Arrhythmogenic RV Cardiomyopathy

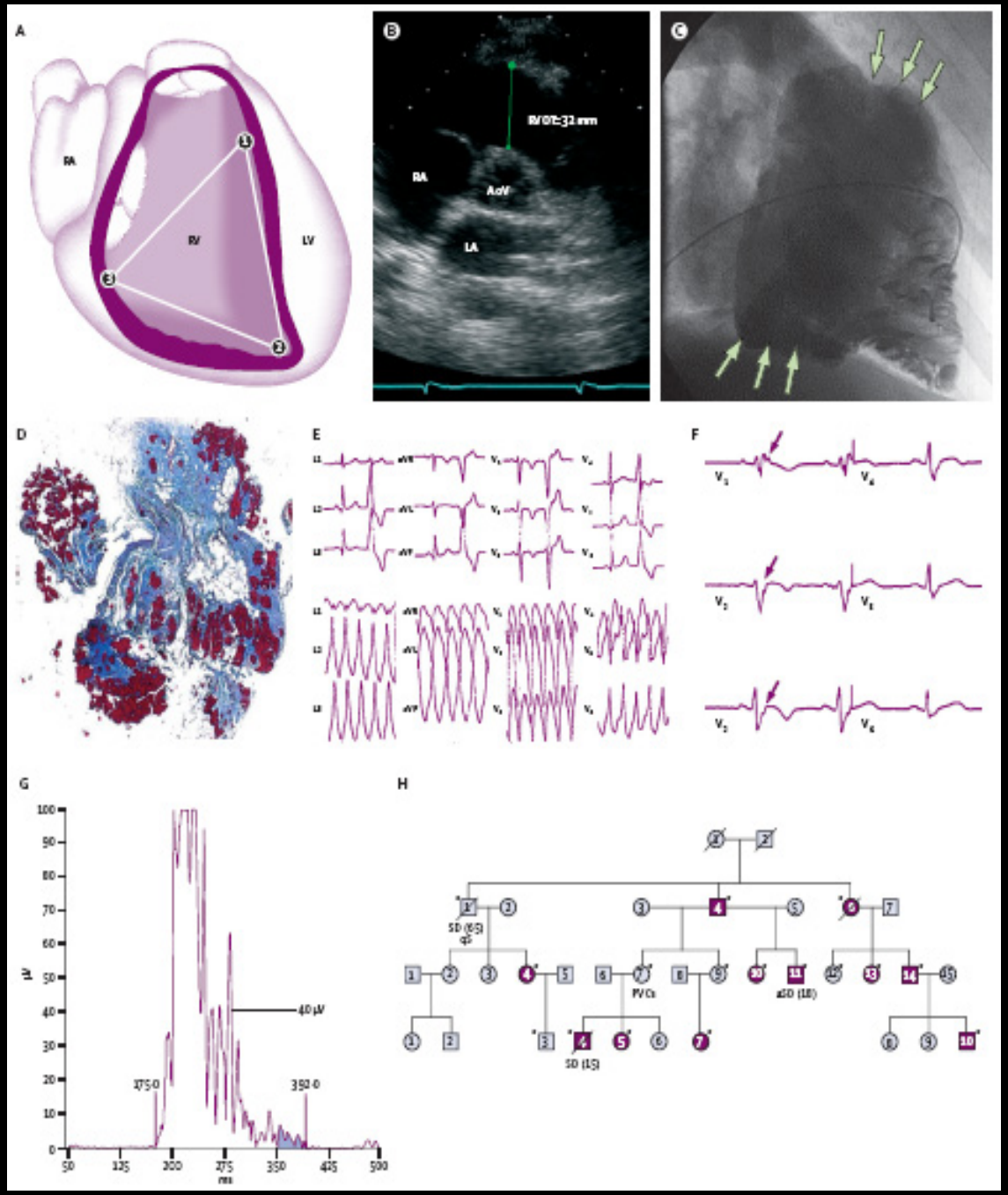
(A non Arrhythmologic Perspective)

Claudio Rapezzi, Bologna

Arrhythmogenic RV Cardiomyopathy (a non-arrhythmologic perspective)

Agenda:

- **Diagnostic pitfalls, mimics and phenocopies**
- **Role of molecular genetic**
- **Role of MRI**
- **ARVC as a cause of HF**
- **From right-side to left-side**
- **Commendation of the standard ECG**



Basso C et al, Lancet 2009

Disease-Causing Mutations in Desmosomal Proteins

Mechanical and electrical uncoupling at desmosomial level :

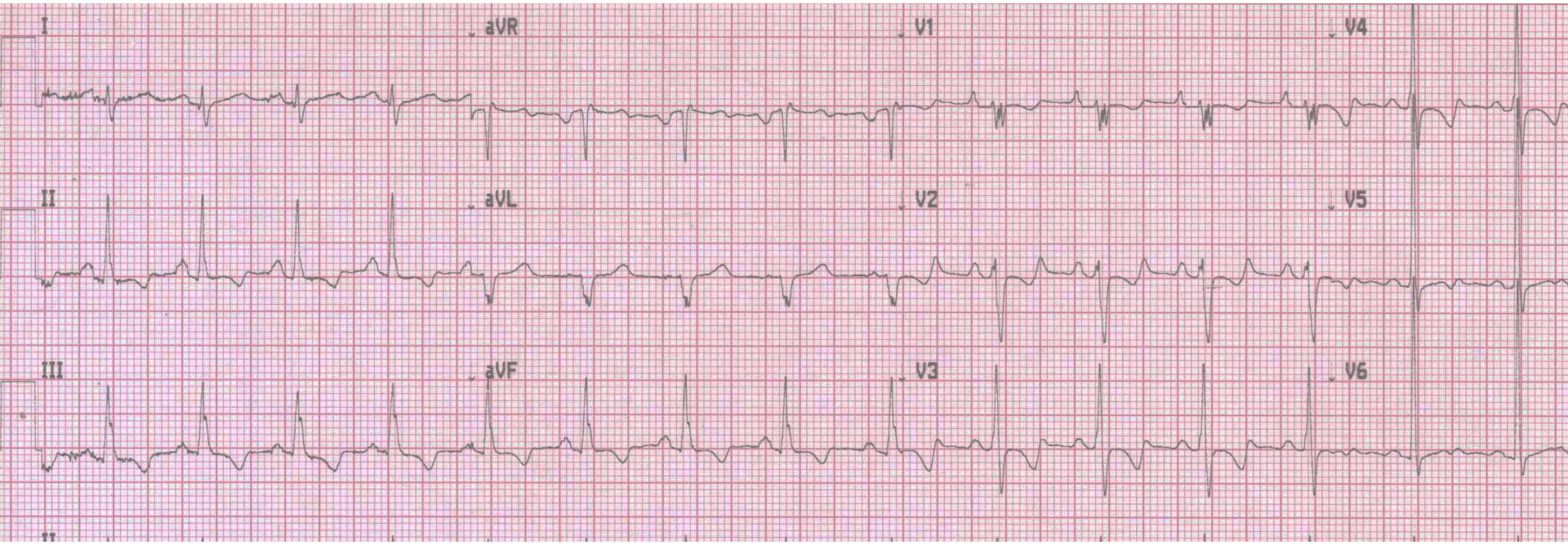
- **Cell death**
- **Fibrosis**
- **Monomorphic arrythmias**
- **Sodium channel dysfunction**
- **Activation delay**

- **Deleterious effect of exercise**
- **Progression by acute bursts**

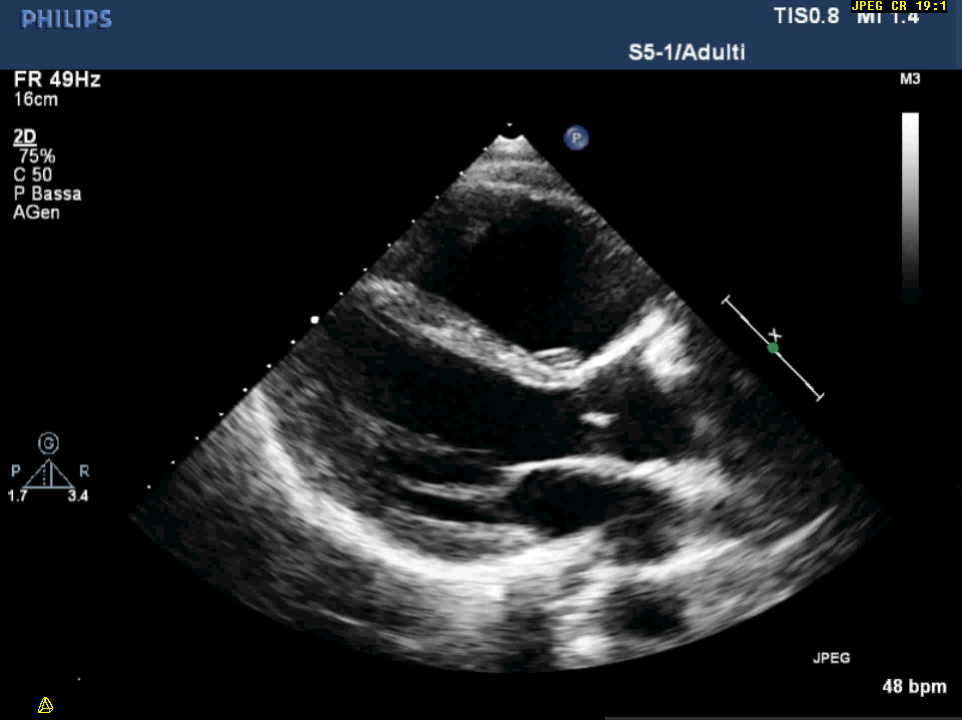
Male, 26 ys

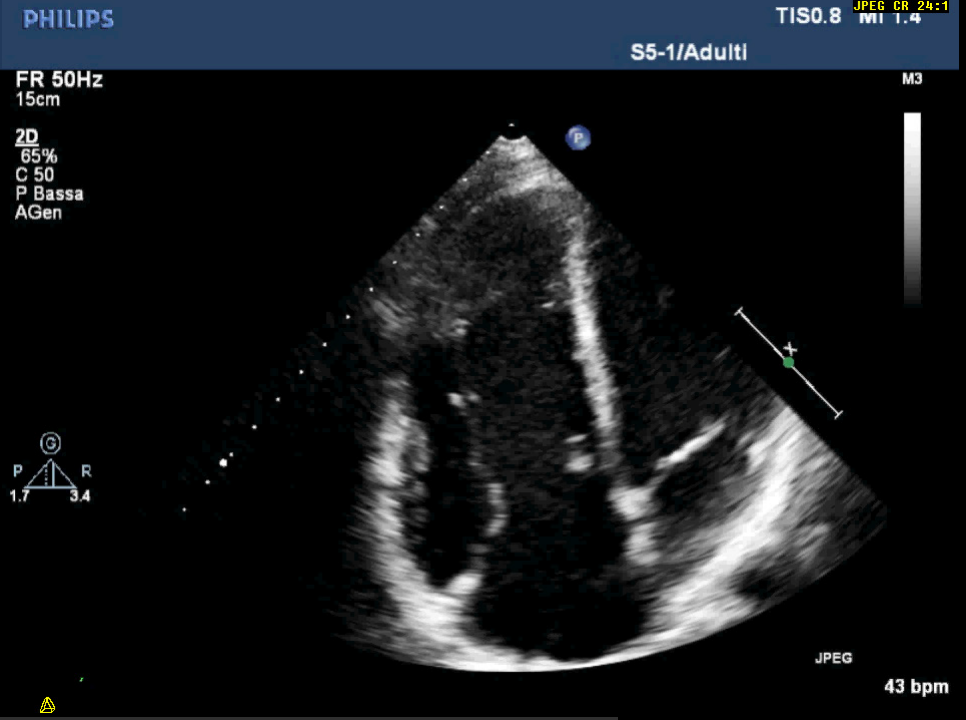
Cardiac history: unremarkable
Family history negative for cardiomyopathy or SD

Pre-partecipation sport screening: RV dilatation and dysfunction → CMR in a peripheral centre with preliminary diagnosis of ARVC



24 h Holter: 55 VPBs (LBBB)


PHILIPS
TIS0.8 MI 1.4
JPEG CR 19:1
S5-1/Adulti
FR 49Hz
16cm
2D
75%
C 50
P Bassa
AGen
M3
P R
1.7 3.4
JPEG
48 bpm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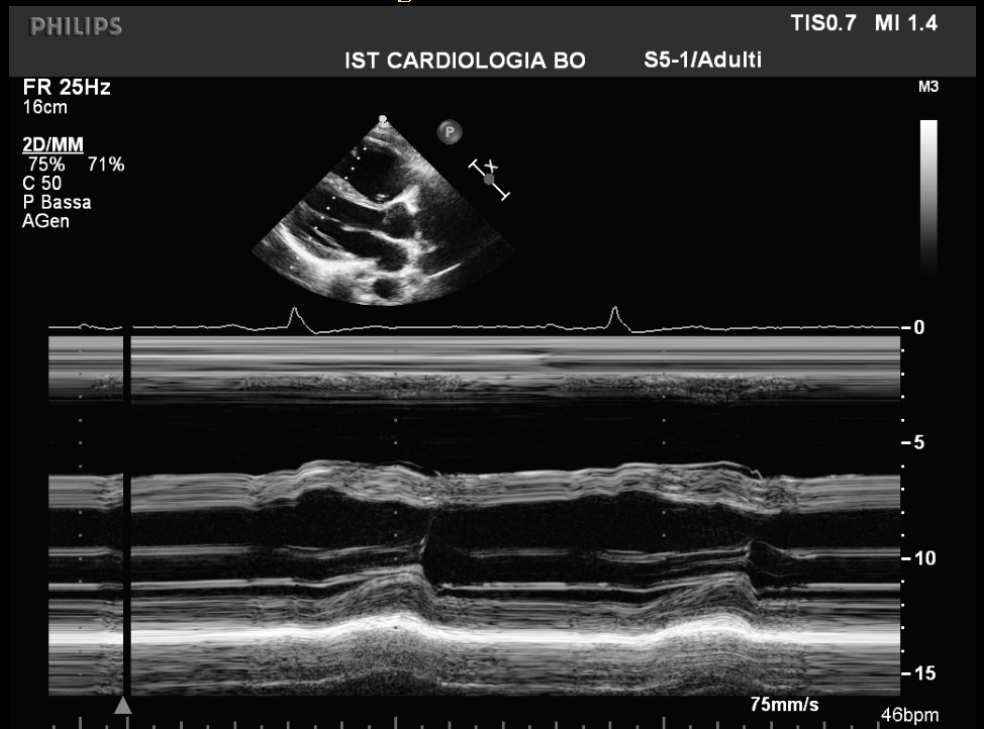
1.7 3.4
JPEG
43 bpm

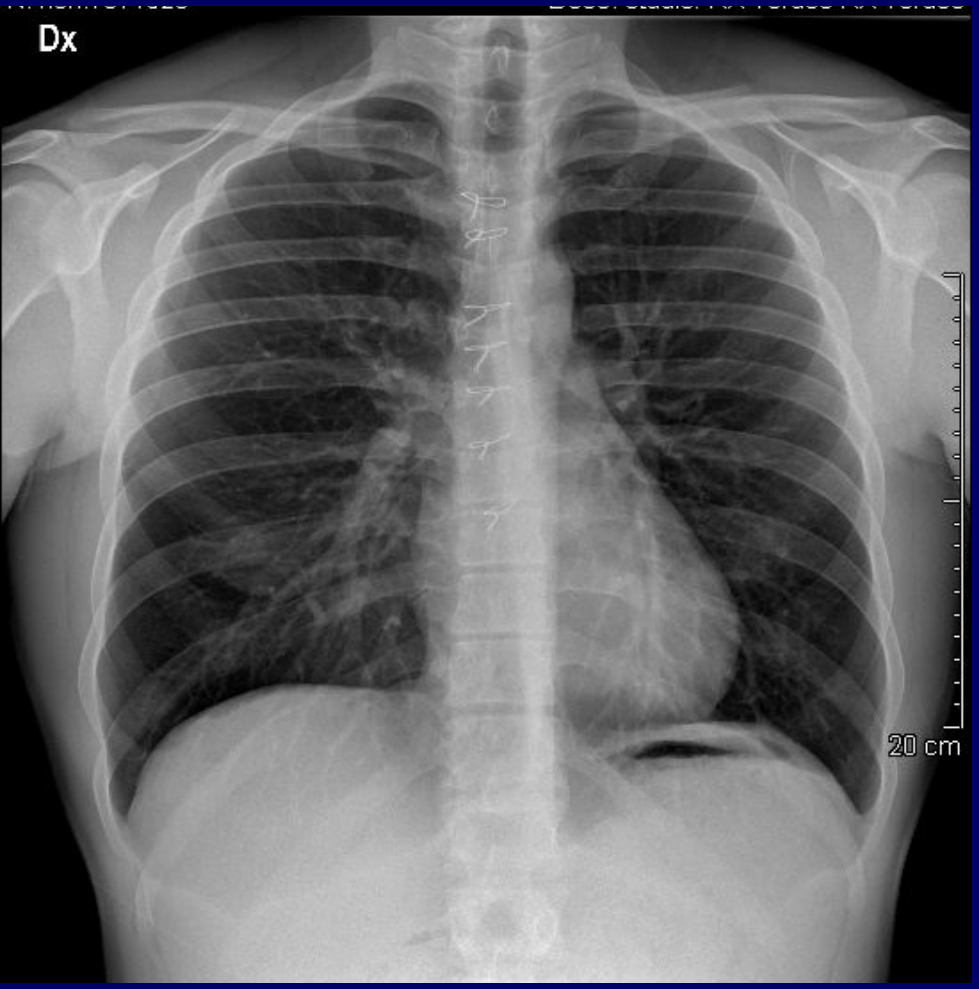

PHILIPS
TIS0.7 MI 1.4
IST CARDIOLOGIA BO S5-1/Adulti
FR 25Hz
16cm
2D/MM
75% 71%
C 50
P Bassa
AGen
M3
0
5
10
15
75mm/s
46bpm

