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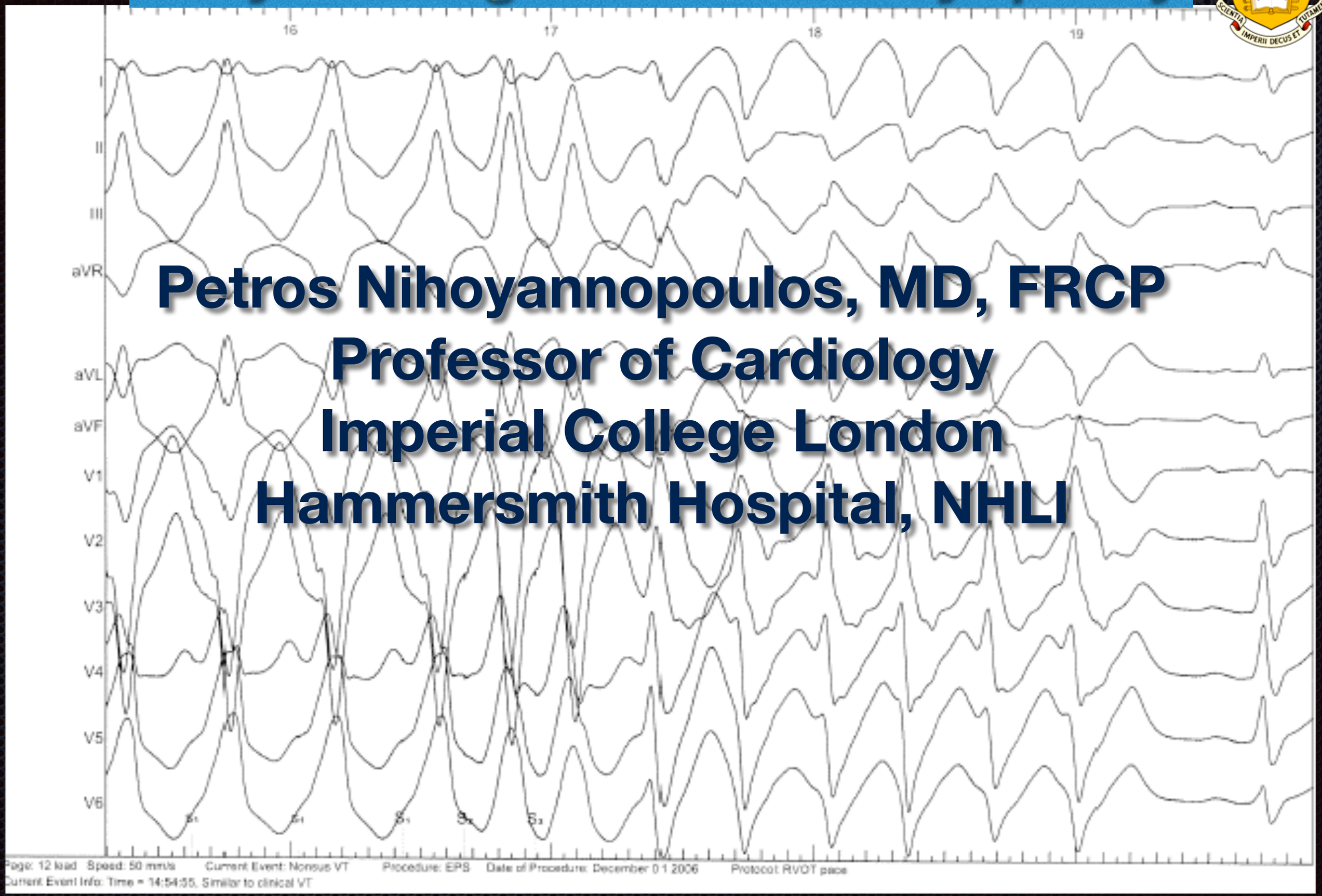
Arryhthmogenic Cardiomyopathy



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

Cardiomyopathies

- HCM
- DCM
- ARVC
- RCM
- Unclassified

Familial / Genetic

- Unidentified gene defect
- Disease sub-type

Non-Familial / Non-Genetic

- Idiopathic
- Disease sub-type

Sudden Cardiac Death

ARVC 

- Inherited cardiomyopathy characterized by fibro-fatty myocardial replacement, ventricular arrhythmia, RV dysfunction and sudden cardiac death

- Genetically determined 1:1000
- Autosomal dominant with incomplete penetrance (genes which encode desmosomal proteins

- Recessive variants have been described, often associated with skin disorders and wooly hair

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ARVC or arrhythmogenic cardiomyopathy?

