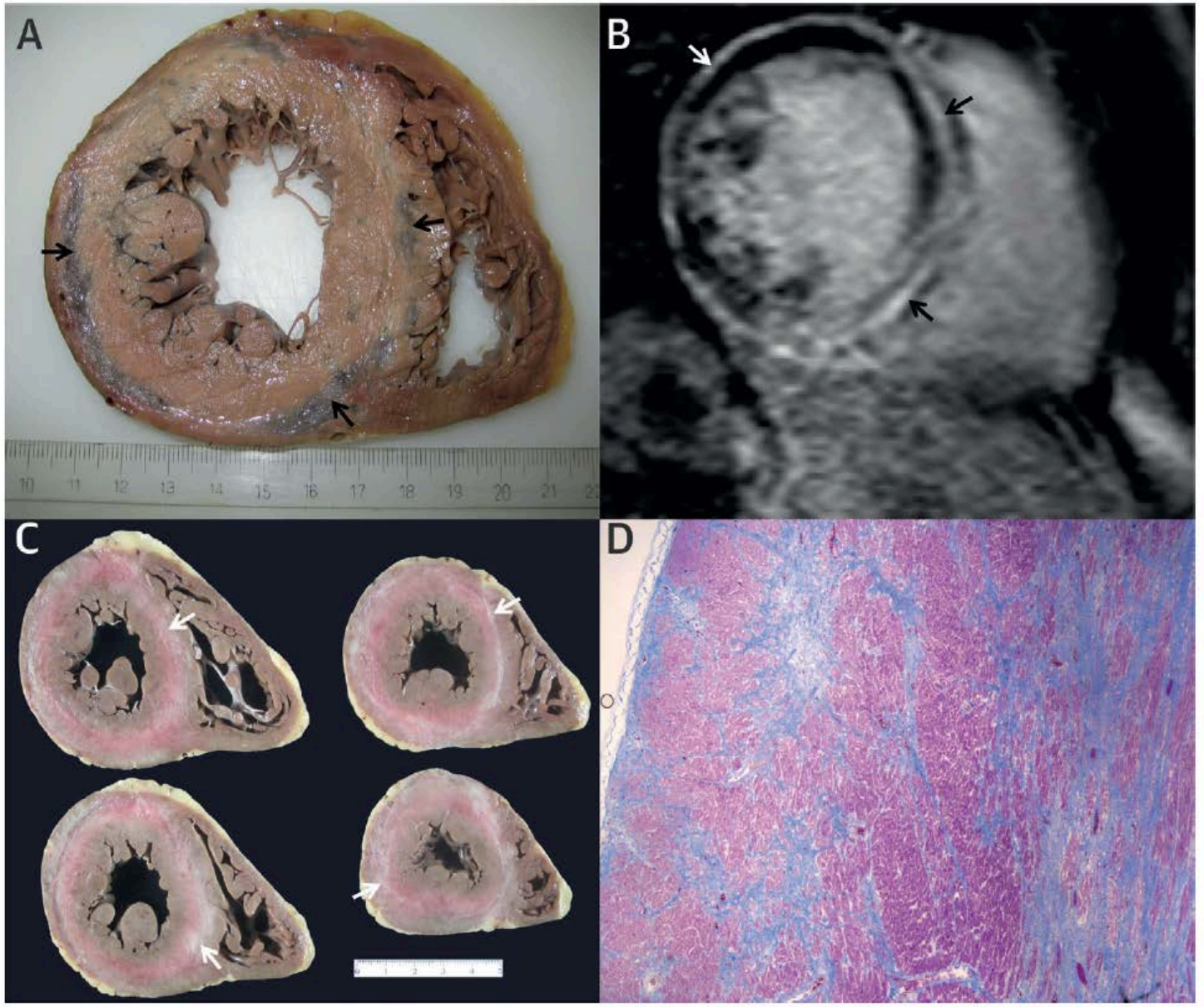
RESULT: POSITIVE

In the sample of this individual, we have confirmed the presence of the variant in *FLNC* that was previously identified in the index case.

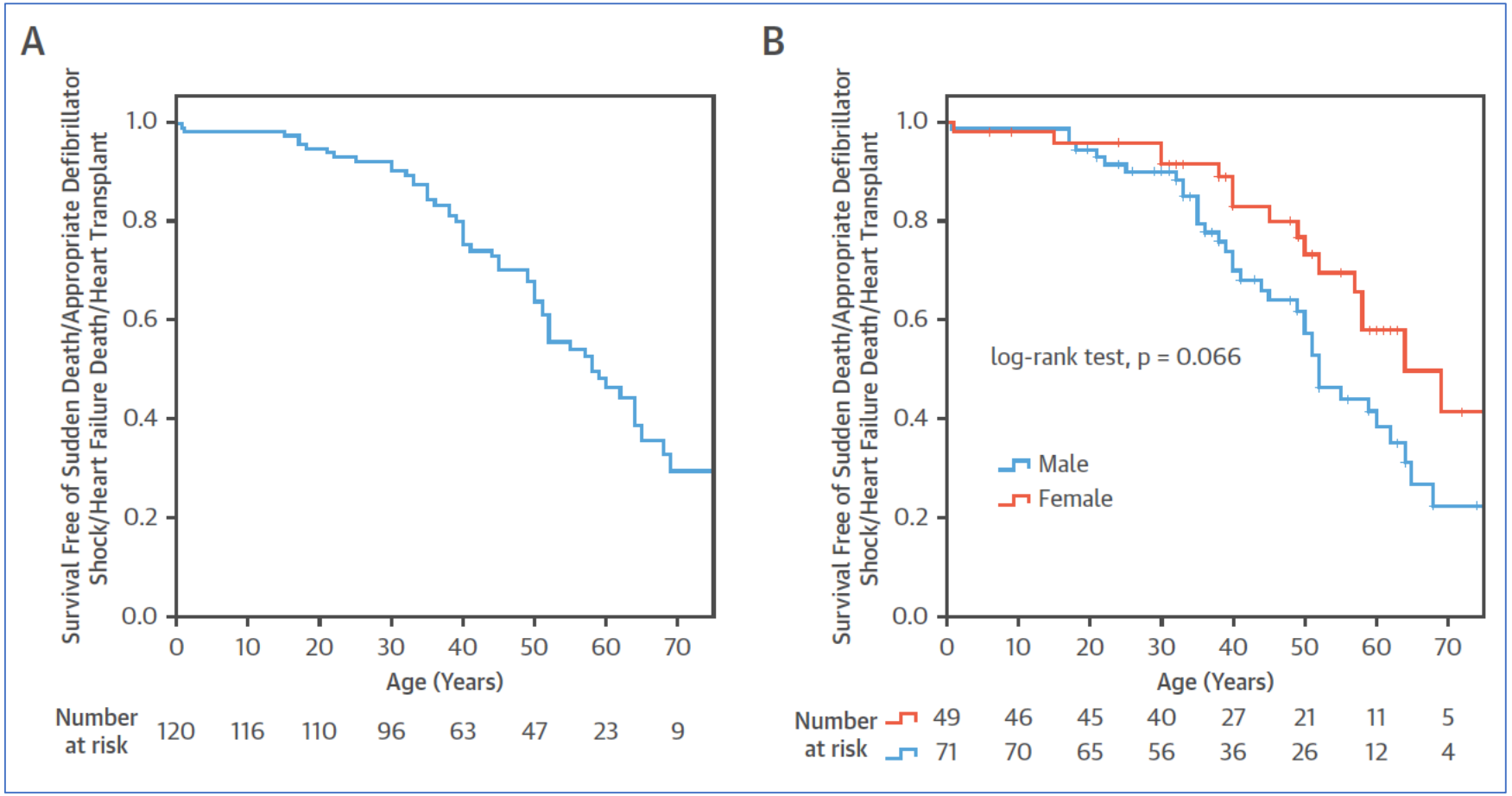
Gene	Variant	Result	Pathogenicity	Population frequency	Number of references
FLNC	NP_001449.3:p.Arg482* NM_001458.4:c.1444C>T NC_000007.13:g.128480109C>T	Heterozygosis	Very likely to be pathogenic or disease-causing (++)	Mutation (not found in controls)	0

Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies

Martín F. Ortiz-Genga, MD,[a,b] Sofía Cuenca, MD, PhD,[c] Matteo Dal Ferro, MD,[d] Esther Zorio, MD, PhD,[e] Ricardo Salgado-Aranda, MD,[f] Vicente Climent, MD,[g] Laura Padrón-Barthe, PhD,[h] Iria Duro-Aguado, MD,[i] Juan Jiménez-Jáimez, MD, PhD,[j] Víctor M. Hidalgo-Olivares, MD,[k] Enrique García-Campo, MD,[l] Chiara Lanzillo, MD, PhD,[m] M. Paz Suárez-Mier, MD, PhD,[n] Hagith Yonath, MD,[o] Sonia Marcos-Alonso, MD, PhD,[p] Juan P. Ochoa, MD,[b] José L. Santomé, BSc,[b] Diego García-Giustiniani, MD,[b] Jorge L. Rodríguez-Garrido, MD,[b,p] Fernando Domínguez, MD,[c] Marco Merlo, MD,[d] Julián Palomino, MD, PhD,[i] María L. Peña, MD,[q] Juan P. Trujillo, MD, PhD,[b] Alicia Martín-Vila, PharmD,[i] Davide Stolfo, MD,[d] Pilar Molina, MD, PhD,[r] Enrique Lara-Pezzi, PhD,[h,s] Francisco E. Calvo-Iglesias, MD, PhD,[i] Eyal Nof, MD,[o] Leonardo Calò, MD,[m] Roberto Barriales-Villa, MD, PhD,[a,p] Juan R. Gimeno-Blanes, MD, PhD,[t] Michael Arad, MD, PhD,[o] Pablo García-Pavía, MD, PhD,[c,u] Lorenzo Monserrat, MD, PhD[a,b]



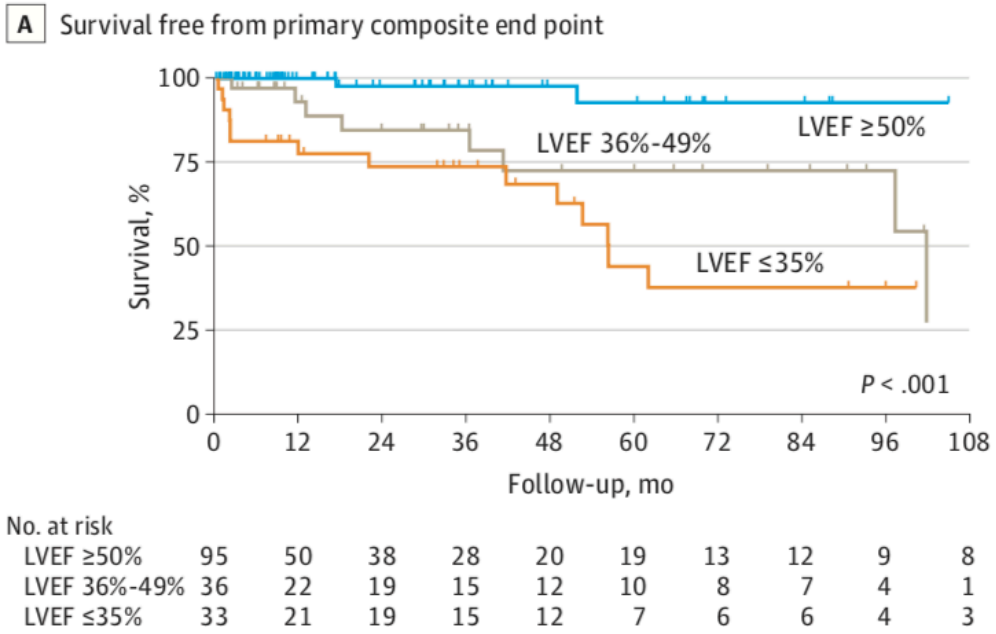
J Am Coll Cardiol. 2016 Dec 6;68(22):2440-2451

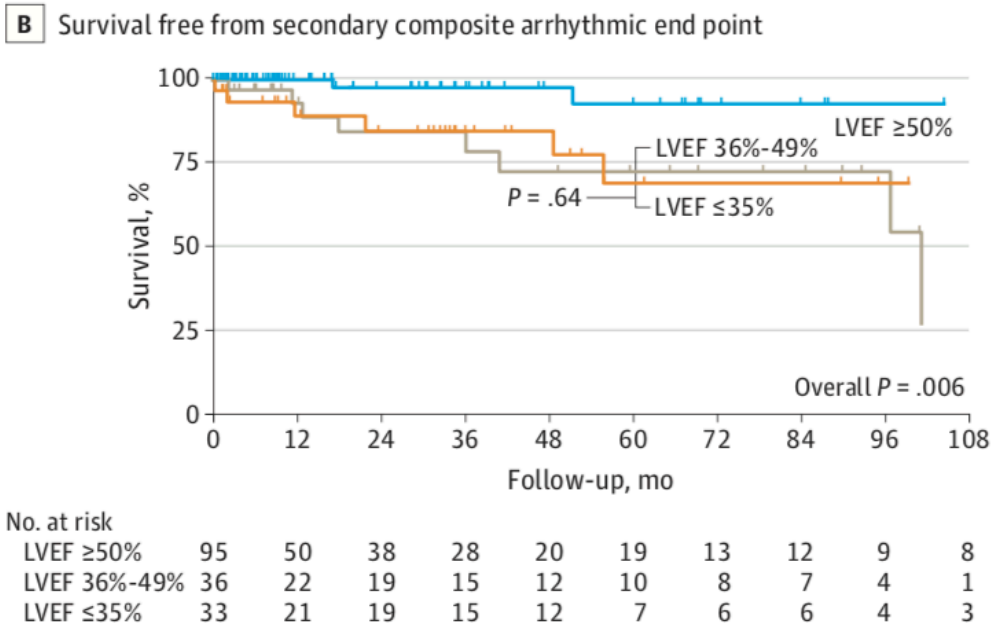


J Am Coll Cardiol. 2016 Dec 6;68(22):2440-2451

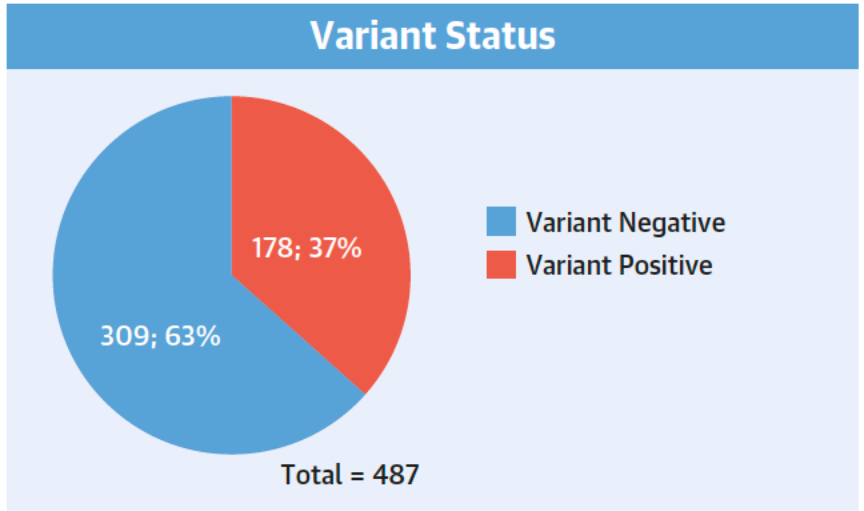
JAMA Cardiology | Original Investigation