RM Cuore

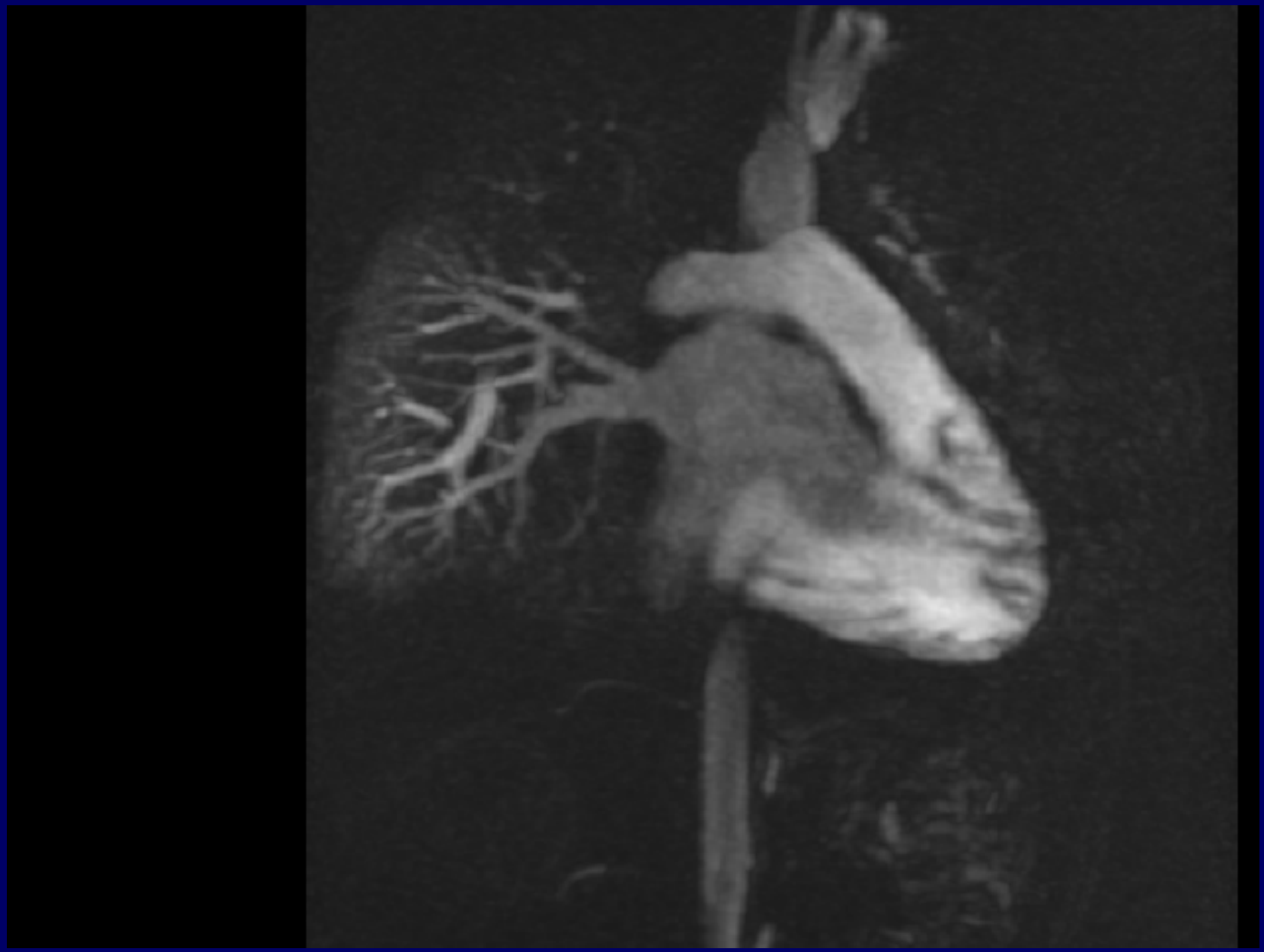
Ventricolo sinistro di normali dimensioni (EDV) e spessori parietali. Non alterazioni della cinetica loco-regionale; funzione sistolica globale ai limiti inferiori della norma.
Ventricolo destro con diametri aumetati e volumi ai limiti superiori della norma con lieve accentuazione della banda moderatrice.
Ipocinesia globale del ventricolo destro, maggiormente accentuata a carico dell'apice, con FE globale ai limiti inferiori della norma.
Lieve dilatazione del tratto di efflusso del ventricolo destro (RVOT 28 mm) con cinetica normale.
Atrio destro ed atrio sinistro di dimensioni ai limiti superiori della norma.
L'indagine non ha evidenziato segni di infiltrazione adiposa intramiocardica.
Non deficit di perfusione allo studio di primo passaggio a riposo.
Non apprezzabili aree di ritardato wash-out di mdc indicative di danno interstiziale\ miocellulare.

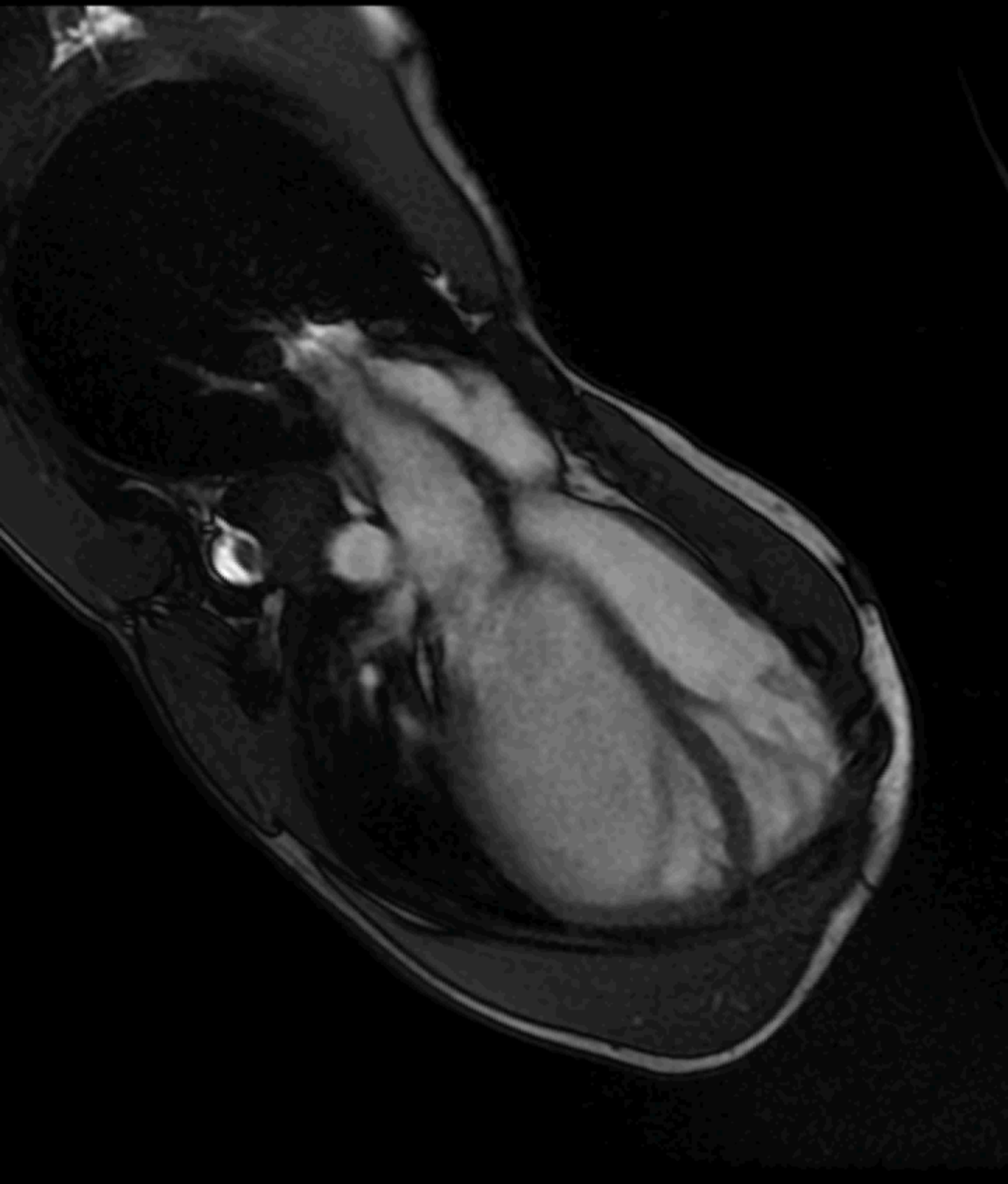
Conc.: l'indagine RM è compatibile con iniziale cardiomiopatia aritmogena del ventricolo destro, soddisfacendo 2 tra i criteri minori secondo gli ultimi aggiornamenti. Si consiglia controllo RM a circa 2 anni se le condizioni cliniche rimangono invariate.

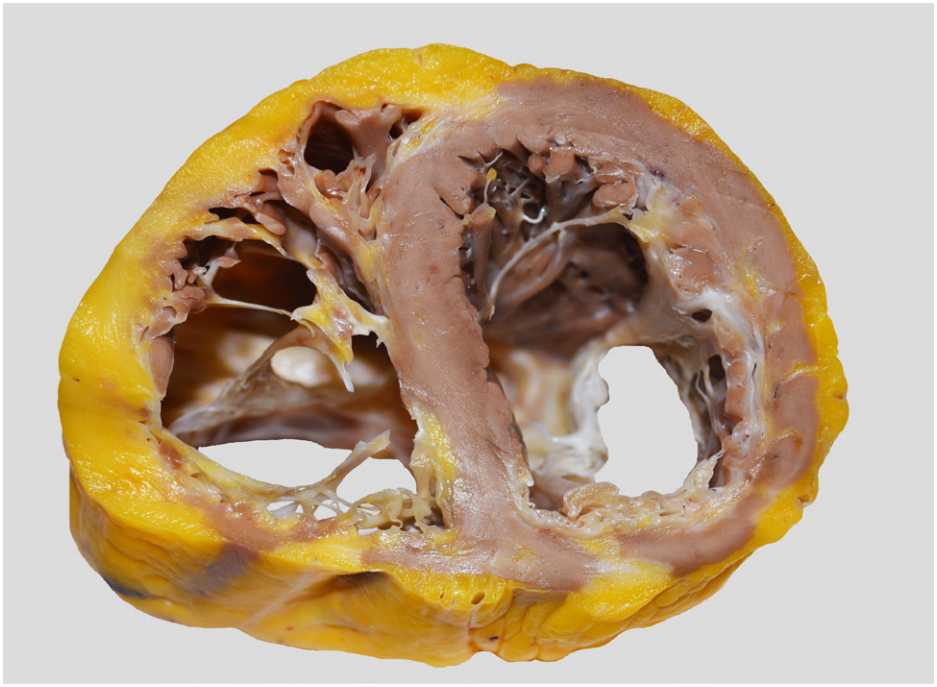
Rx torace

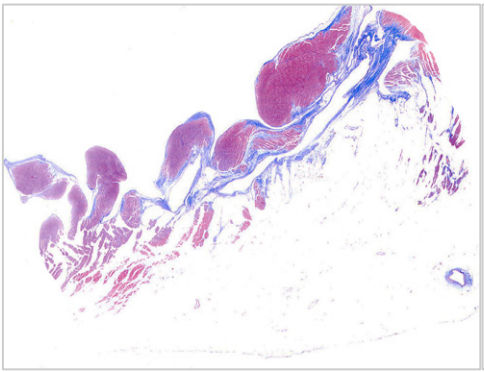

Dx
20 cm

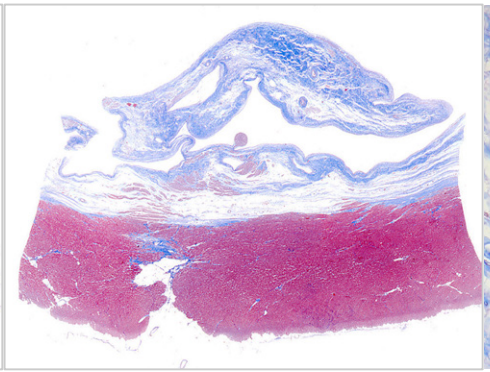

2-1
Lateralità: U
N. rich.7671520
10-dic-2013
120kV
Desc. studio: RX Torace RX Torace
20 cm