The LV is so frequently involved as to support the adoption of the broad term “arrhythmogenic cardiomyopathy”

Basso C et al. Lancet 2009;373:1289-1300

- **Classic** (isolated RV disease or LV involvement after notable RV disease)
- **Left dominant** (prominent LV involvement, relatively mild RV-sided disease))
- **Biventricular** (equal bilateral involvement)

Sen Chowdhry, et al. Circulation 2007;115(3):1710-20

Population to Target

- Young middle-aged patients with symptoms of arrhythmia (palpitation, pre-syncope or syncope, CP, SOB
- Survivors of VF arrest
- 1st/2nd-degree relatives of SCD with pathologically proven ARVC
- Relatives of index cases with a clinical diagnosis of ARVC
- Relatives of SCD victims with “negative” post-mortem - ARVC may be missed on autopsy! - retain tissue for expert cardiac pathologist!
- Patients with isolated RHF in the absence of PHT
- Patients with apparent DCM but predominantly arrhythmic manifestations - FHx of SCD

Diagnosis

- Difficult
- No single test to establish or exclude diagnosis
- Based on a constellation of clinical, ECG, Echo and other features
- Important to make the correct diagnosis
- Imaging of questionable use in early disease, few cell can be substrate for fatal arrhythmia
- Dilated RV non-specific

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A single test is seldom sufficient to establish a clinical diagnosis of ARVC

- Full History
- Detail pedigree (SCD)
- ECG (ICD, iRBBB, RBBB, inverted T-waves V1-3)
- Signal-average ECG for late potentials
- 2DE ± contrast (by experienced operators)
- ETT for ventricular arrhythmia
- Ambulatory monitoring
- cMR (by an experienced operator)

(fibro-fatty replacement not discernible by imaging

Criteria for diagnosis of ARVC

Original Task Force Criteria

*McKenna WJ, et al. Br Heart J **1994**;71:215-18*

1. Global or regional dysfunction and structural alterations

MAJOR

a. Severe dilatation and reduction of RV function with no LV impairment (only mild)
b. Localised RV aneurysms (akinetic or dyskinetic areas with diastolic buldging)
c. Severe segmental dilatation of the RV

MINOR

a. Mild global RV dilatation or reduced ejection fraction with normal LV
b. Mild segmental dilatation of the RV
c. Regional RV hypokinesia.

2. Tissue characterization of walls

MAJOR

Fibrofatty replacement of myocardium on endomyocardial biopsy

3. Repolarisation abnormalities

MINOR

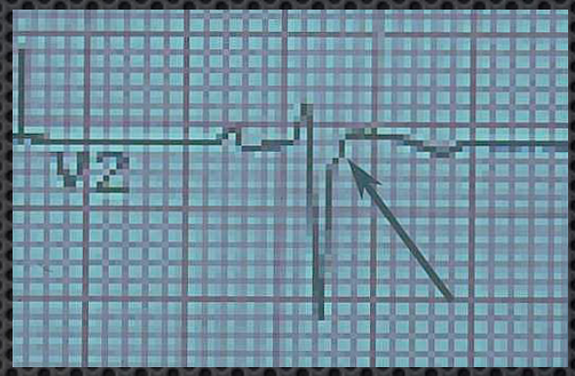
Inverted T waves in right precordial leads
(V2 and V3) in people aged more than 12 yrs in absence of RBBB).

Criteria for diagnosis of ARVC

4. Depolarisation/Conduction abnormalities

MAJOR

Epsilon waves or localized prolongation (>110 msec) of the QRS complex
In right precordial leads (V1 to V3).



MINOR

Late potentials (signal averaged ECG)

5. Arrhythmia

MINOR

a. LBBB type ventricular tachycardia (sustained and non-sustained)
b. Frequent ventricular extrasystoles (more than 1000/24h) on Holter

6. Family history

MAJOR

Familial disease confirmed at necropsy or surgery

MINOR

a. Familial history of premature sudden death (<35yrs) due to suspected RV dysplasia.
b. Familial history (clinical diagnosis based on present criteria)