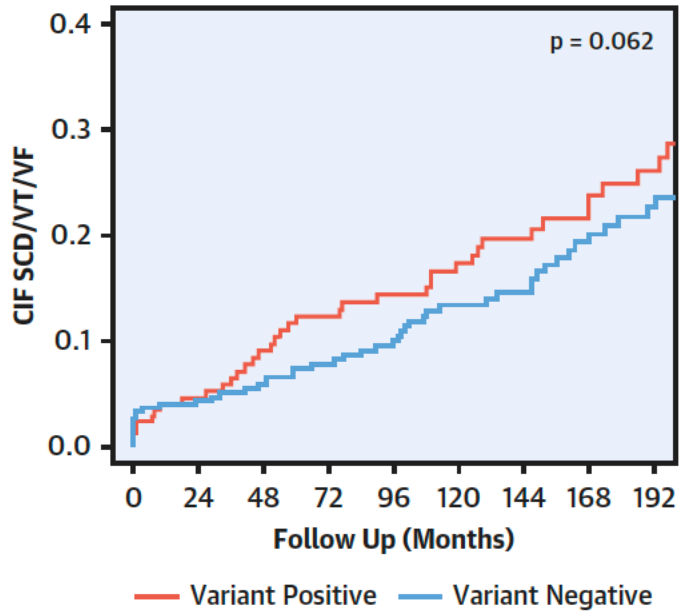
Association of Left Ventricular Systolic Dysfunction Among Carriers of Truncating Variants in Filamin C With Frequent Ventricular Arrhythmia and End-stage Heart Failure