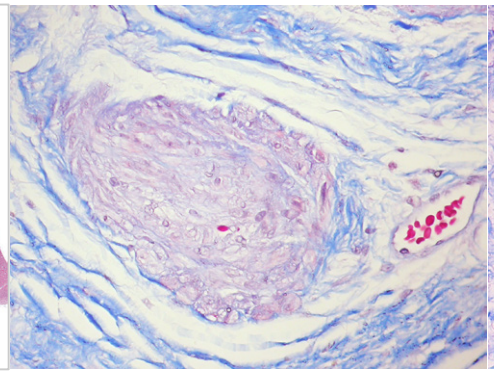


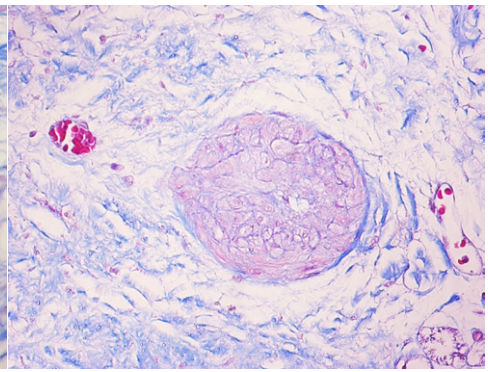








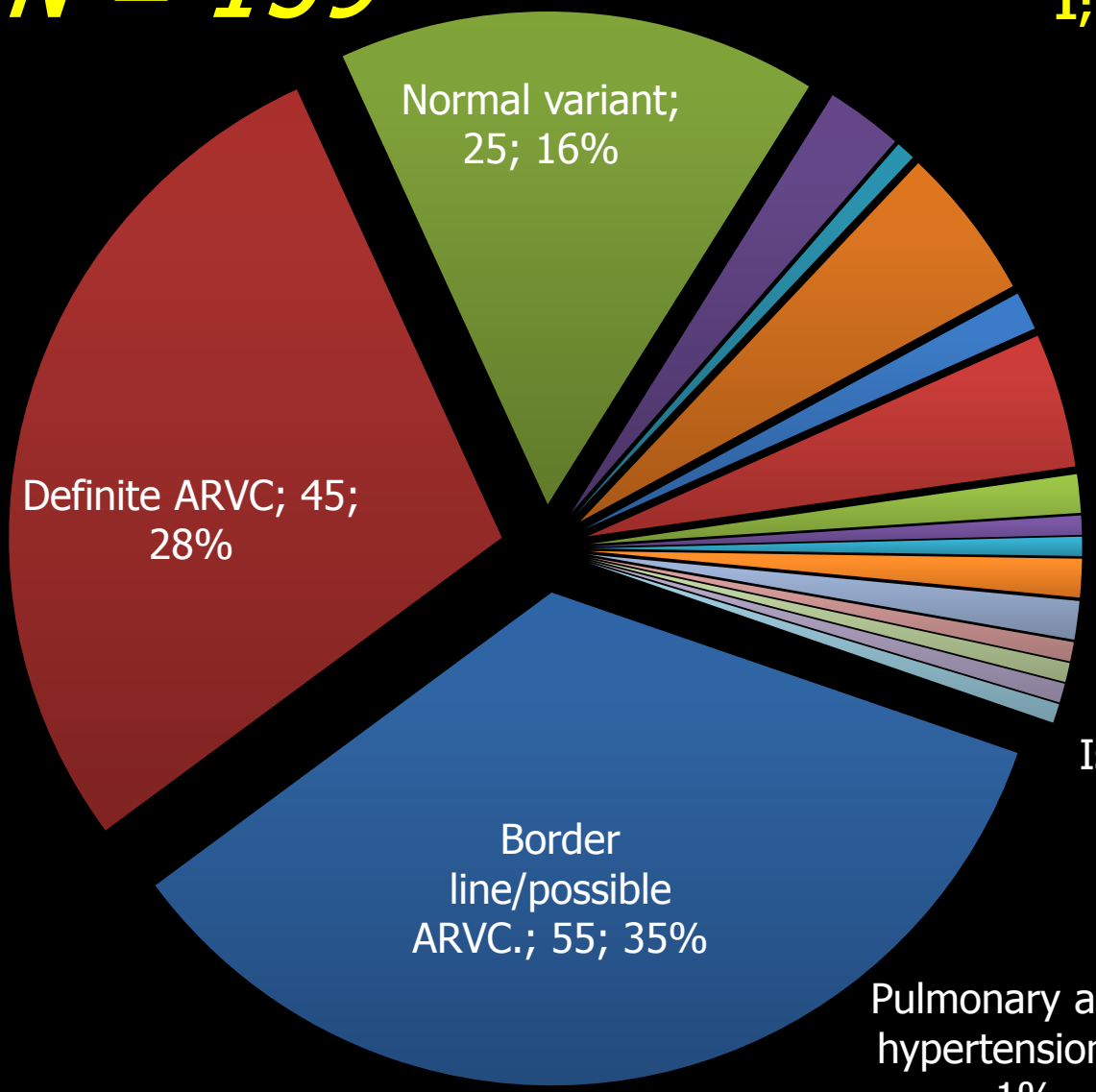




sclerodermia

Mimics of ARVC

N = 159



RVAP; 4; 3%

ASD ostium II; 1; 1%

Severe TR; 8; 5%

Pectus excavatum; 2; 1%

Systemic sclerosis, 7, 4%

Sarcoidosis; 2; 1%

Emery-Dreifuss Syndrome; 1; 1%

Laminopathy; 1; 1%

CMPD + NC; 2; 1%

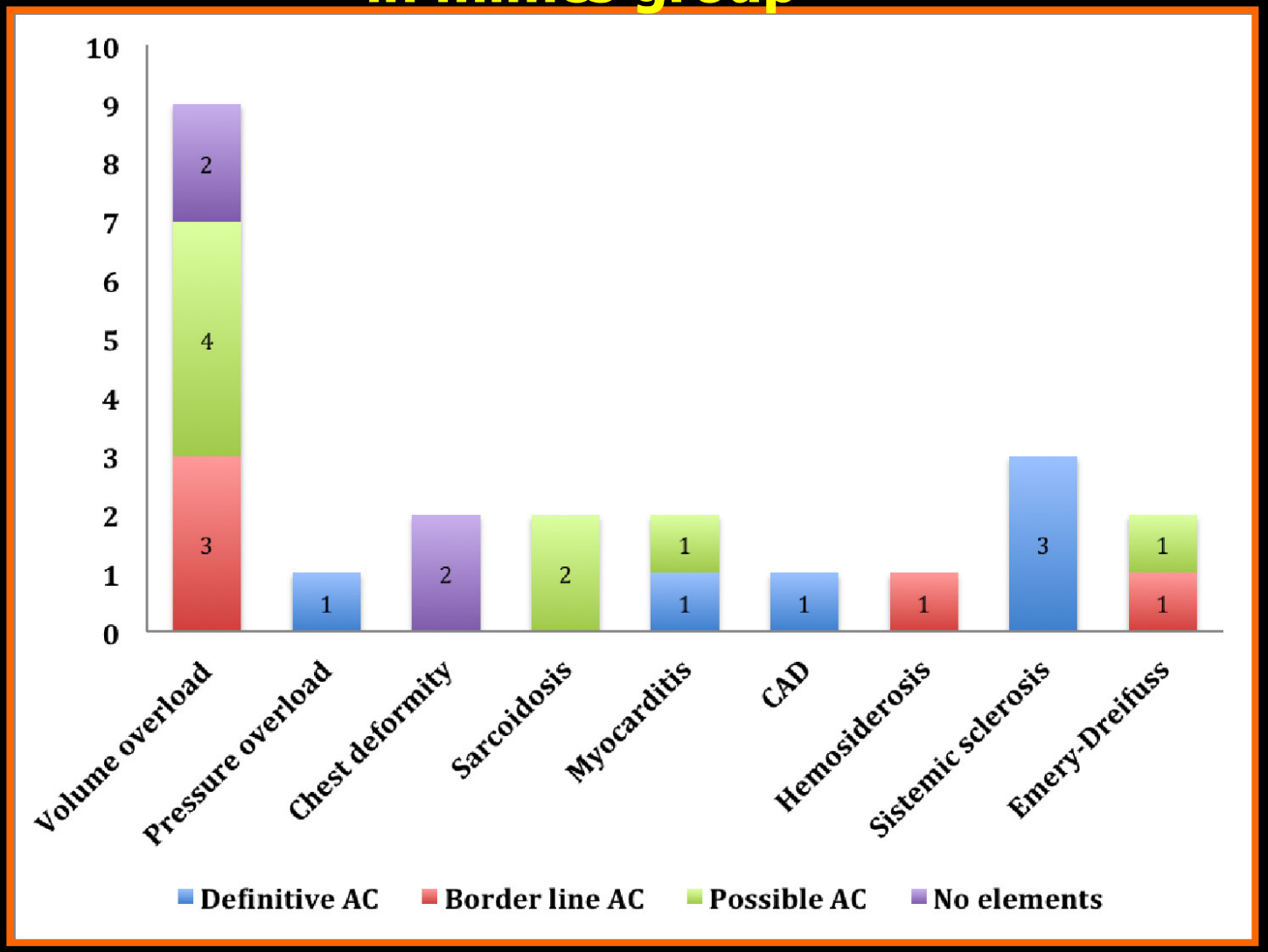
Myocarditis; 2; 1%

Haemochromatosis ; 1; 1%

Sarcomeric ; 1; 1%

Graziosi M. et al , submitted

Diagnosis of AC according to Task Force criteria in mimcs group



Definitive diagnosis AC 6 pt

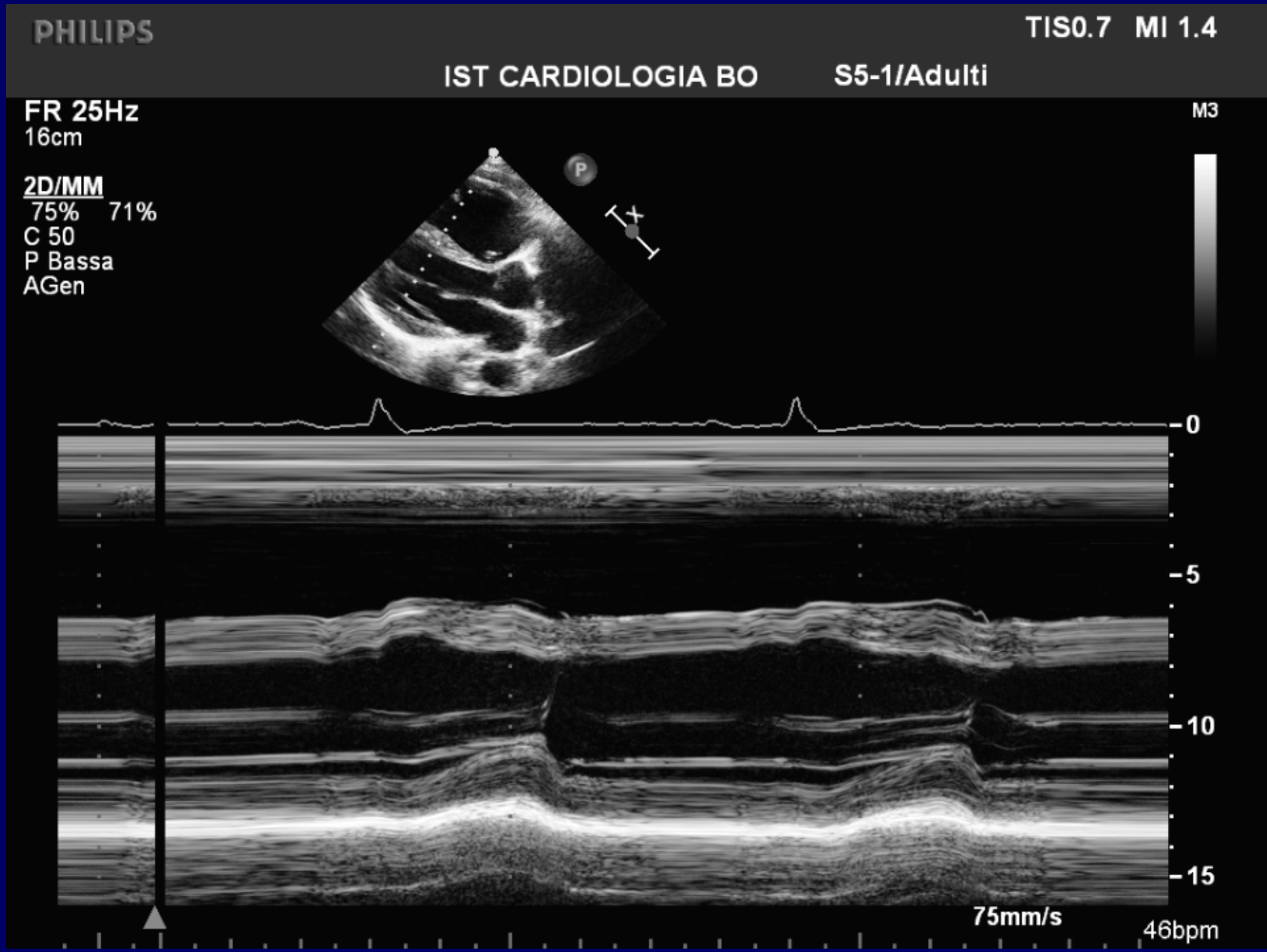
Border line diagnosis of AC 7pt

Possible diagnosis of AC 7 pt

Not enough elements for dg of AC 3 pt

"Pathogenesis" of the cognitive error

- Deficit of observation/interpretation
- Operational superficiality
- Ideological superficiality (tipically an uncritical reliance on pathognomonic signs and biomarkers)
- Cultural deficit
- Excess of recent culture (fashion effect)
- Hypersemiotic thought process:
  - Use of generic diagnostic categories («hypercontainers»)
  - Focus on "hypersignificant" ("blinding") elements
  - Absence of method


PHILIPS
TIS0.7 MI 1.4
IST CARDIOLOGIA BO
S5-1/Adulti
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16cm
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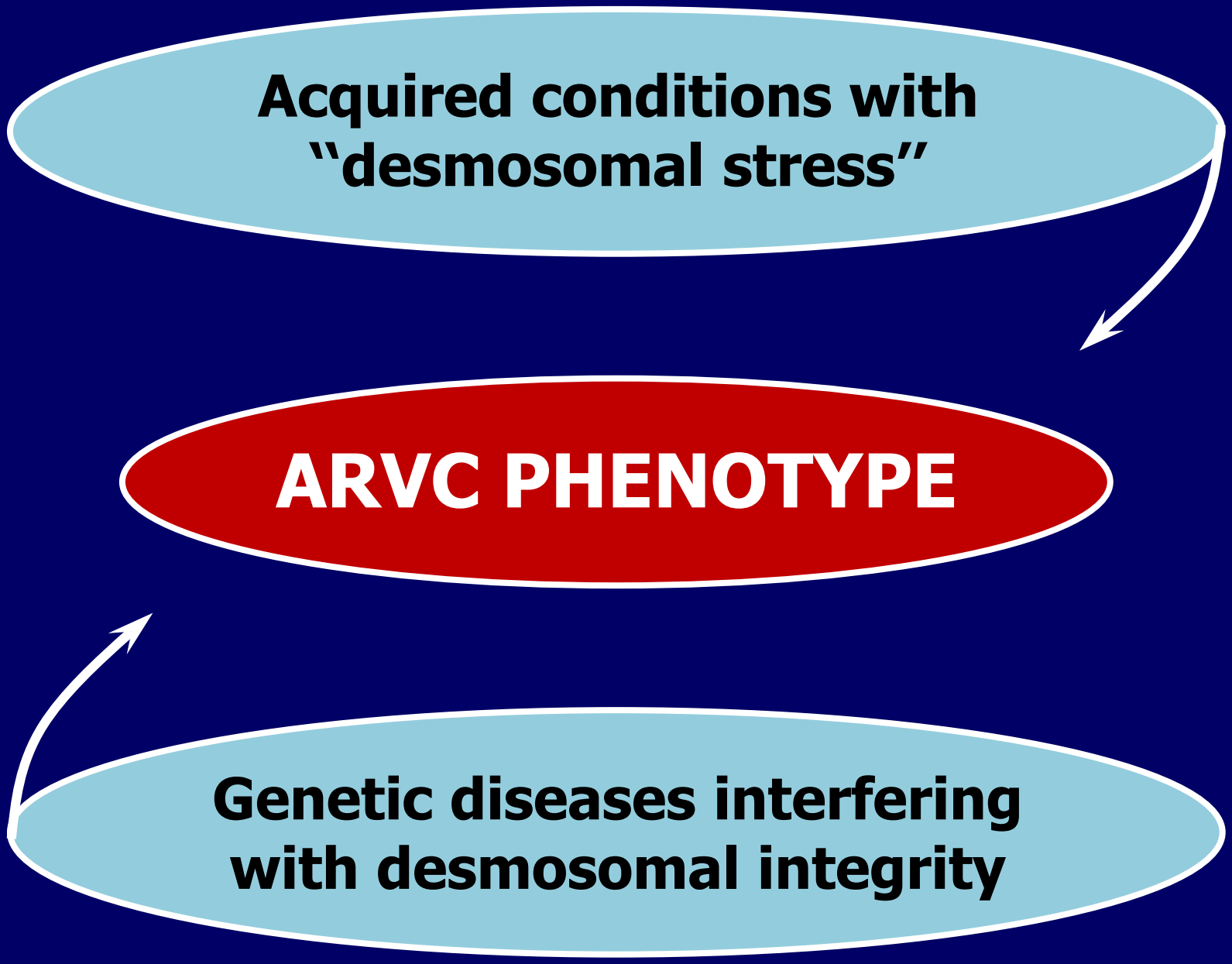
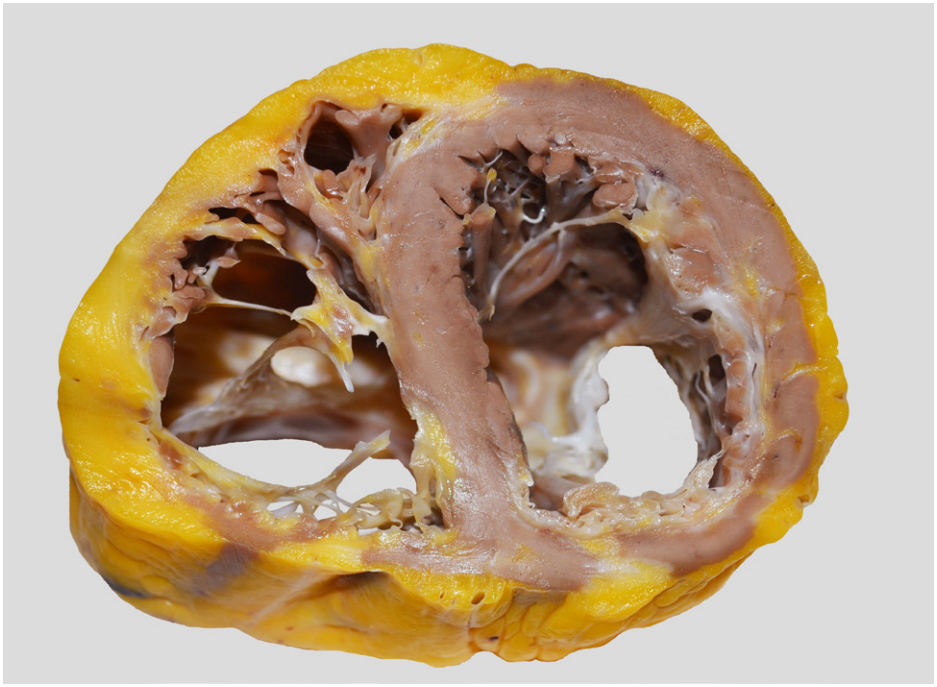
75% 71%
C 50
P Bassa
AGen
M3
P
0
5
10
15
75mm/s
46bpm

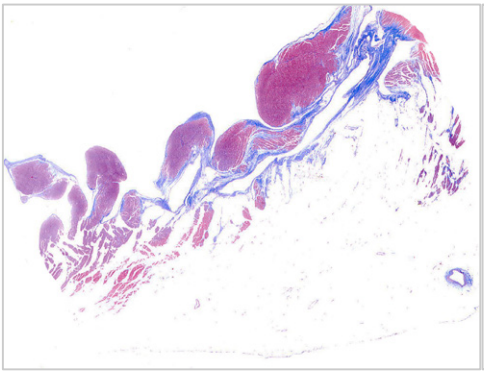
C Calore et al
European Heart Journal (2016) 37, 2515–2527

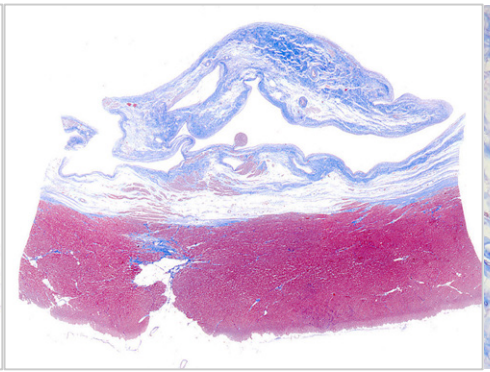
The long and winding road to ARVC

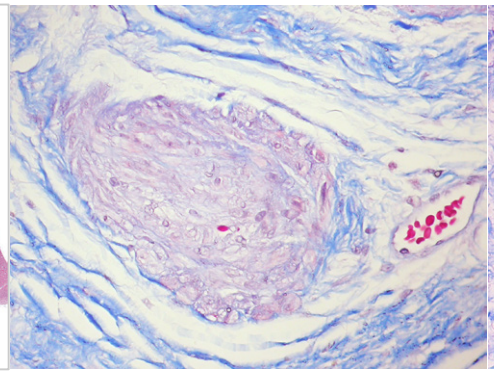
- Mimics/pitfalls
- Phenocopies
- Genocopies

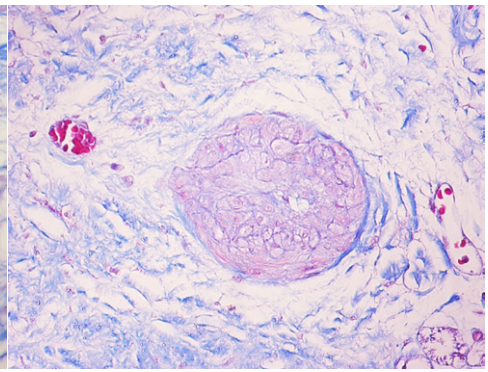

Acquired conditions with "desmosomal stress"
ARVC PHENOTYPE
Genetic diseases interfering with desmosomal integrity