*McKenna WJ, et al. Br Heart J **1994**;71:215-18*

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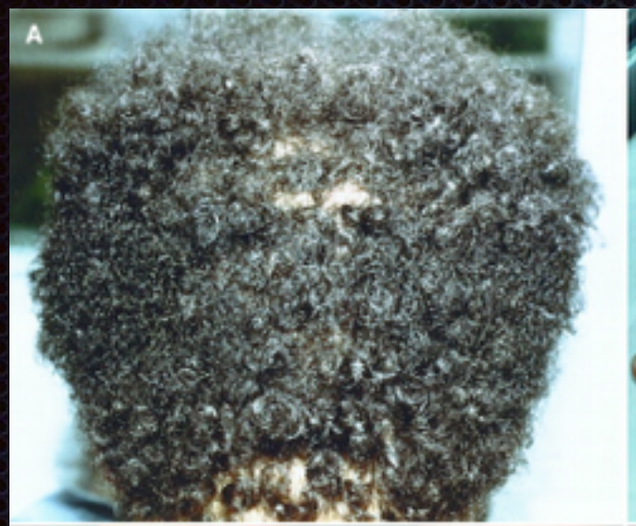
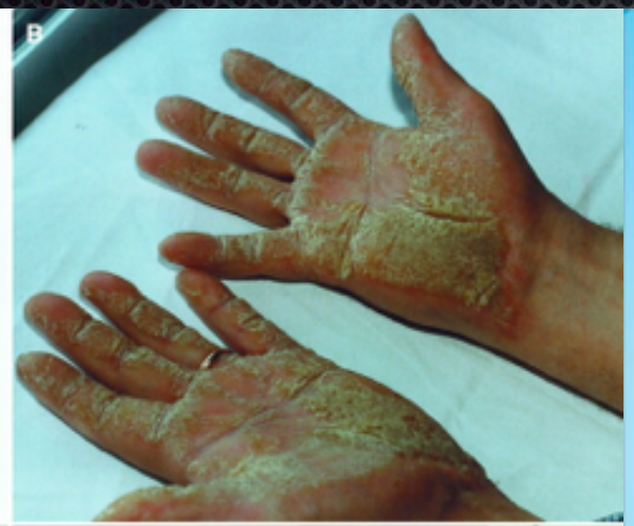
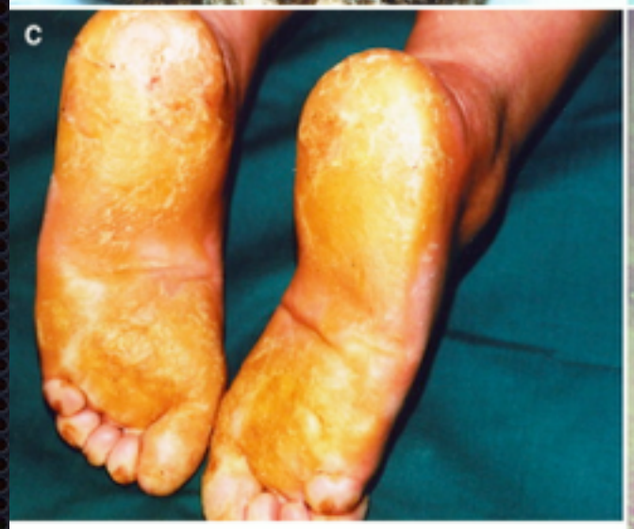
Diffuse Non-epidermolytic Palmoplantar Keratoderma and Woolly Hair (Naxos Disease) Maps to 17q21