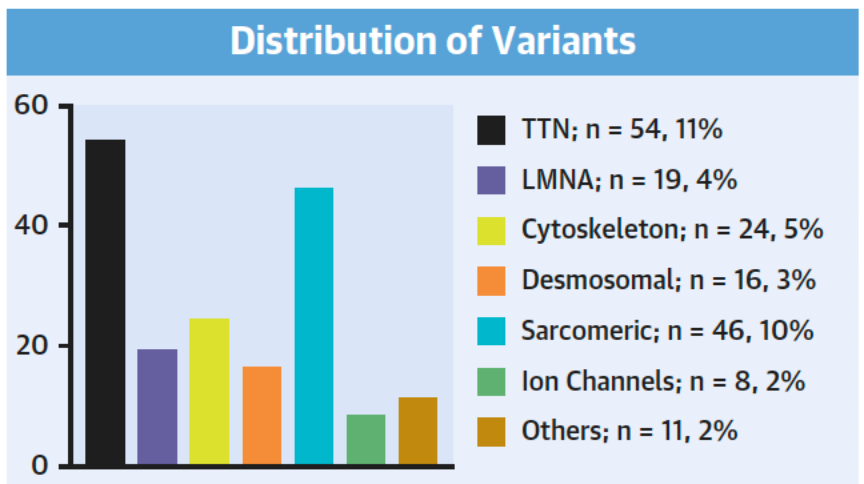


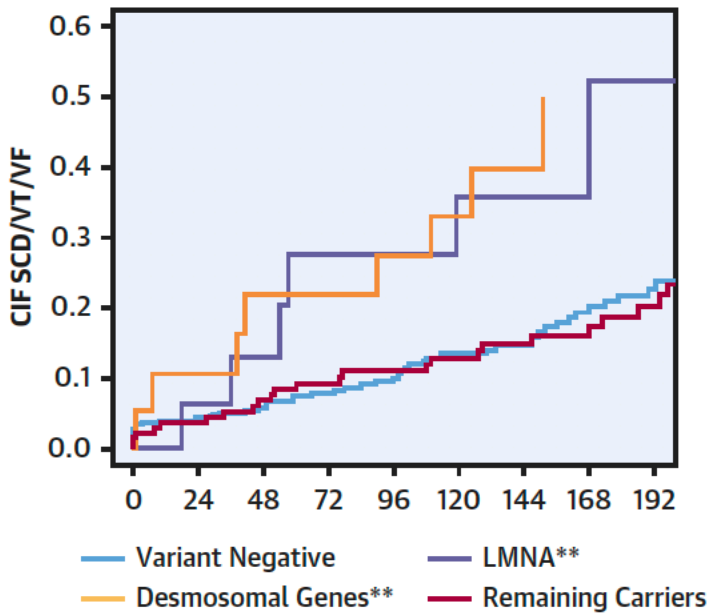


JAMA Cardiol. doi:10.1001/jamacardio.2021.1106



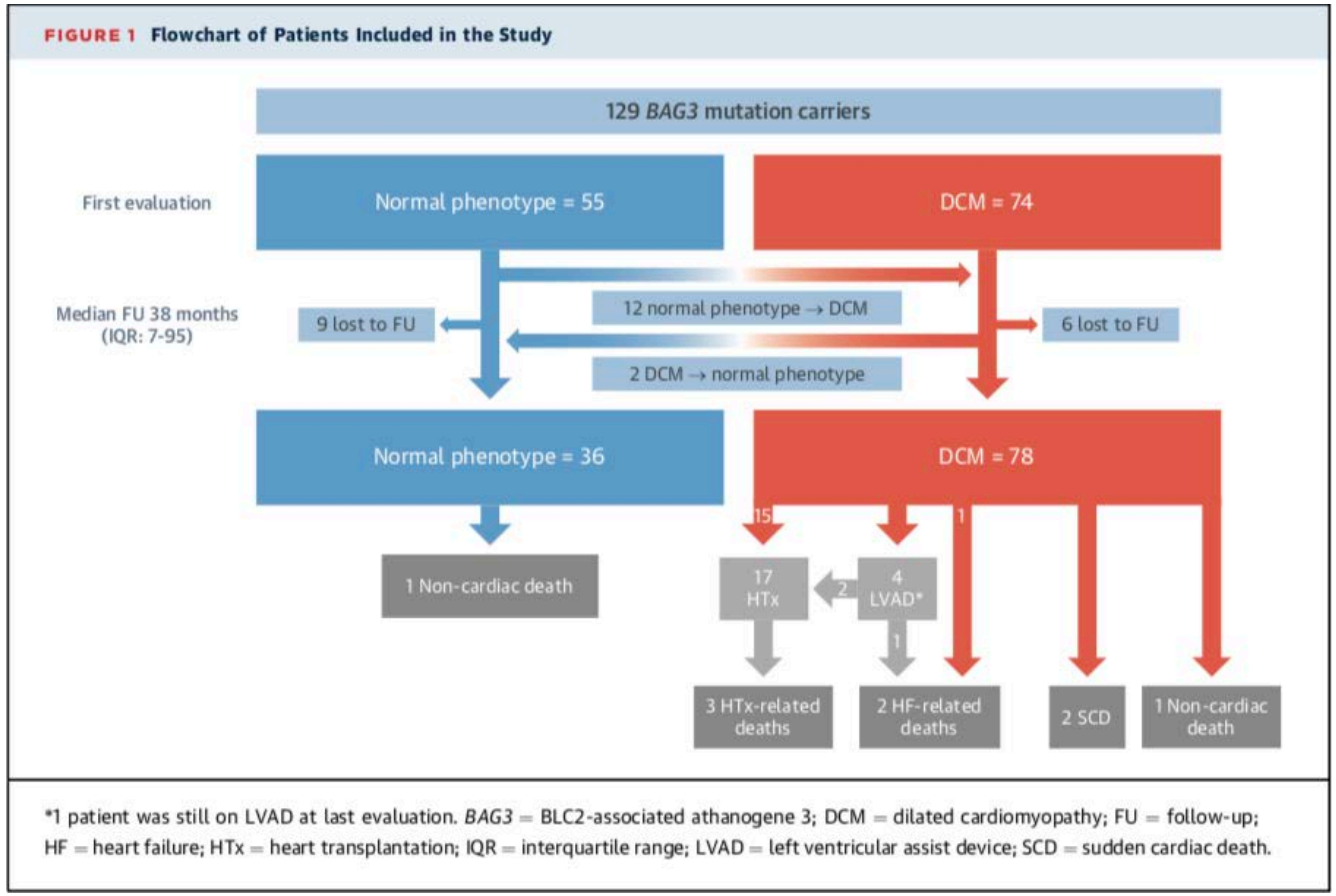






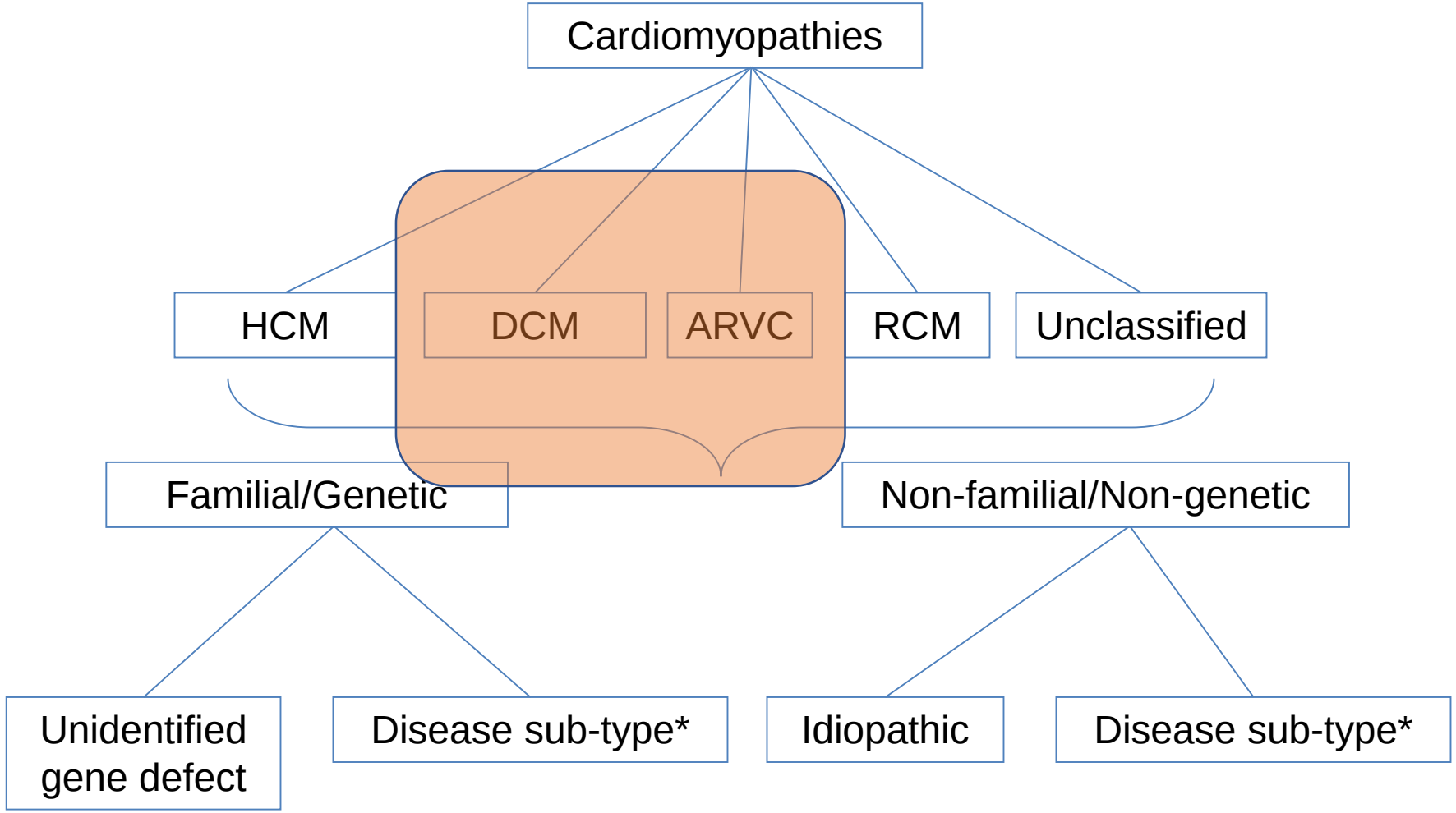
Gigli, M. et al. J Am Coll Cardiol. 2019;74(11):1480-90.

Dilated Cardiomyopathy Due to BLC2-Associated Athanogene 3 *(BAG3)* Mutations



J Am Coll Cardiol 2018;72:2471–81

What do we learn from all this?