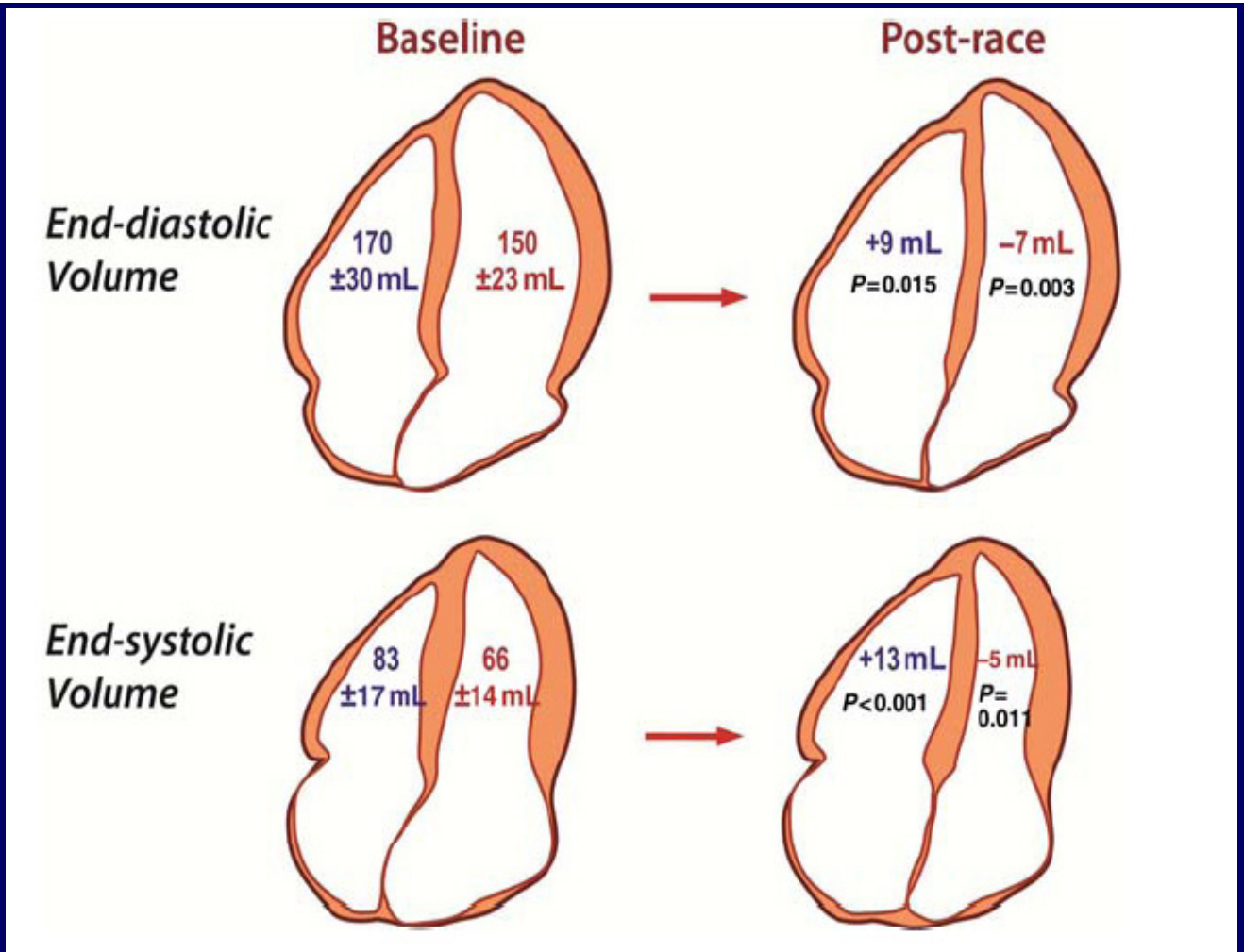


sclerodermia

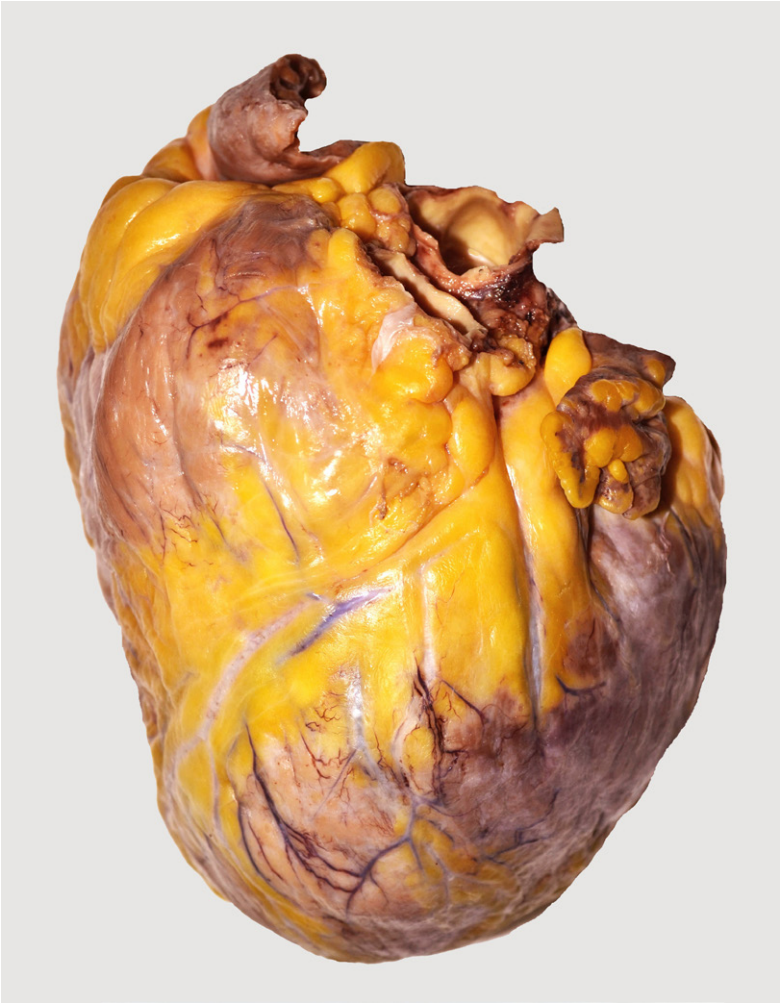
Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes

André La Gerche[1,2*], Andrew T. Burns[3], Don J. Mooney[3], Warrick J. Inder[1], Andrew J. Taylor[4], Jan Bogaert[5], Andrew I. MacIsaac[3]. Hein Heidbüchel[2]. and David L. Prior[1,3]

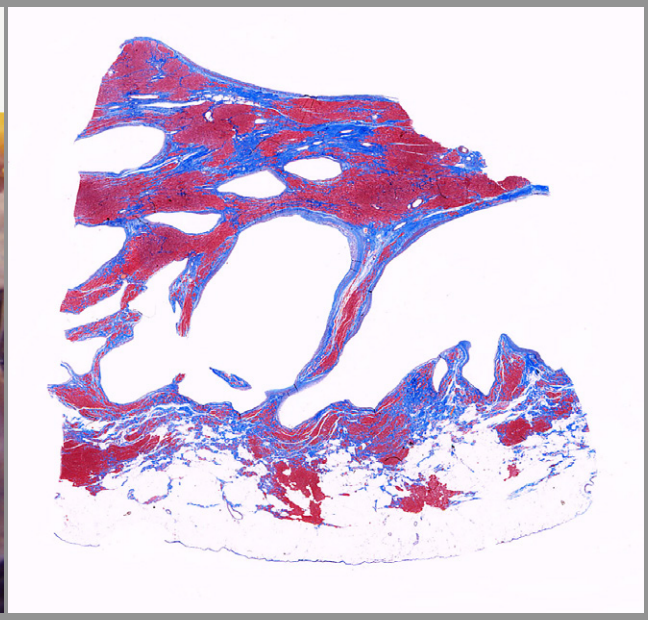
European Heart Journal (2012) **33**, 998–1006

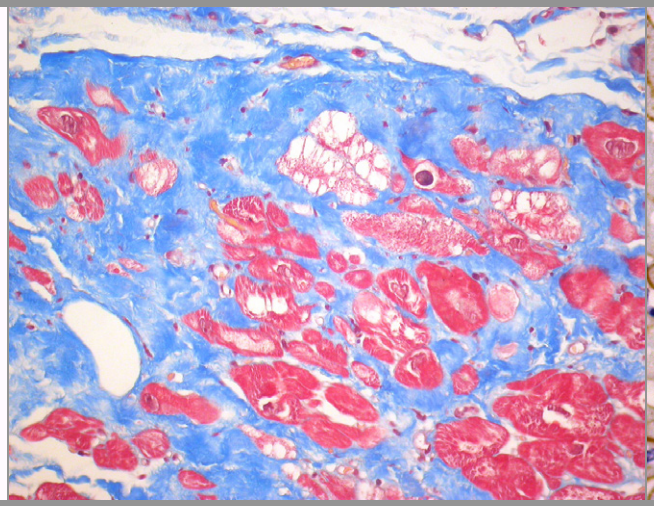


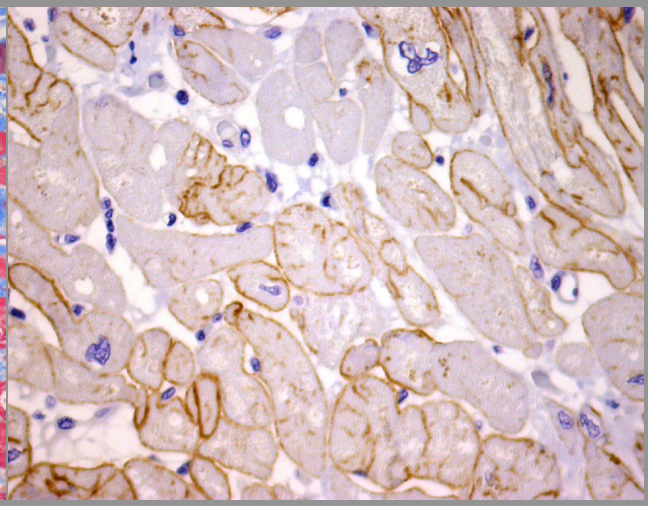
BELELLI – sarcoidosi



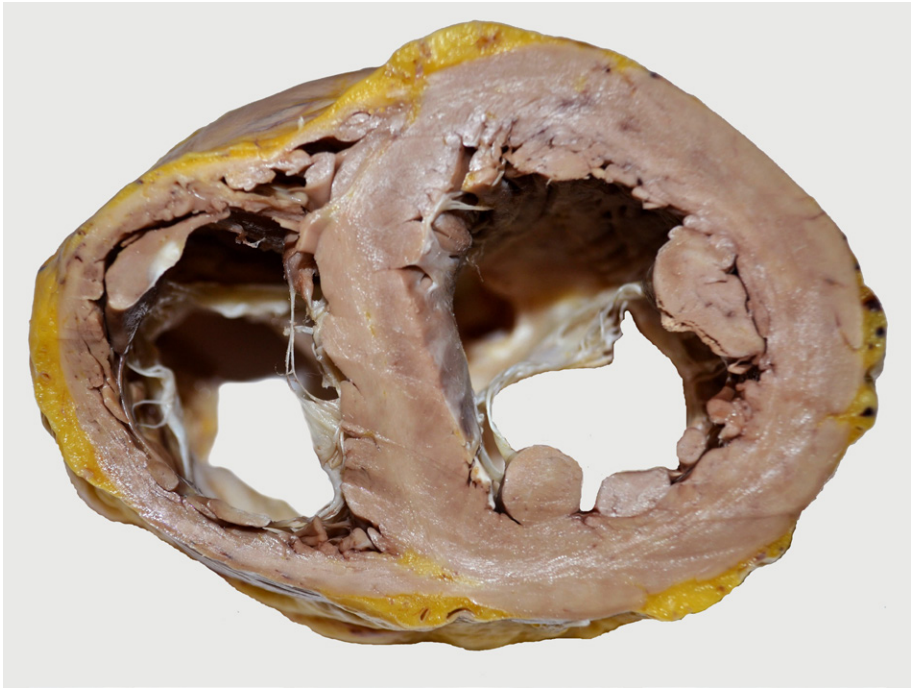
Becker Distrophy







Laminopathy



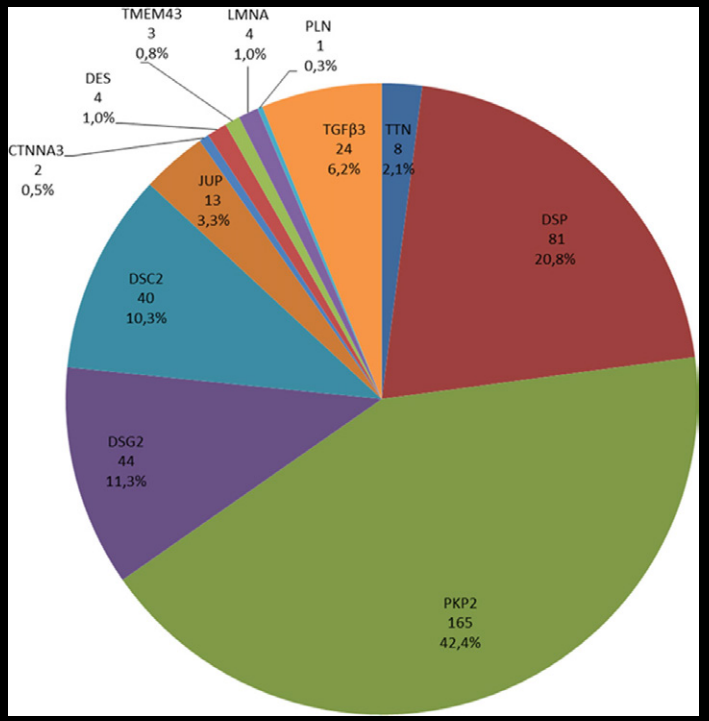
Genes associated with ARVC

Desmosomal

- Desmocollin-2 (DSC2)
- Desmoglein-2 (DSG2)
- Desmoplakin (DSP)
- Junctional Plakoglobin (JUP)
- Plakophilin-2 (PKP2)

Non-Desmosomal

- Desmin (DES)
- Lamin A/C (LMNA)
- Phospholamban (PLN)
- Ryanodine Receptor (RYR2)
- Transmembrane Protein 43 (TMEM43)
- Titin (TTN)



Arrhythmogenic RV Cardiomyopathy (a non-arrhythmologic perspective)

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- Diagnostic pitfalls, mimics and phenocopies
- Clinical role of molecular genetic
- Role of MRI
- ARVC as a cause of HF
- From right-side to left-side
- Commendation of the standard ECG

Molecular Biology of CMPs
Paradigm shifts

1. One gene → one disease
2. Many genes → one disease
3. One gene → many diseases

Molecular genetics in diagnosis and prognosis of ARVC

> 11	identified genes
40 %	of cases with definite ARVC and negative genetic analysis
6	times higher, is the risk of developing a disease in carriers, but....
> 50 %	of carriers do not develop the disease
> 2	desmosomal mutations in the same patient probably = worse prognosis

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MYOCARDIAL SUBSTRATE CHARACTERIZATION BY MR

- Fat
- Water (oedema)
- Iron
- Extra Cellular Volume (fibrosis/inflammatoty cells/ amyloidosis)

- T1 fs
- T2
- T2*
- LGE; Eq-CMR; T1 map

La ricerca dell'infiltrazione miocardica adiposa mediante RM

Limiti tecnici

Pitfalls

Varianti normali

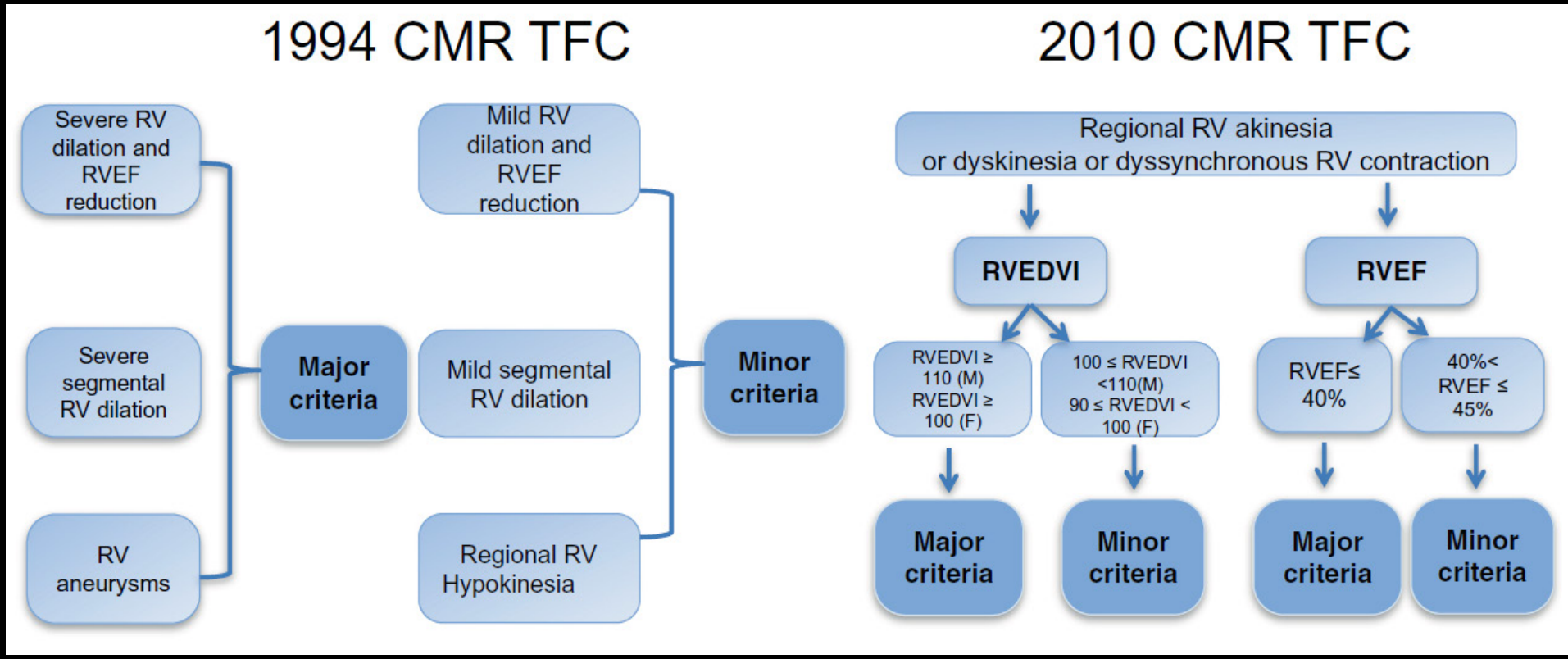
Scarsa riproducibilità

Aufferman W et al AJR 1999
Tandri H et al J Cardiovasc Electrophysiol 2003
Bluemke DA et al Cardiology 2003
Tandri H et al JACC 2006
Tandri H et al AHJ 2008