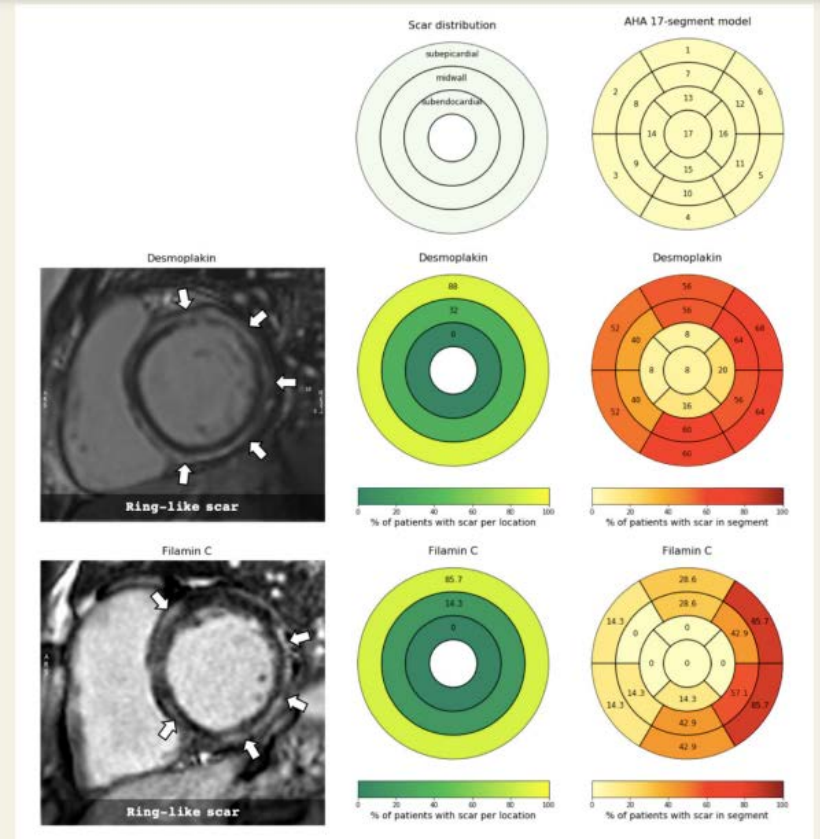


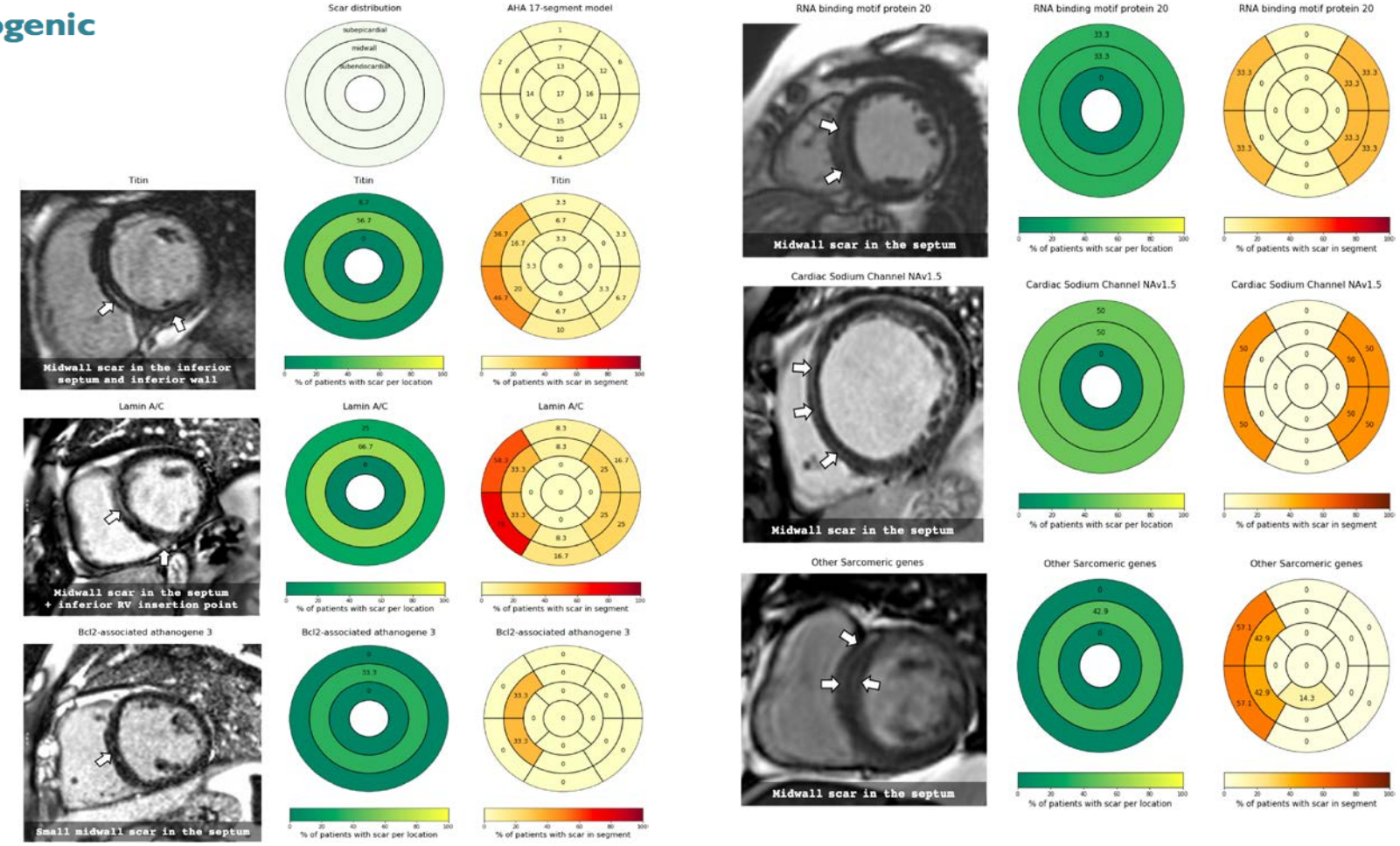
European WG on Myocardial and Pericardial Diseases (Elliott P et al. EHJ 2007)

Clinical translation of omics platforms in inherited heart muscle disease

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2020) **21**, 326–336
doi:10.1093/ehjci/jez188

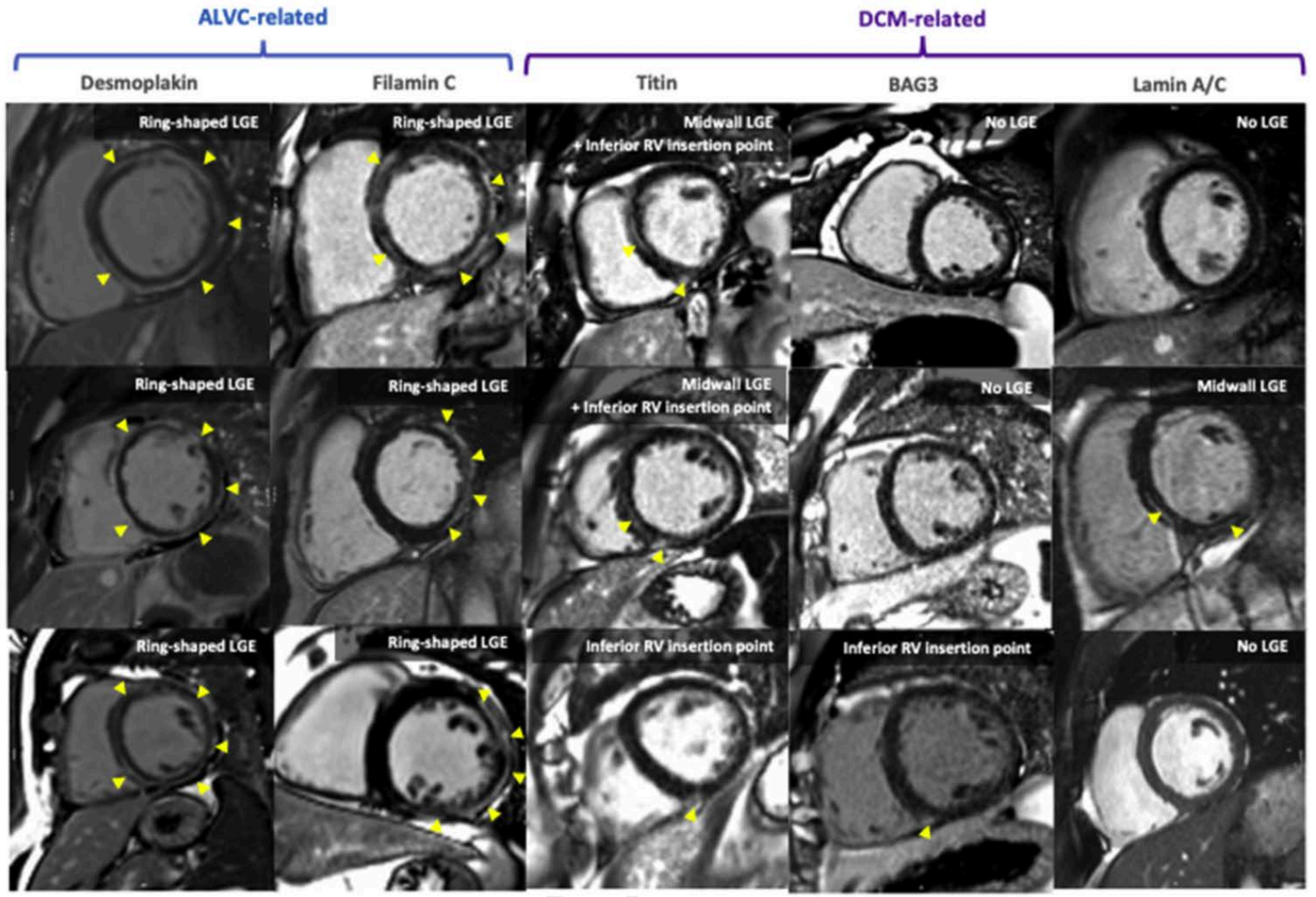
Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: a comprehensive genotype-imaging phenotype study





Distinctive imaging phenotypes define arrhythmogenic left ventricular cardiomyopathy (ALVC)

YOU SEE, BUT YOU DO NOT OBSERVE



Some possible options?

1

Do nothing

2

Tinker with existing definitions

3

Redesign to resolve current confusion

4

Move to a new aetiology-based classification

Cardiomyopathy: Definition

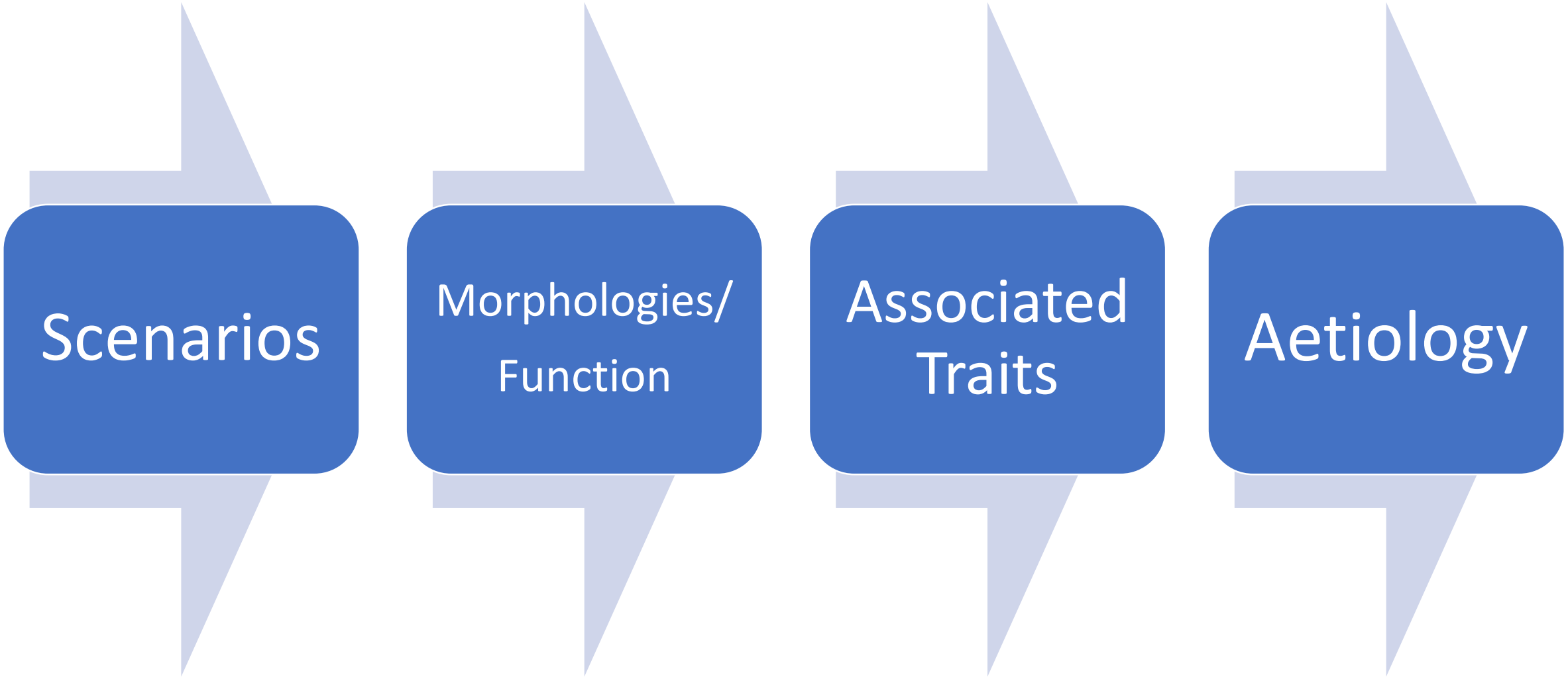
- *A structural and or functional abnormality of left and or right ventricle (or atria) unexplained solely by abnormal loading conditions or coronary artery disease.*

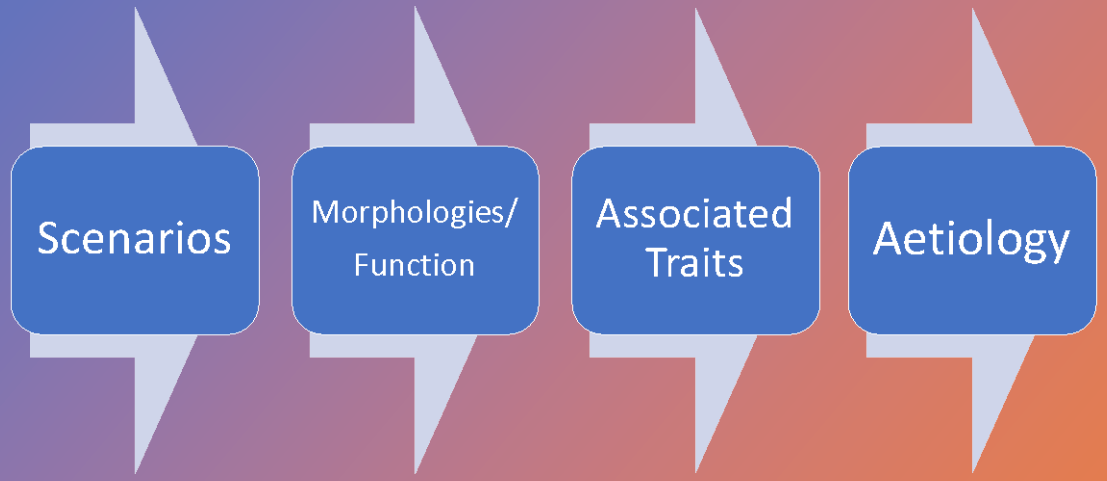
- STRUCTURAL=hypertrophy, dilatation, systolic/diastolic impairment (global/regional), scar and fat.