MRI in ARVC

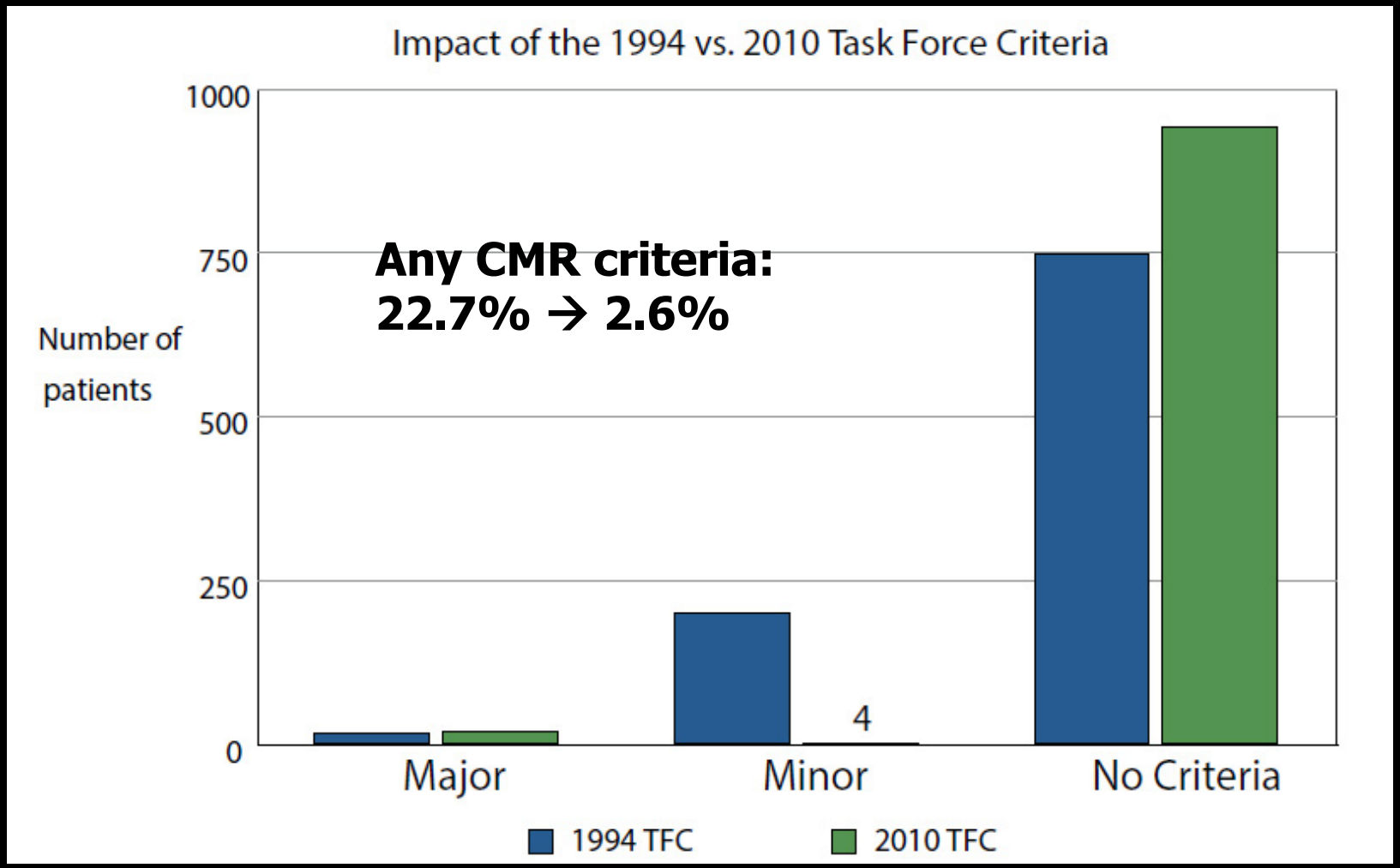
Change of focus

- From search of fat infiltration to morpho-functional definition of the RV
- From fat to fibrosis
- From right to left


1994 CMR TFC
Severe RV dilation and RVEF reduction
Severe segmental RV dilation
RV aneurysms
Major criteria
Mild RV dilation and RVEF reduction
Mild segmental RV dilation
Regional RV Hypokinesia
Minor criteria
2010 CMR TFC
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
RVEDVI
RVEF
RVEDVI ≥ 110 (M) RVEDVI ≥ 100 (F)
100 ≤ RVEDVI <110(M) 90 ≤ RVEDVI < 100 (F)
RVEF≤ 40%
40%< RVEF ≤ 45%
Major criteria
Minor criteria
Major criteria
Minor criteria

Effect of the 2010 task force criteria on reclassification of cardiovascular magnetic resonance criteria for arrhythmogenic right ventricular cardiomyopathy

Liu *et al. Journal of Cardiovascular Magnetic Resonance* 2014, **16**:47



MRI in ARVC

Change of focus

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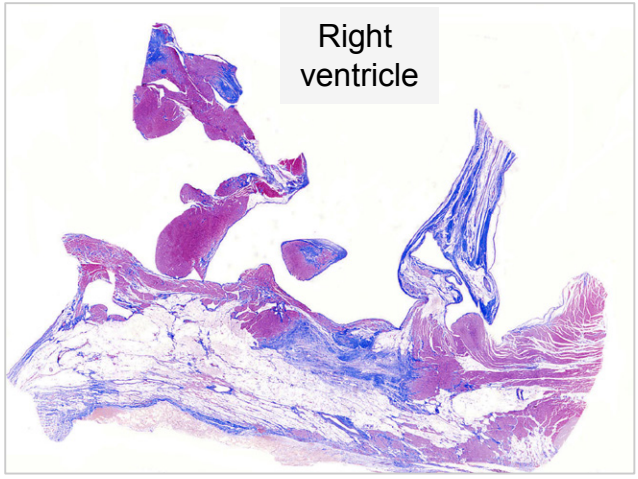
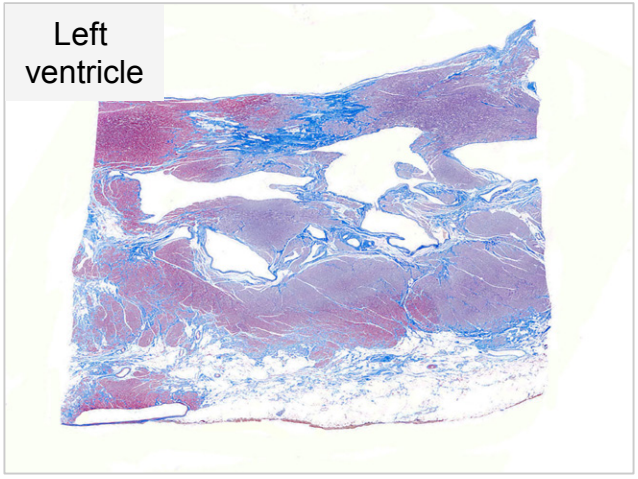
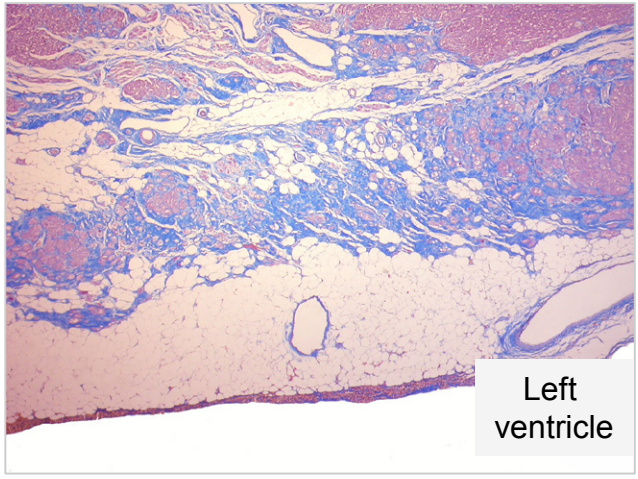
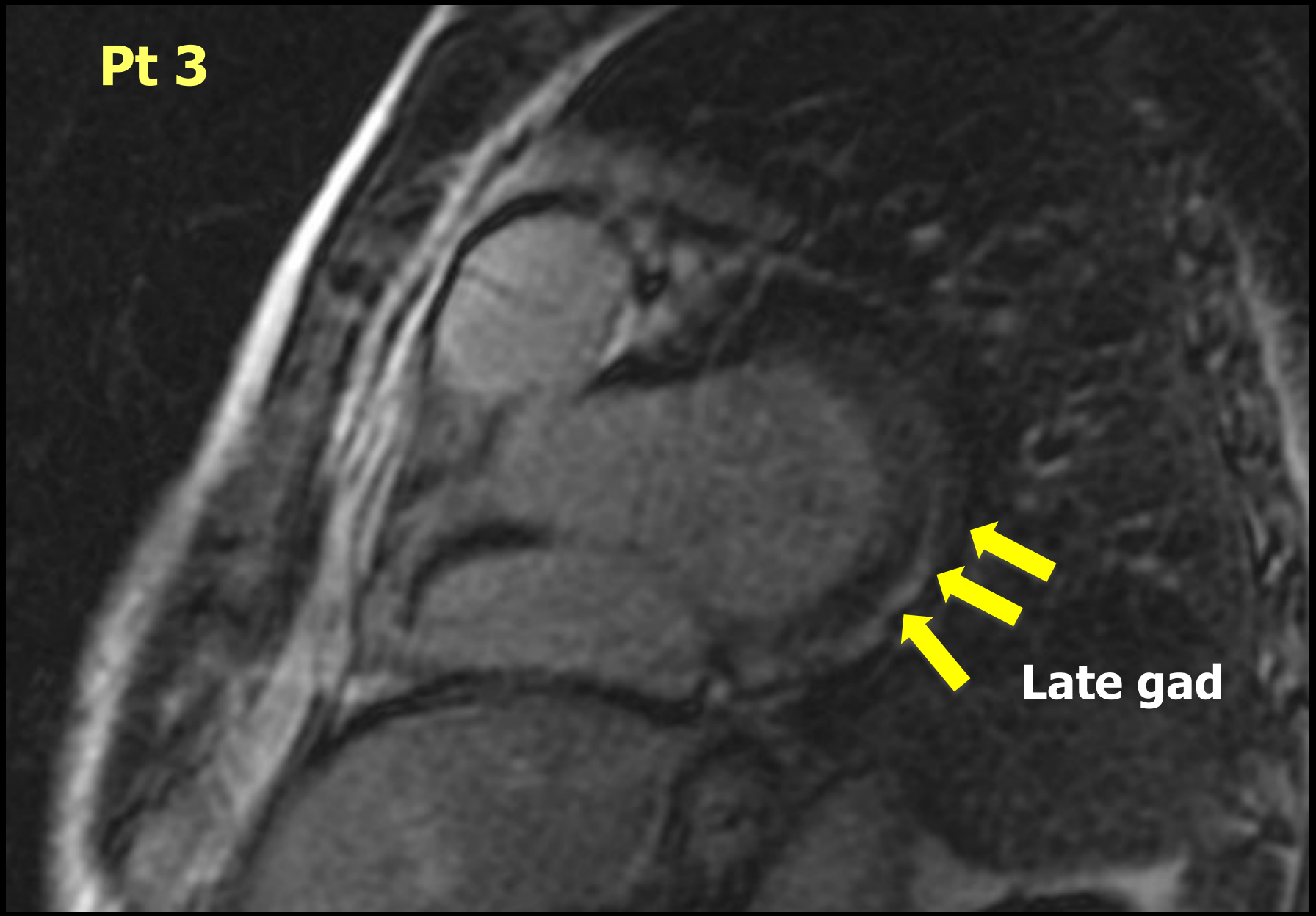
ARVC with LV involvment








Pt 3
Late gad

ARVC and LV involvement

ARVC with associated segmental involvement of the LV

BIVENTRICULAR AC

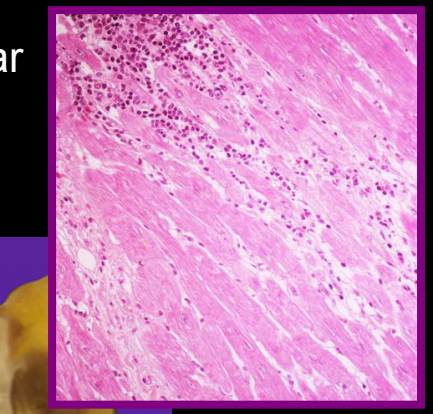
Isolated ALVC (left dominant)

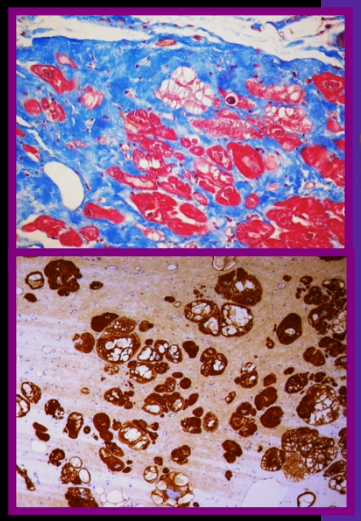
36 explanted hearts

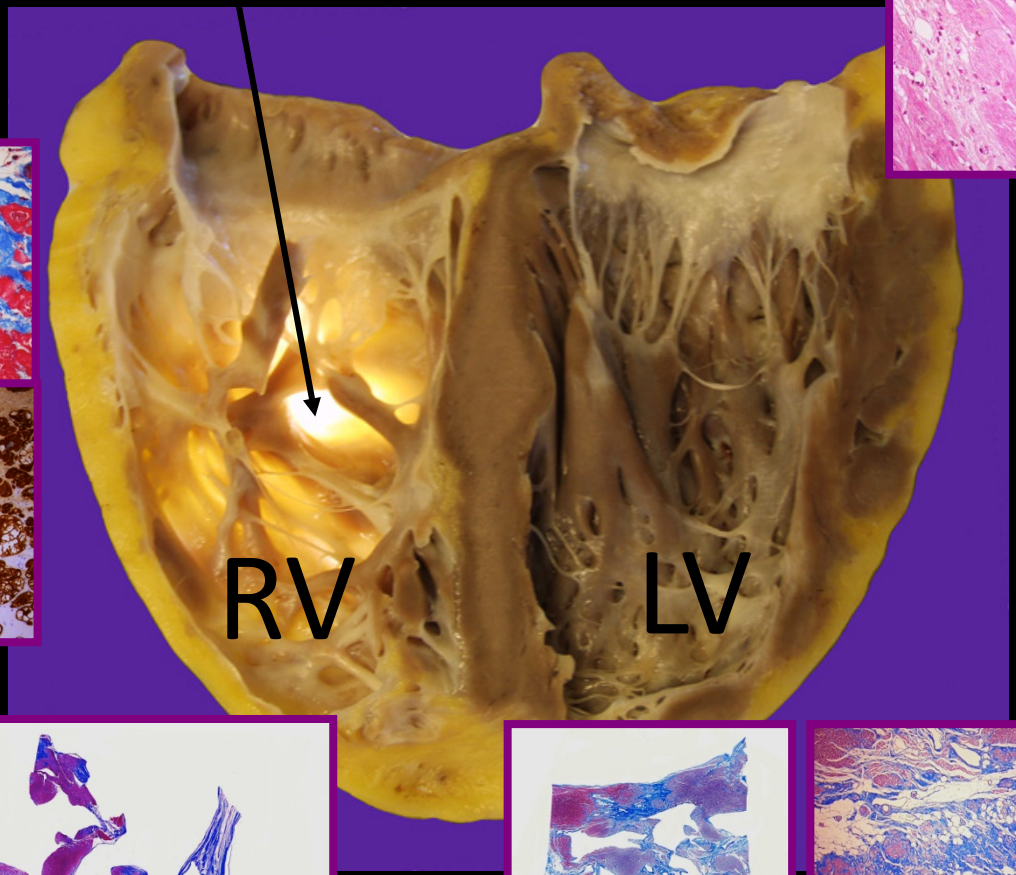
Damage of myocytes (hypertrophy, dysmetry, sarcoplasmic vacuolization