- NOT DEFINED BY PRESENCE OR ABSENCE OF ARRHYTHMIA

Cardiomyopathy: Diagnostic Pathway

Diagnostic Pathway

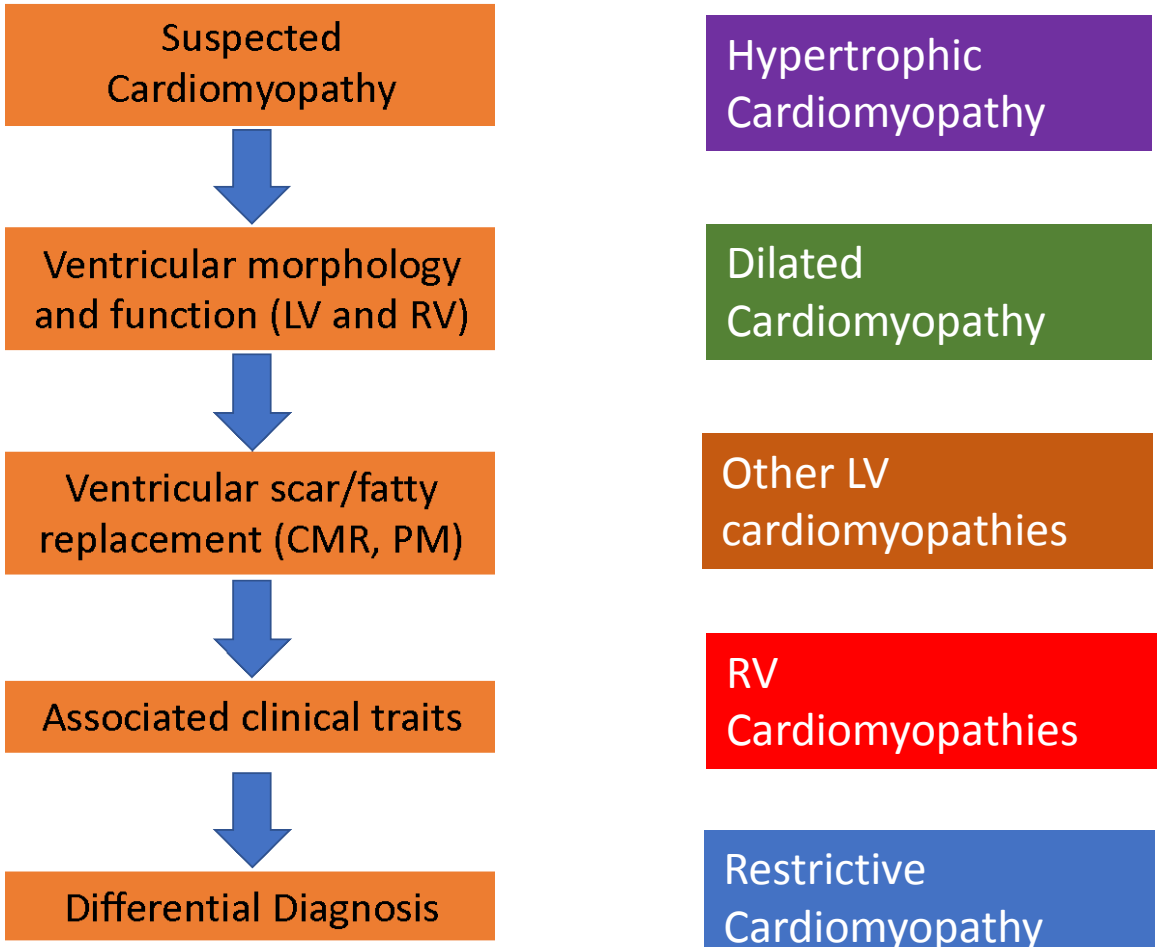


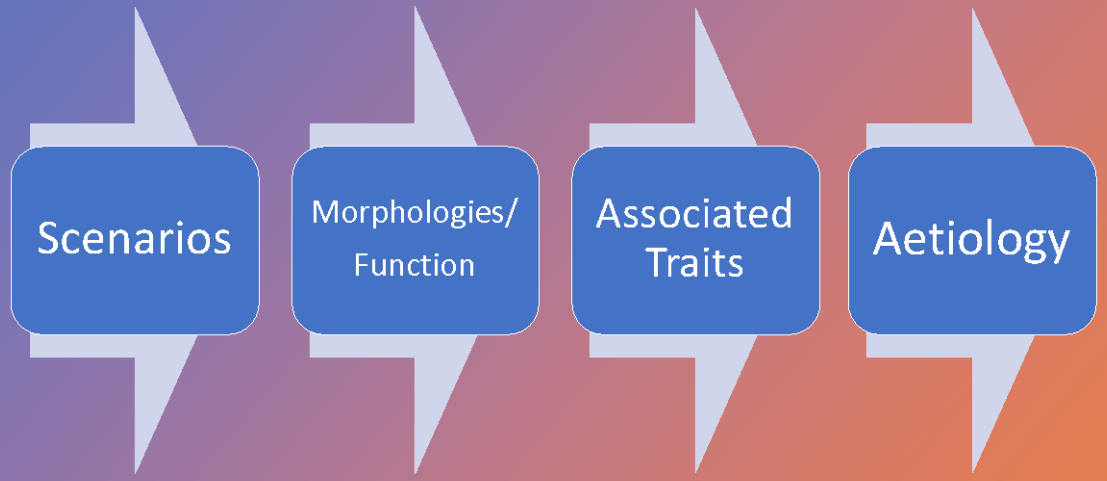


Scenarios

- Symptomatic
- Arrhythmia
- Family Screening
- Incidental

Morphological and functional subtypes of cardiomyopathy

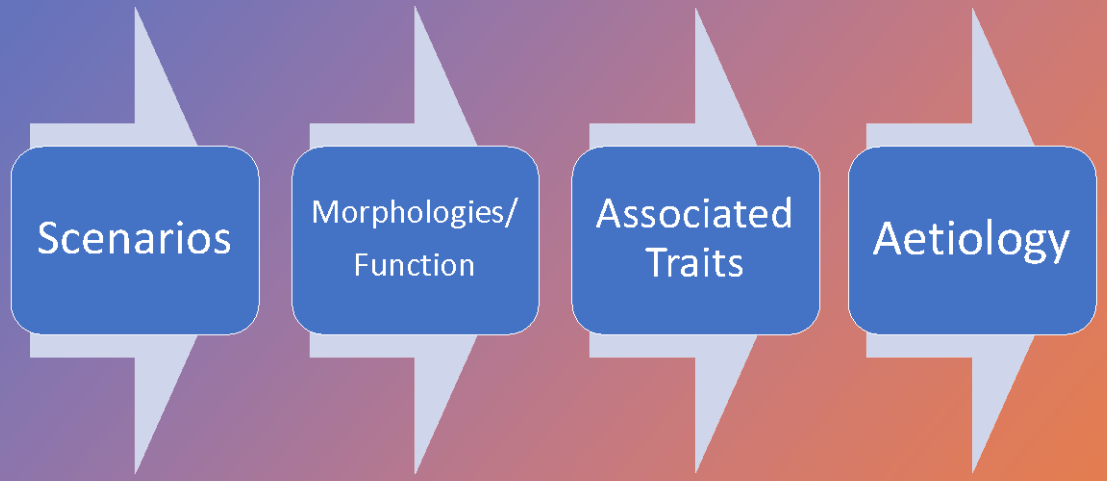




Associated Traits*

Cardiac	Extra-cardiac
Atrial Arrhythmia	Somatic dysmorphism
Ventricular Arrhythmia	Neuropathy
AV Block	Renal dysfunction
Excessive Trabeculation	Muscular dystrophy

(*including family history)



Aetiology

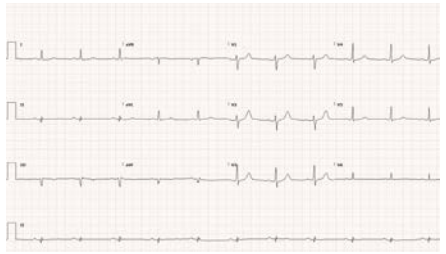
- Genetic
- Inflammatory
- Infiltrative
- Toxic

DIAGNOSTIC PATHWAY

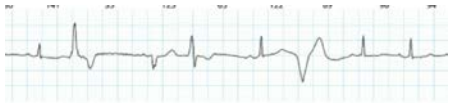
History

46 year old male
Myocarditis presentation
No family history
Normal physical examination

ECG/Arrhythmia

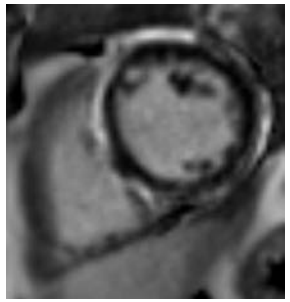


Sinus rhythm, low voltage



900 VEs/24 h

Cardiac Structure/function



Non-dilated LV cardiomyopathy LVEF subepicardial scar

Genotype

DSP p.Arg425*

Truncating variant in desmoplakin

APPROACHES TO 'CLASSIFICATION'