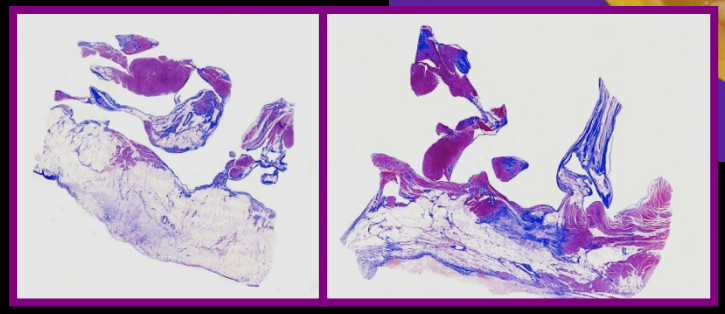
Wall transillumination

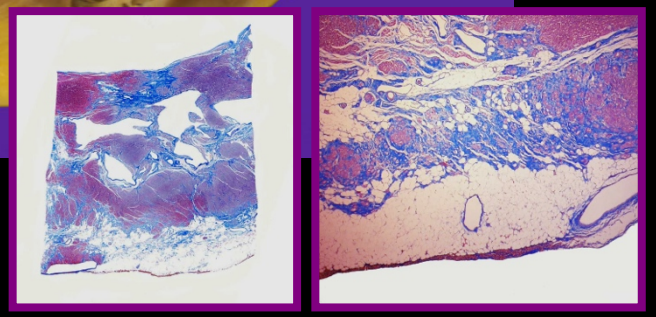
Biventricular flogistic infiltration







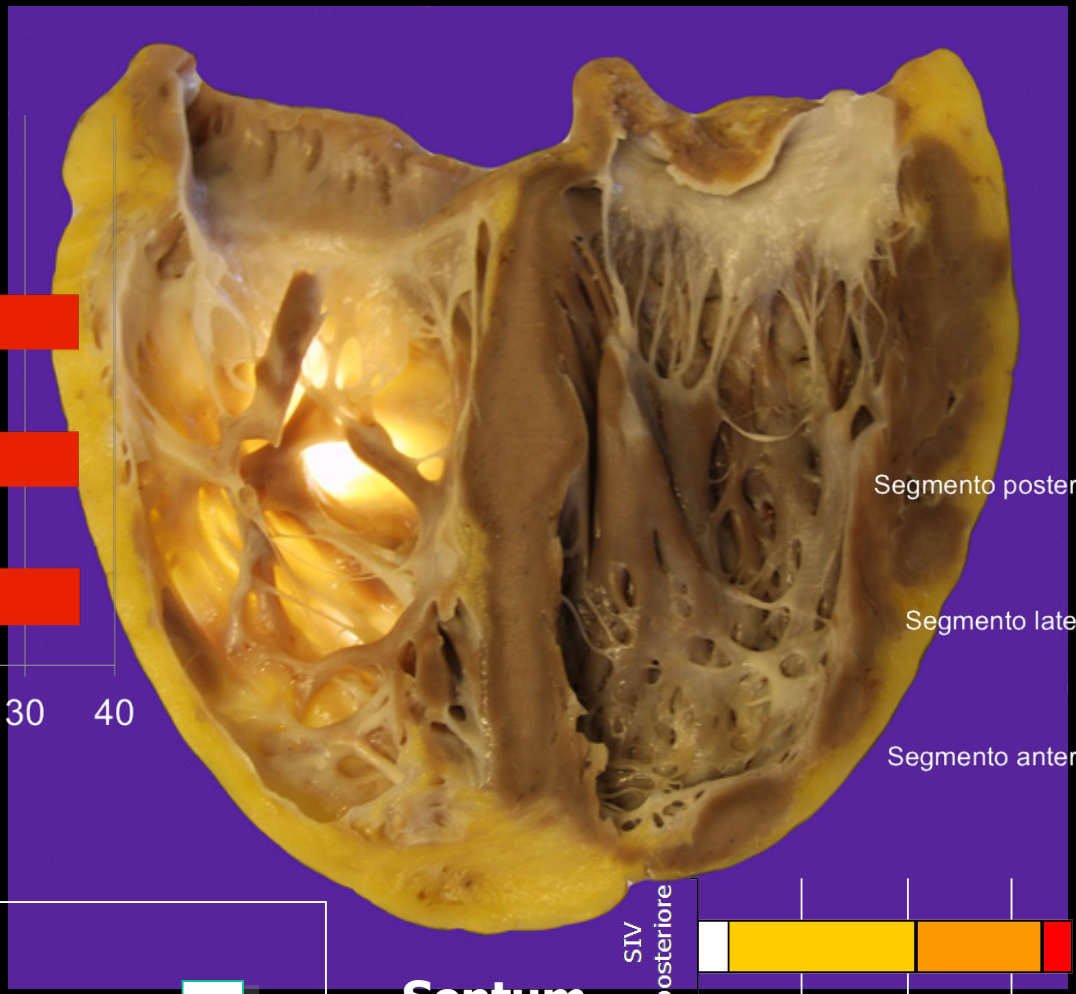




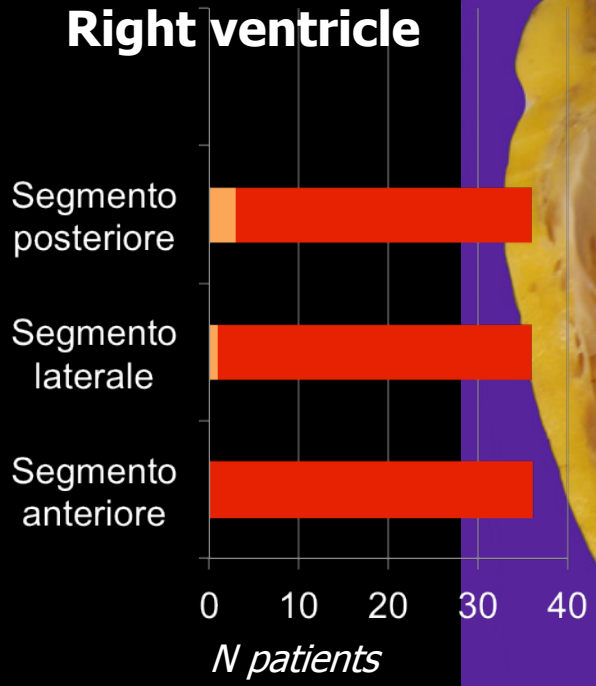
Transmural fibro-fatty infiltration of RV

Fibro-fatty infiltration of LV (prevalent fibrosis)

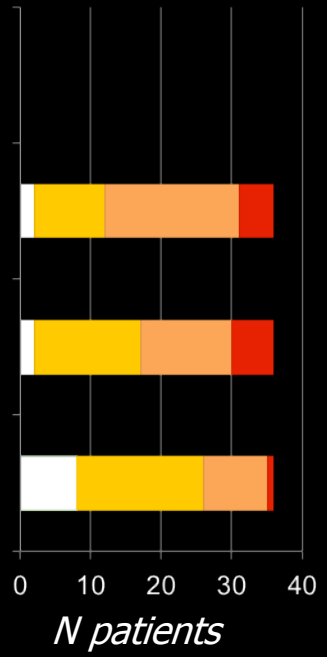
Different degrees of fibro-fatty infiltration of ventricles (medioventricular transversal section)



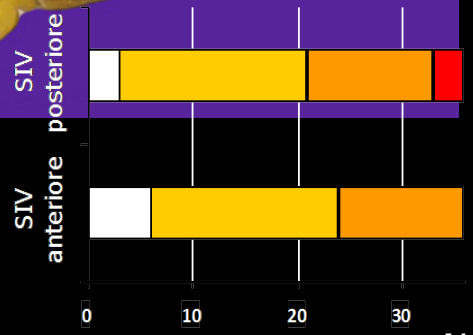
Right ventricle



Left ventricle



Septum



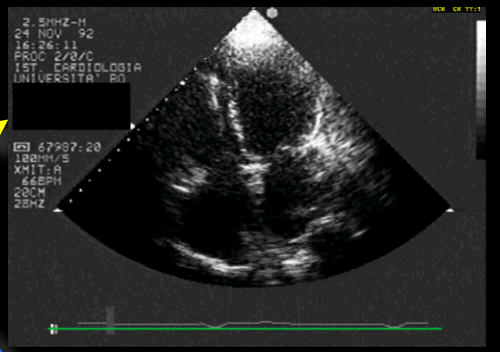
Legend

- Normal myocardium
- Subepicardial infiltration
- Mediomural infiltration
- Transmural infiltration

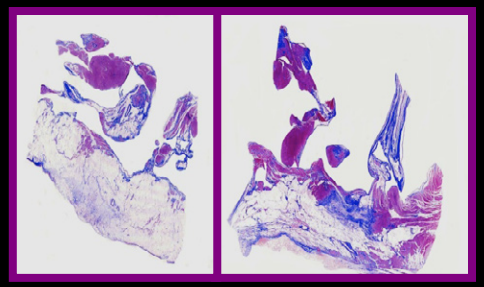
Pathophysiology of severe HF in ARVC

Severe global RV dysfunction

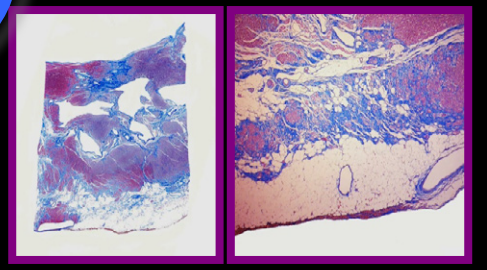
LV involvement



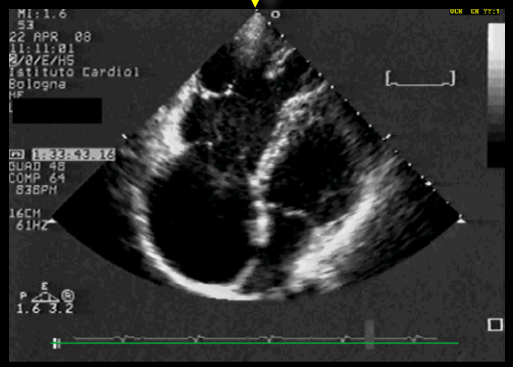
End stage HF



Transmural fibro-fatty infiltration

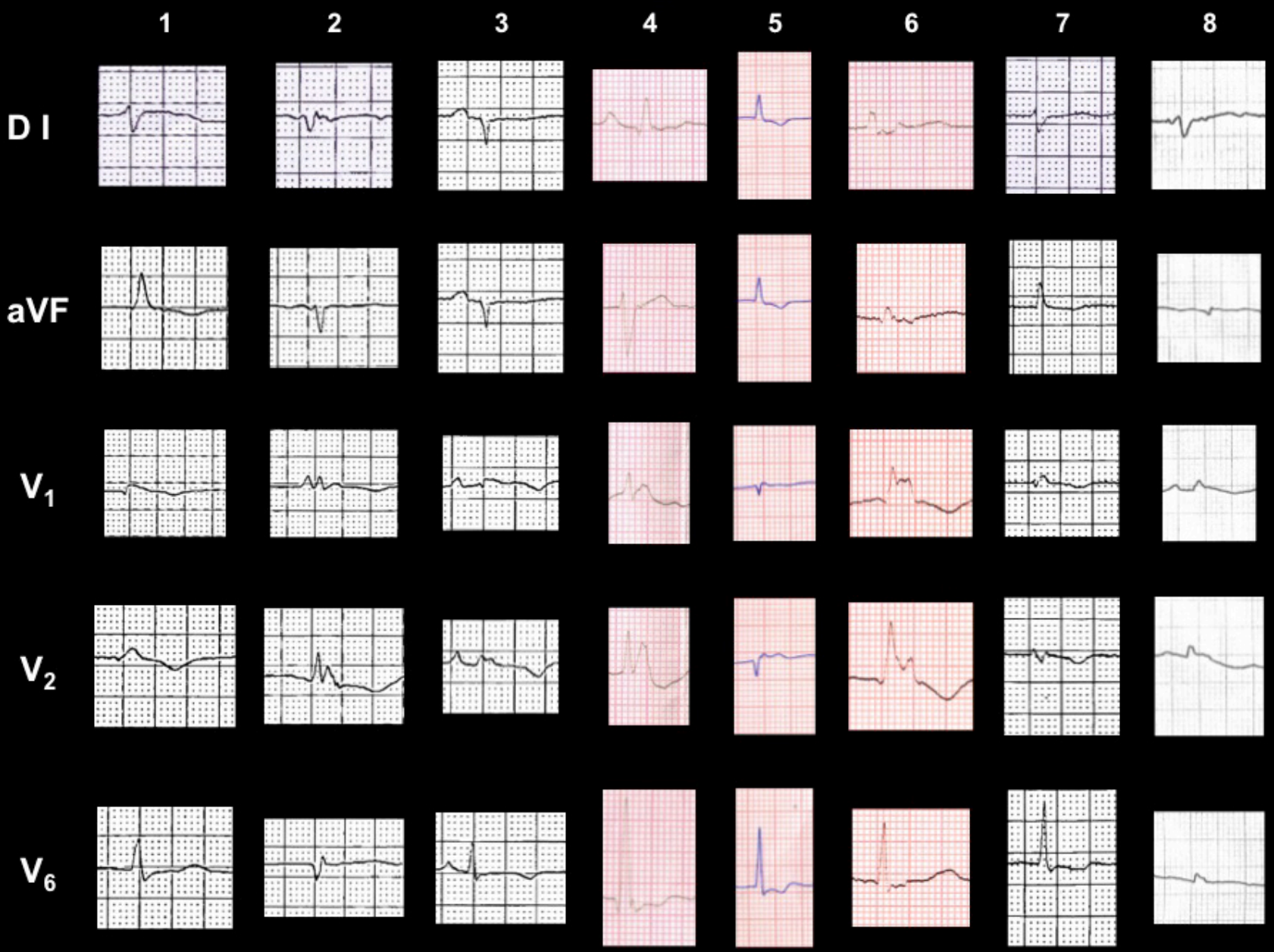


Fibro-fatty infiltration with prevalent fibrosis

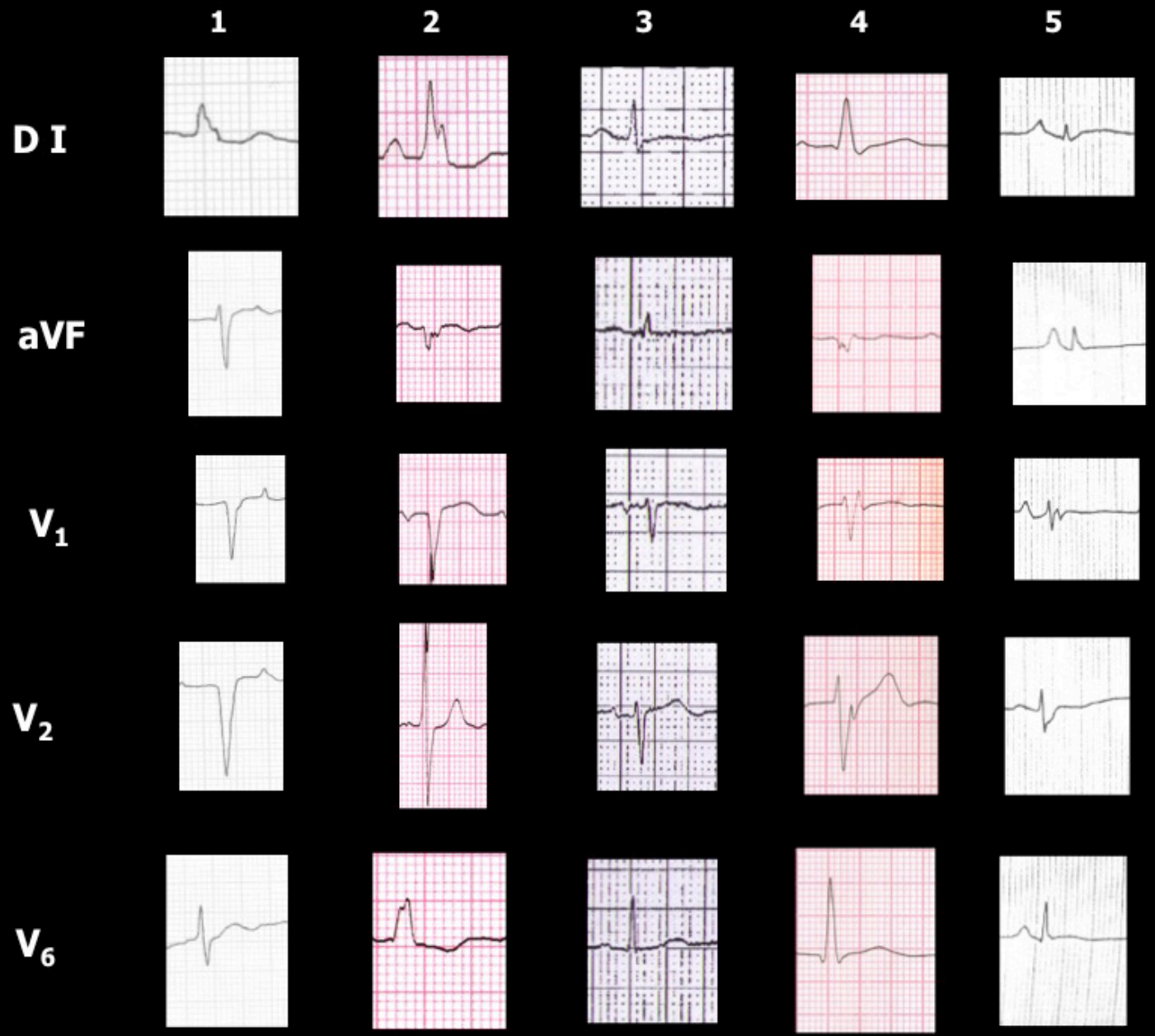


Extreme inflow dilation leading to massive TR

Peculiar ECG in pt who underwent heart transplantation: RBBB like



Peculiar ECG in pt who underwent heart transplantation: LBBB like



ARVC and LV involvement

ARVC with associated segmental involvement of the LV

BIVENTRICULAR AC

Isolated ALVC (left dominant)

Characterization of the Left-Sided Substrate in Arrhythmogenic Right Ventricular Cardiomyopathy

Benjamin Berte, MD; Arnaud Denis, MD; Sana Amraoui, MD; Seigo Yamashita, MD, PhD; Yuki Komatsu, MD; Xavier Pillois, MD, PhD; Frédéric Sacher, MD, PhD; Saagar Mahida, MD, PhD; Jean-Yves Wielandts, MD, MSc; Jean-Marc Sellal, MD; Antonio Frontera, MD; Nora Al Jefairi, MD; Nicolas Derval, MD; Michel Montaudon, MD, PhD; François Laurent, MD; Mélèze Hocini, MD; Michel Haïssaguerre, MD; Pierre Jaïs, MD, PhD; Hubert Cochet, MD, PhD

Circ Arrhythm Electrophysiol. 2015;8:1403-1412.