Modified Existing Morphological Classification

Arrhythmic cardiomyopathy

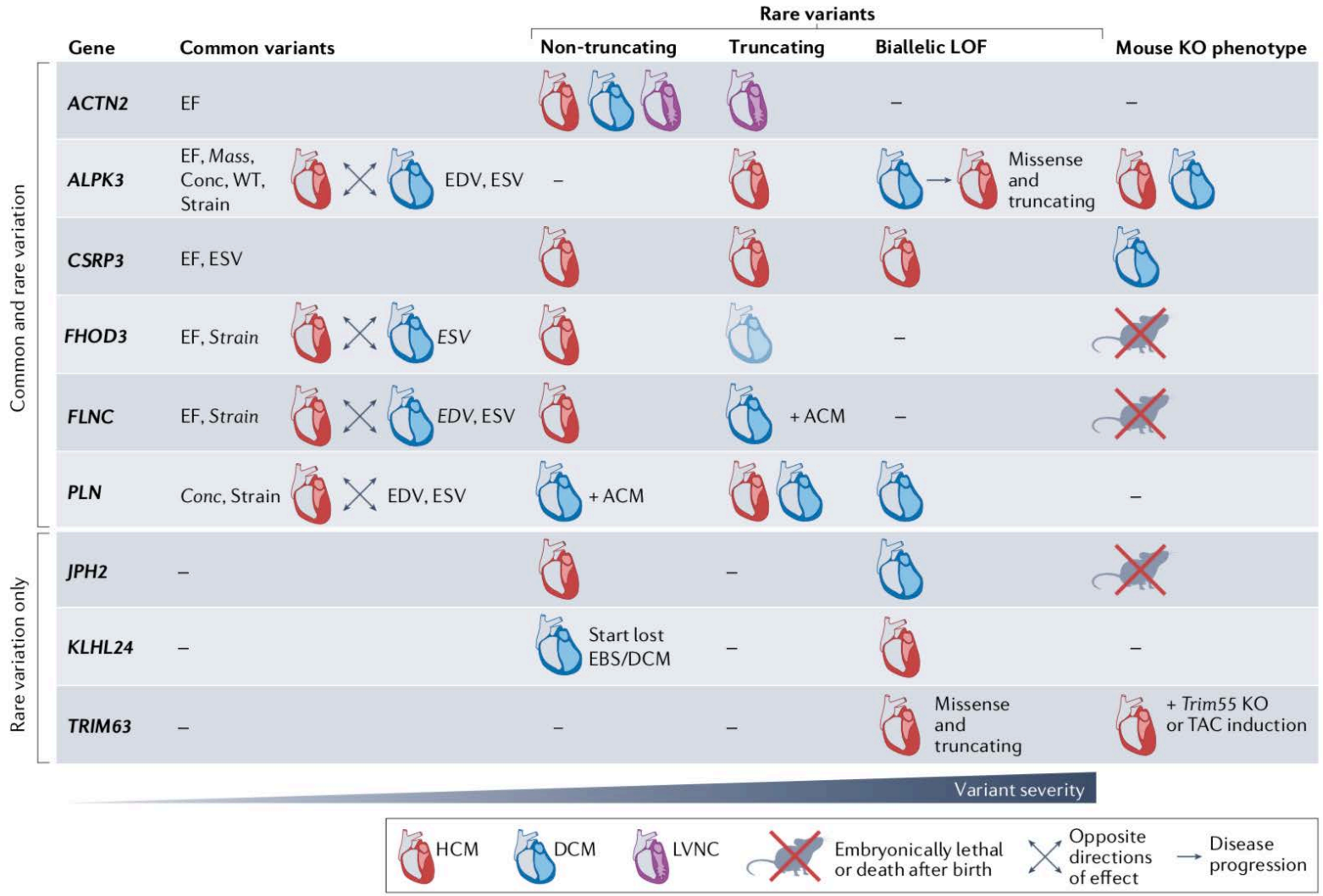
ALVC

Integrated aetiology/phenotype description

Autosomal dominant DSP-related non-dilated LV cardiomyopathy with mildly impaired LVEF and subepicardial scar

Minor hypertrophic cardiomyopathy genes, major insights into the genetics of cardiomyopathies

Roddy Walsh[1]✉, Joost A. Offerhaus[1], Rafik Tadros[2] and Connie R. Bezzina[1]



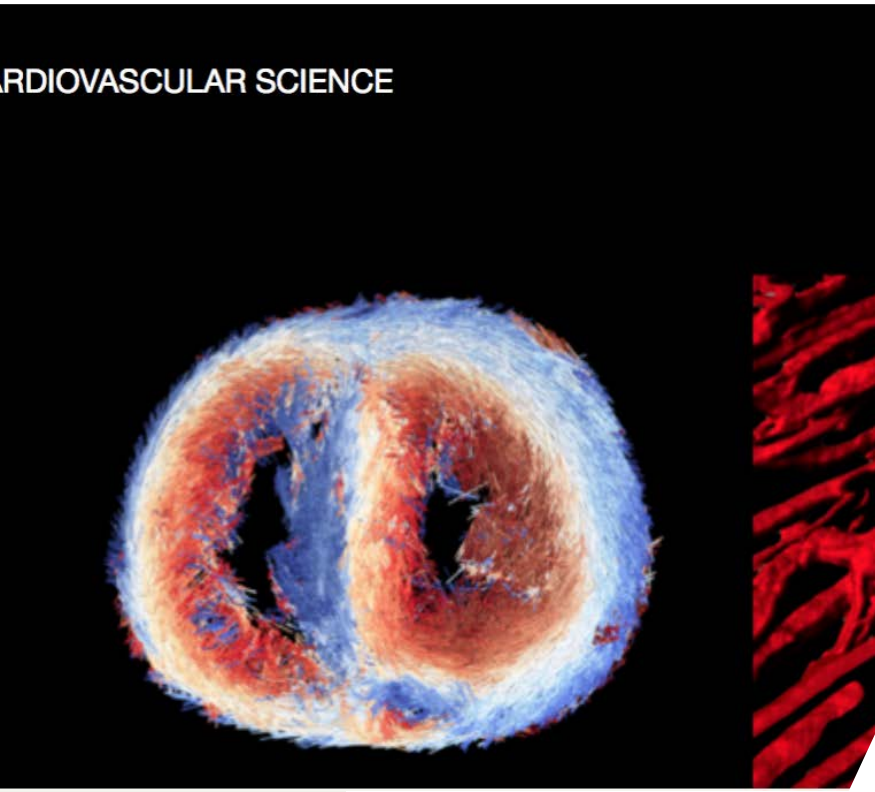
NOTATI	MORPHO-FUNCTIONAL PHENOTYPE	ORGAN/SYSTEM INVOLVEMENT	GENETIC INHERITANCE PATTERN	ETIOLOGY	STAGE
CHARACTERISTICS	Proband's cardiomyopathy (CM) diagnosis (DCM, HCM, RCM, ARVC/D, LVNC)	Clinical history and evaluation – Organ involvement: Extracardiac organs/tissues – Multidisciplinary evaluation according per clinical needs or diagnostic hypothesis	Genetic counseling with pedigree – Familial Inheritance AD, AR XL (R or D) or Matrilineal – Non-familial; Phenotypically sporadic – Informative and non-informative families – Consultant non-informed about family history Clinical family screening – Affected, asymptomatic relative unaware of the disease – Relatives with ECG and/or Echo abnormalities – Healthy family members with normal ECG and ECHO	Genetic testing in the proband – Positive Cascade genetic testing in relatives – Negative – New tests novel genes – Regular monitoring in relatives	Functional status ACC/AHA, NYHA
SUBSCRIPT	**D** Dilated **H** Hypertrophic **R** Restrictive **R EMF** Endomyocardial fibrosis *LV=left ventricle* *RV=right ventricle*	**H** Heart *LV=left ventricle* *RV=right ventricle* *RLV=biventricular* **M** Muscle (skeletal) **N** Nervous **C** Cutaneous	**N** Family history negative **U** Family history unknown **AD** Autosomal dominant **AR** Autosomal recessive **XLD** X-linked dominant **XLR** X-linked recessive	**G** Genetic cause **OC** Obligate carrier **ONC** Obligate non-carrier **DN** *De novo* **Neg** Genetic test negative for the known familial mutation **N** Genetic defect not identified	ACC-AHA stage represented as letter **A, B, C, D** **NA** not applicable **NU**

Frontiers: New Armoury

- ß-blockers
- RAAS inhibitors
- Statins
- Vasodilators
- Antiplatelets
- Anticoagulants
- Devices

If it doesn't fit, then do not force it

ARDIOVASCULAR SCIENCE



THANK YOU

Summary: Is it time for a new classification?

- Update required to account for LV disease not described in current system
- No single scheme can meet every purpose
- For clinicians, focus should be on logical pursuit of a diagnosis guided by an iterative description of a phenotype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