…Imaging abnormalities were found in 32 (100%) and **21 (66%)** patients on the RV and **LV**, respectively, intramyocardial fat on multidetector computed tomography being the most sensitive feature….

Prevalence of Desmosomal Protein Gene Mutations in Patients With Dilated Cardiomyopathy

Perry Elliott, MD; Constantinos O'Mahony, MBBS (Lond); Petros Syrris, PhD; Alison Evans, PhD; Christina Rivera Sorensen, MSc; Mary N. Sheppard, MD; Gerald Carr-White, PhD; Antonios Pantazis, MD; William J. McKenna, DSc

- Mutation screening of 5 genes implicated in ARVC (plakoglobin, desmoplakinm plakophillin-2, desmoglein-2, desmocollin-2) in 100 consecutive unrelated pt with idiopathic dilated cardiomyopathy
- 5 pt were found to carry pathogenic mutation
- 13 pt had sequence variants of uncertain significance
- None of 5 carriers of desmosomal mutation fulfilled current diagnostic criteria for ARVC, but 1 ah fibrofatty infiltration at autopsy
- Pt with desmosomal mutation had a phenotype indistinguischable from the other

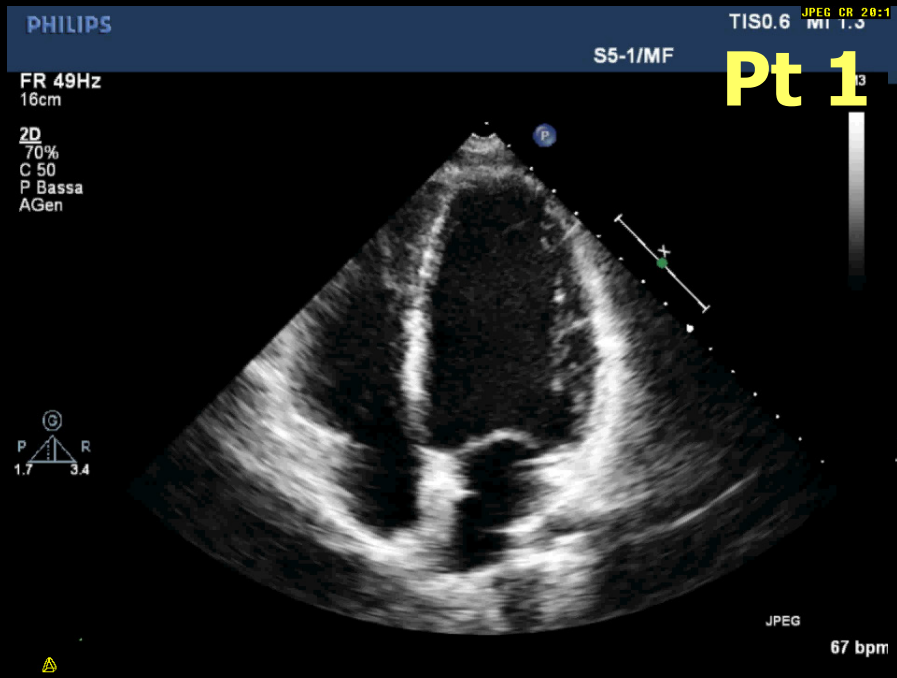
Circ Cariovasc Genet 2010

Desmosomal protein gene mutations in patients with idiopathic dilated cardiomyopathy undergoing cardiac transplantation: a clinicopathological study

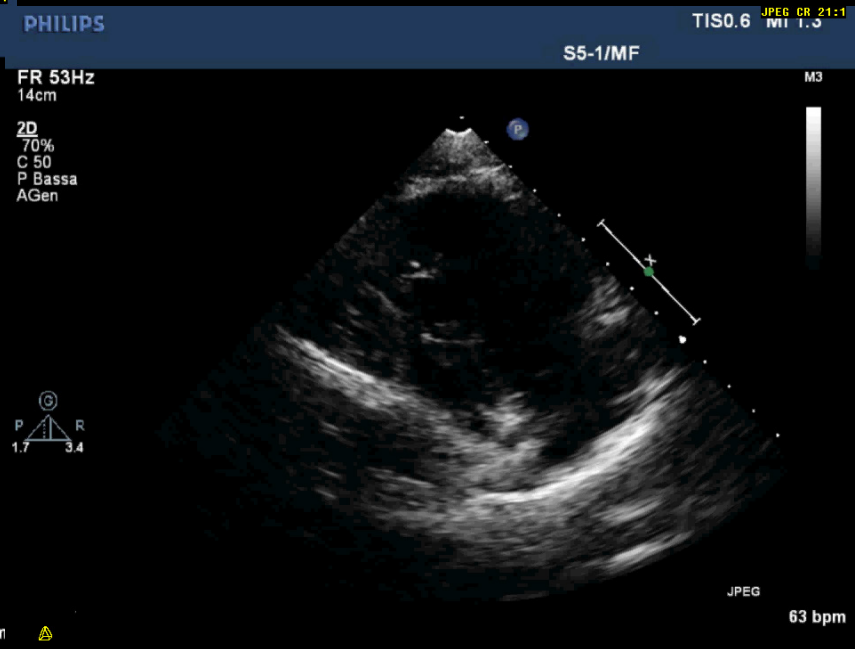
Pablo Garcia-Pavia,[1] Petros Syrris,[2] Clara Salas,[3] Alison Evans,[2] Jesus G Mirelis,[1] Marta Cobo-Marcos,[1] Carlos Vilches,[4] Belen Bornstein,[5] Javier Segovia,[1] Luis Alonso-Pulpon,[1] Perry M Elliott[2]

- Genetic screening of 5 desmosamal genes (PKP2, DSP, DSC2, DSG2 and JUP) in 89 unrelated pt transplanted for end-stage DCM
- Pathogenic mutations identified in 12 pt (13%). Five additional pt (6%) had genetic variant of unknown significance

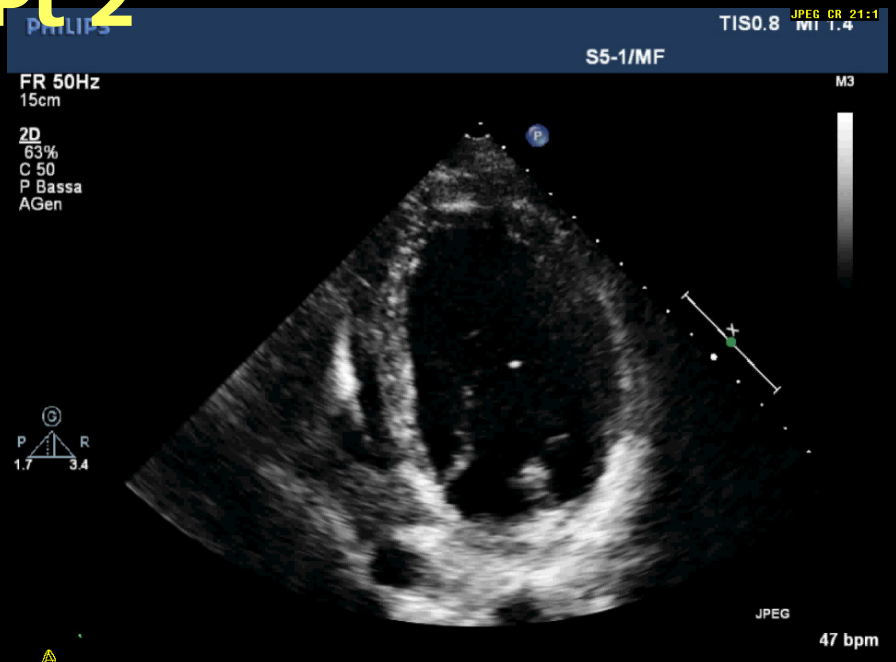
Heart 2011


PHILIPS
TIS0.6
S5-1/MF
FR 49Hz
16cm
2D
70%
C 50
P Bassa
AGen
JPEG
67 bpm

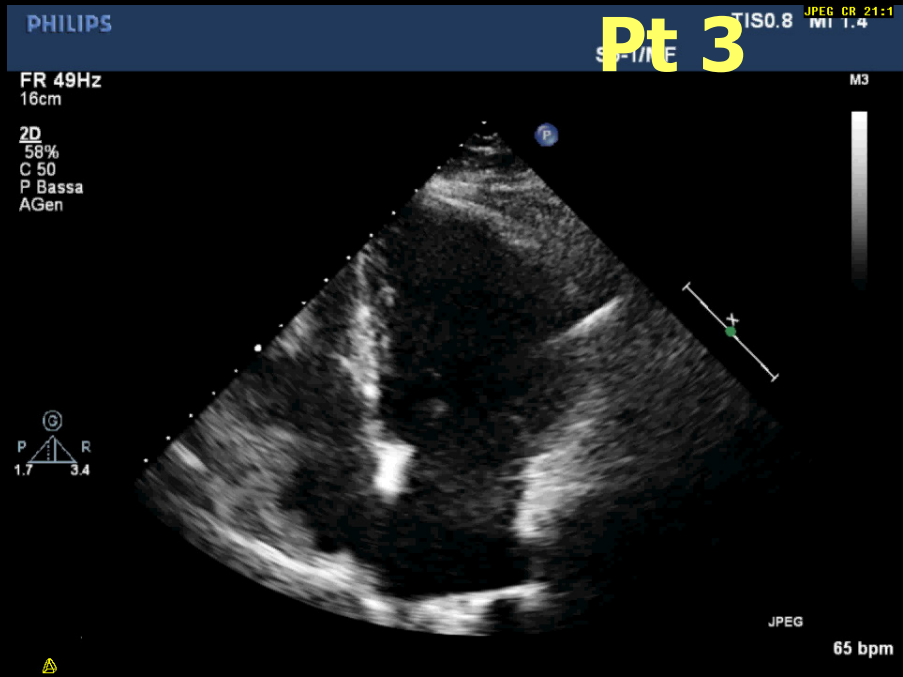
Pt 1

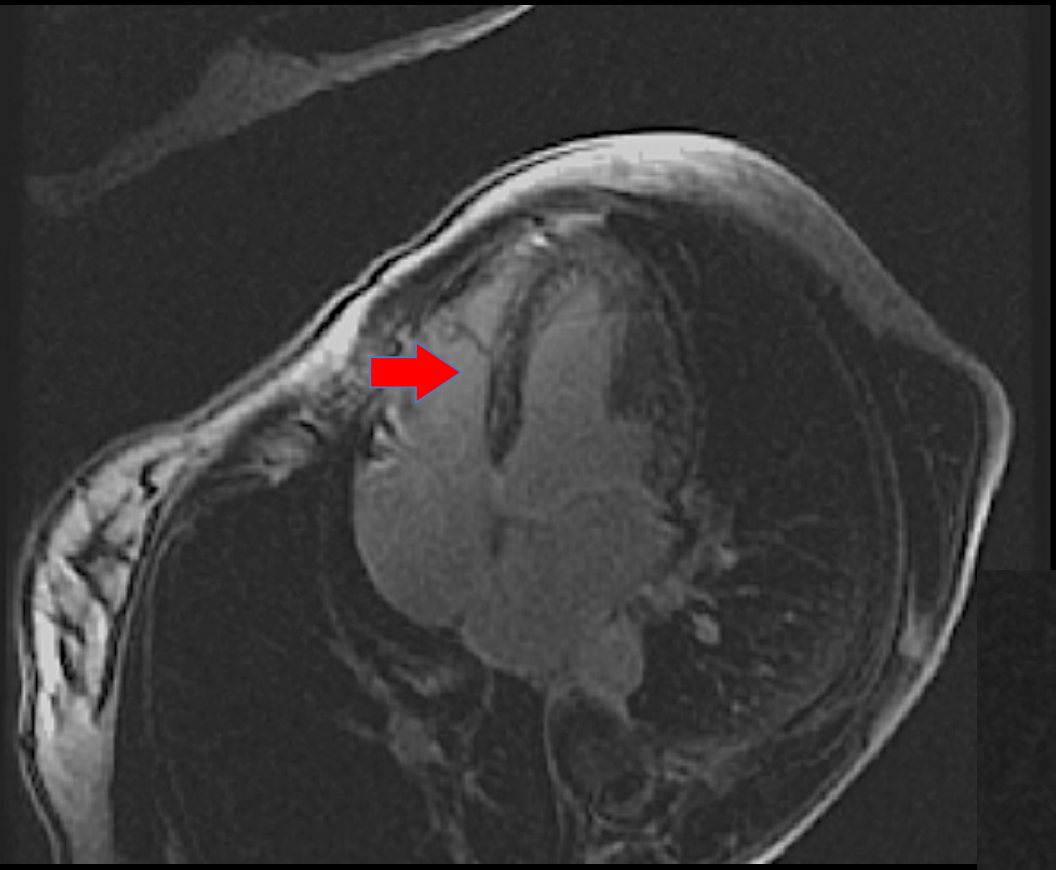

PHILIPS
TIS0.6
S5-1/MF
FR 53Hz
14cm
2D
70%
C 50
P Bassa
AGen
JPEG
63 bpm

Pt 2


TIS0.8
S5-1/MF
FR 50Hz
15cm
2D
63%
C 50
P Bassa
AGen
JPEG
47 bpm

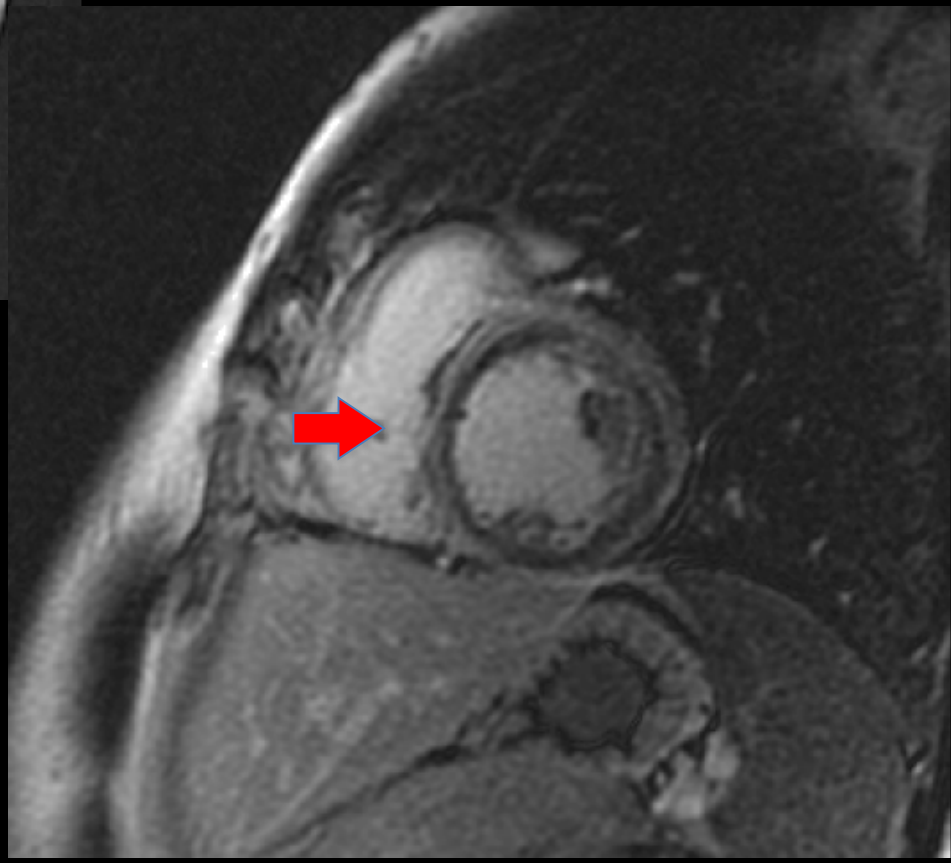
Pt 3


PHILIPS
TIS0.8
FR 49Hz
16cm
2D
58%
C 50
P Bassa
AGen
JPEG
65 bpm



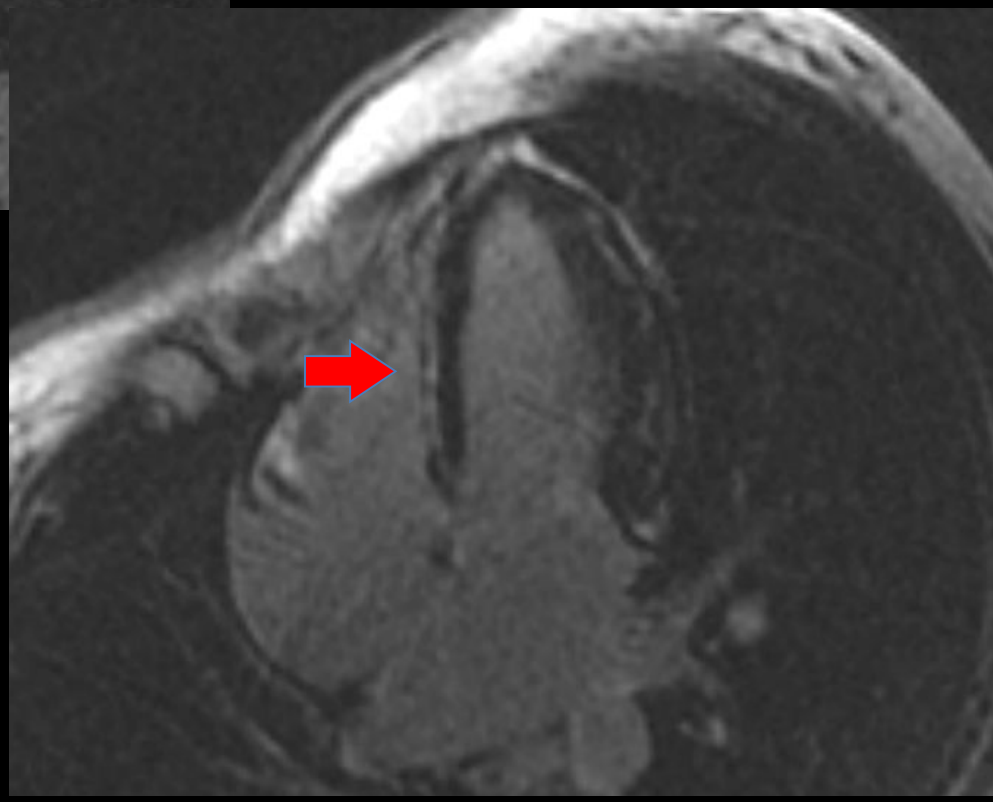
Pt 1

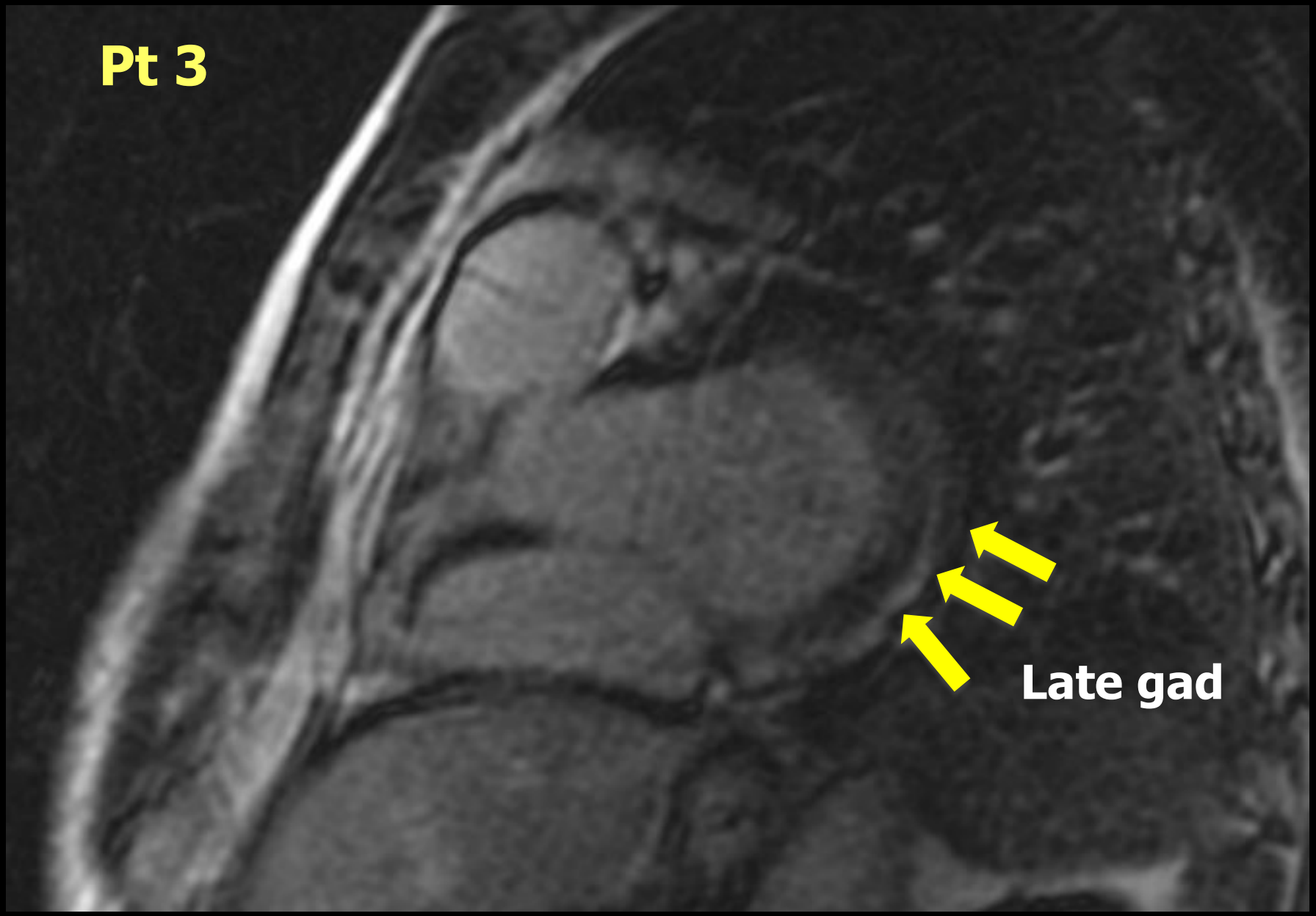
Late gad



Pt 2

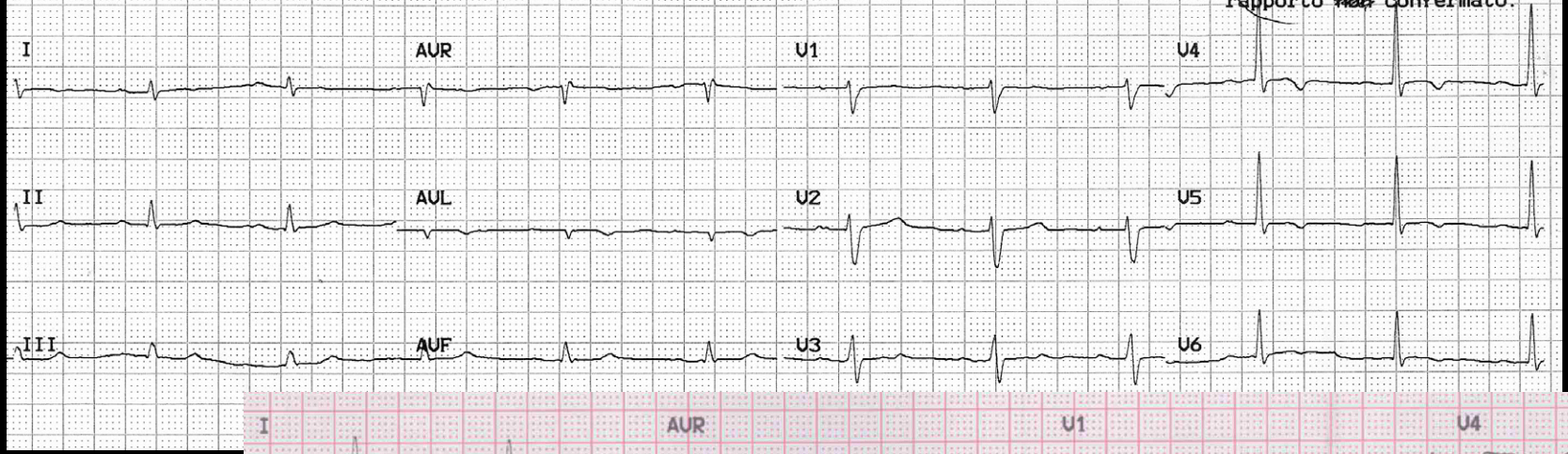
Late gad



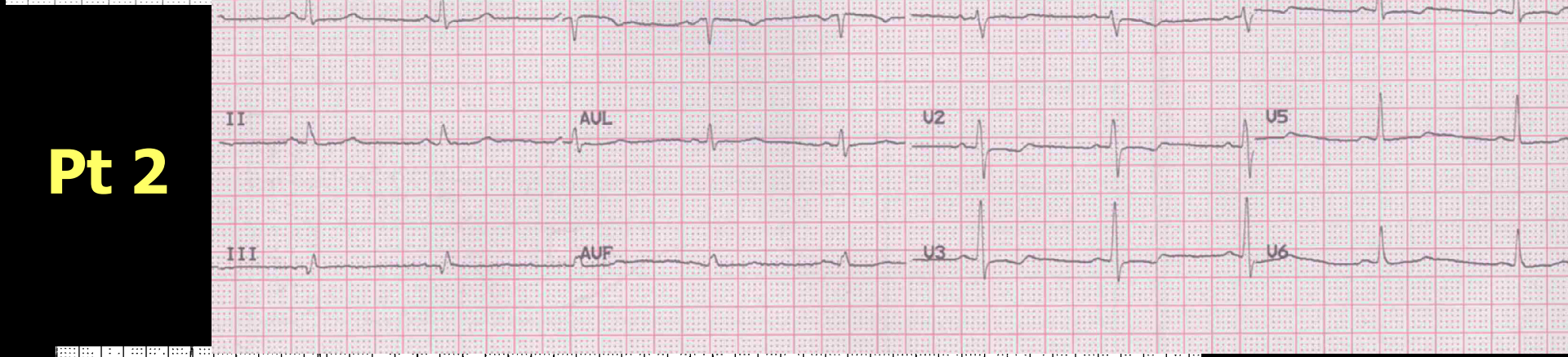

Pt 3
Late gad

- **Molecolar screening:**

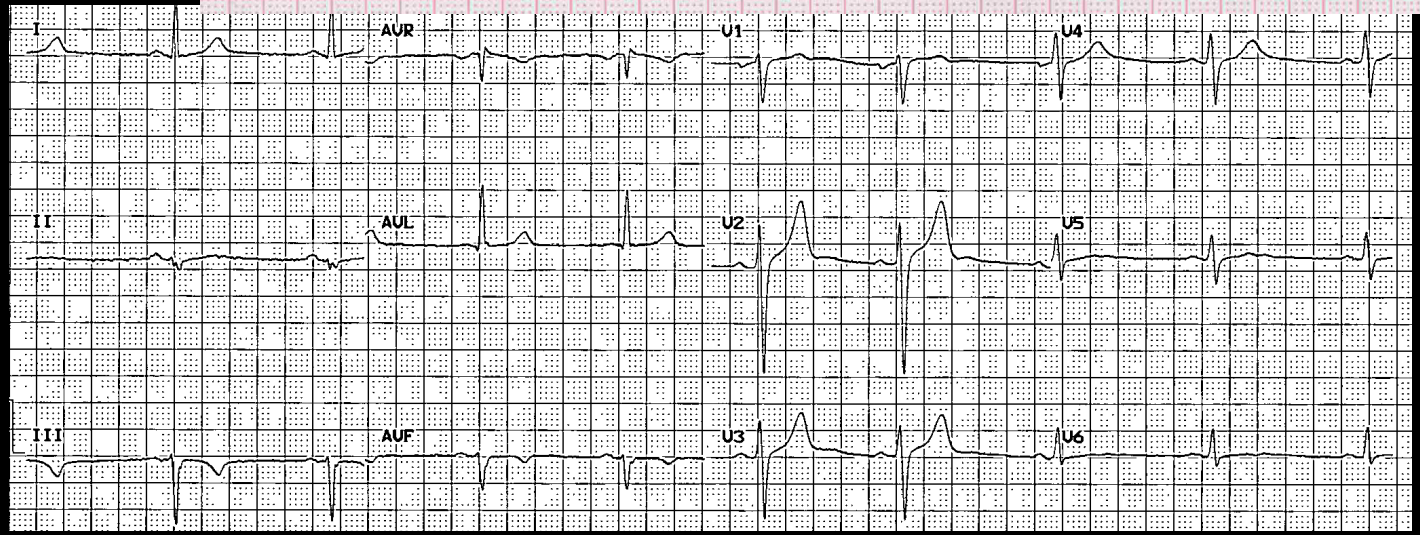
Desmoplakin + 3 pt
Titin 1 pt
Negative 1 pt
Ongoing 7pt


I
AUR
U1
U4
II
AUL
U2
U5
III
AUF
U3
U6

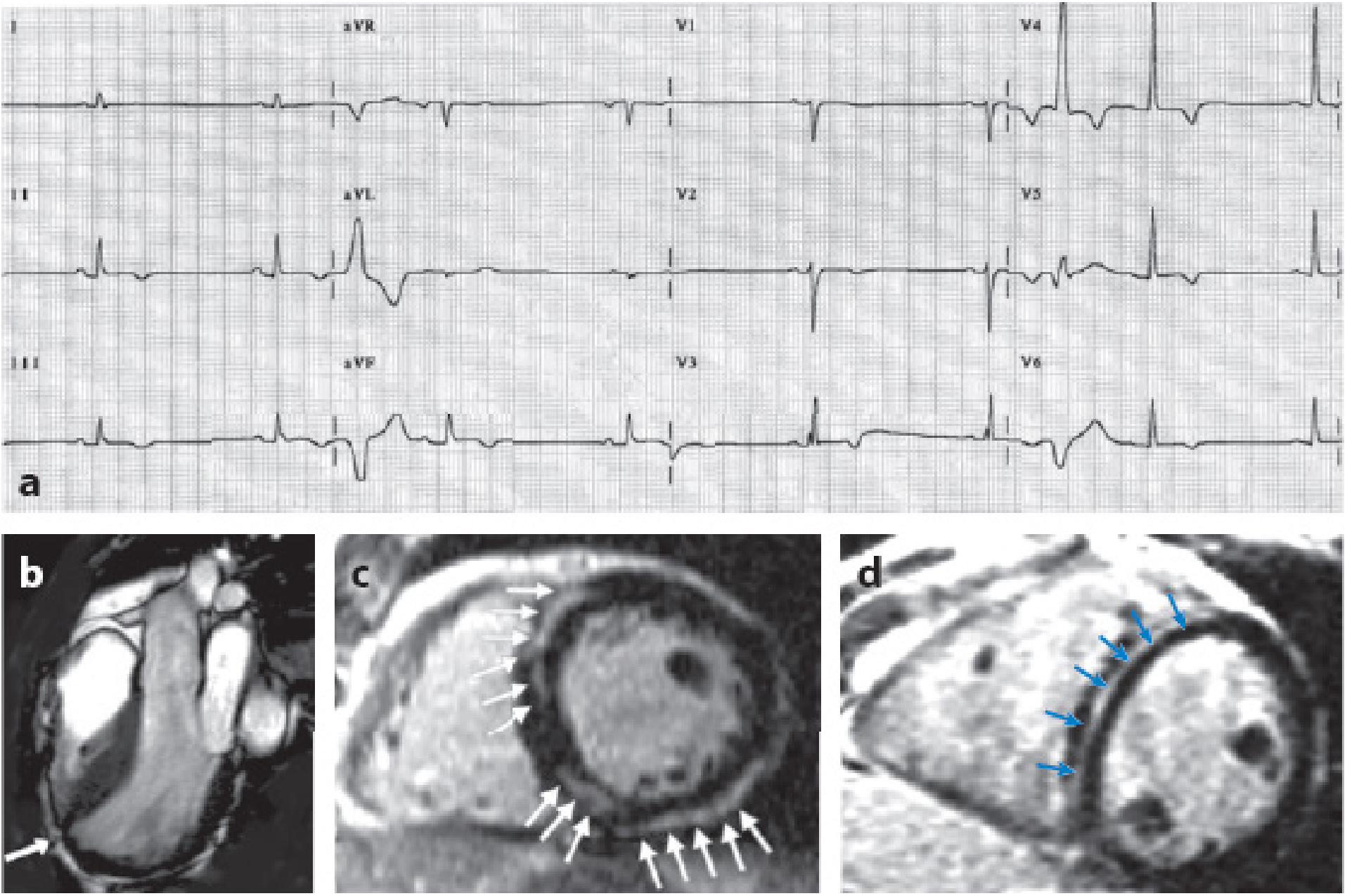
Pt 1


I
AUR
U1
U4
II
AUL
U2
U5
III
AUF
U3
U6

Pt 2


I
AUR
U1
U4
II
AUL
U2
U5
III
AUF
U3
U6

Pt 3



Sen-Chowdhry S et al Annu Rev Med 2010;61:233

ARVC

- Phenotypic and genotypic spectrum wider than expected
- Risk of under- but also of over-diagnosis (cognitive error from excess of recent culture)
- Genetics clinically usefull only for cascade family screening; limited role in identifing probands
- MRI useful mainly for morpho-functional definition and evaluation of myocardial LGE
- ALVC → true "challenge" for clinicians
- Don't forget standard ECG