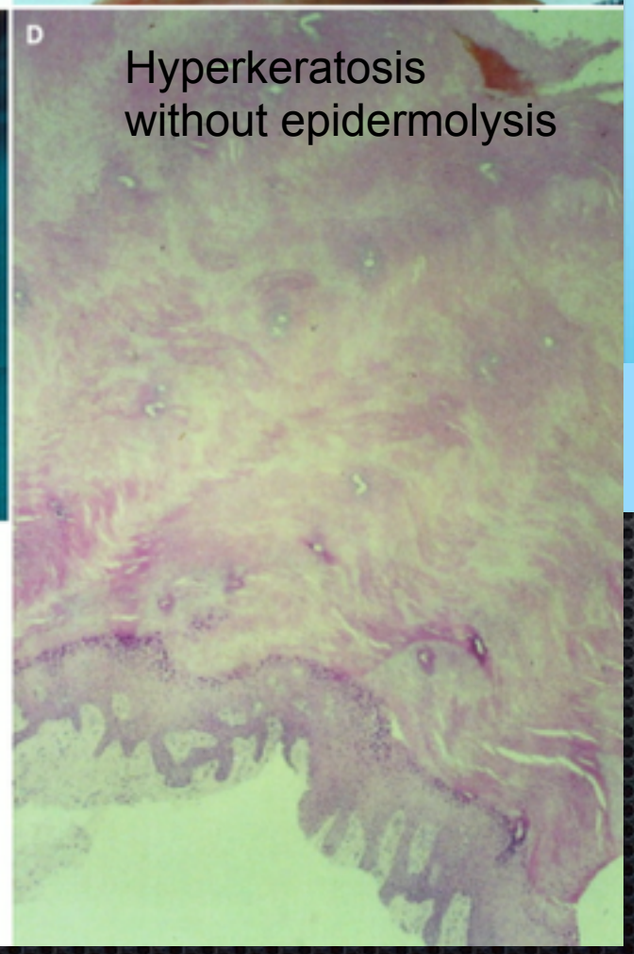






Palmar
plantar keratoderma

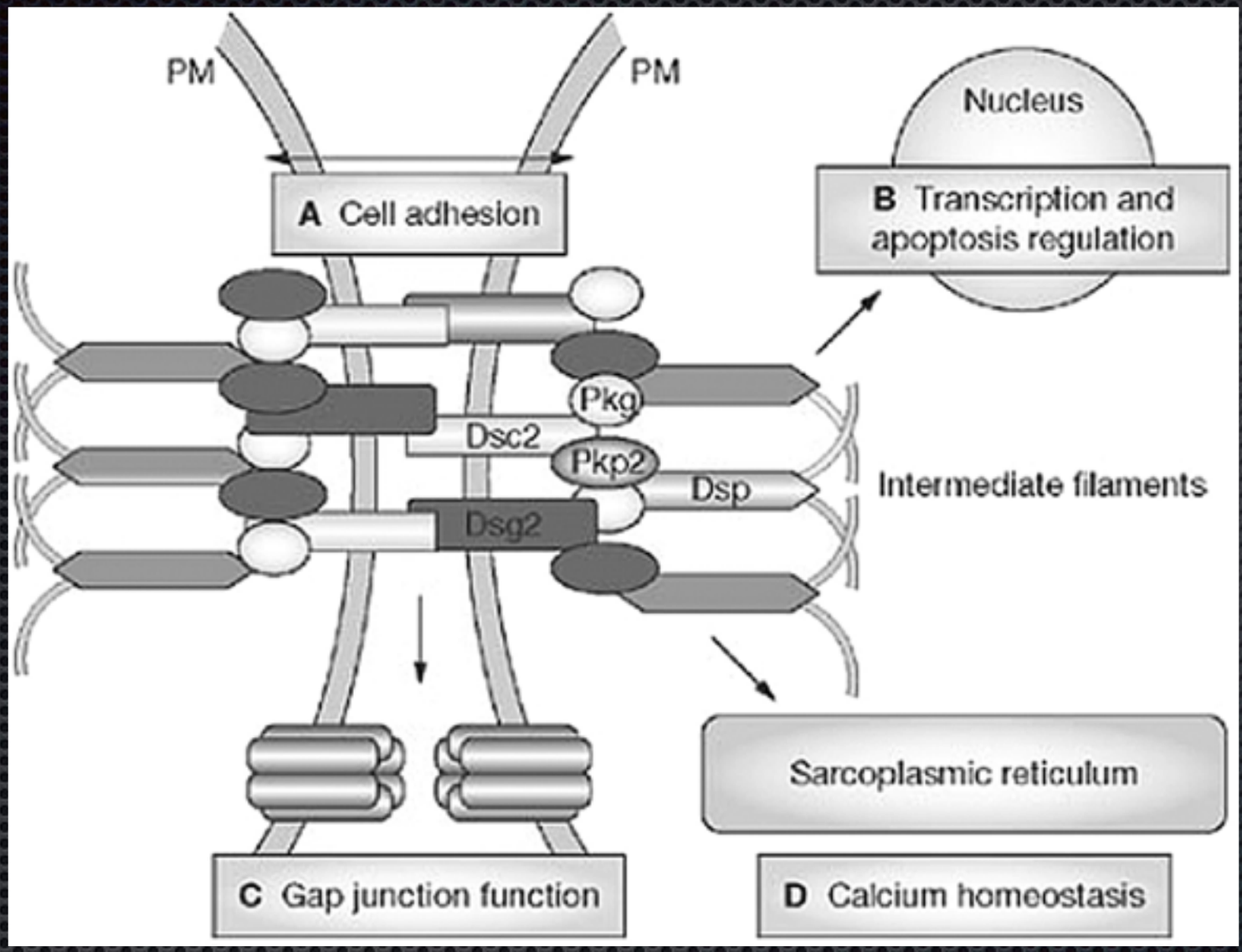
Locus 17q21



- Population: 12,089
- Area: 126.957 km^2 (49 sq mi)
- Density: 95 /km^2 (247 /sq mi)

Coonar AS, Protonotarios N, Tsatsopoulou A, Needham EWA, Houlston RS, Cliff S, Otter MI, Murday VA, Mattu RK, McKenna WJ.
Circulation, 1998;97:2049 - 2058

The cardiac desmosome



- desmocollin
- desmoglein
- desmoplakin
- plakoglobin
- plakophilin

- Support structural stability: cell-cell adhesion
- Regulate gene transcription for adipogenesis, apoptosis
- Maintain electrical conductivity through gap junctions and Ca^{++} homeostasis

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Diagnosis of ARVC/D

Genetic Heterogeneity

ARVD1	AD	(14q23-q24)	TGF b3
ARVD2	AD	(1q42-q43)	RyR2 - idiopathic VT
ARVD3	AD	(14q12-q22)	?
ARVD4	AD	(2q32.1-q32.3)	?
ARVD5	AD	(3q23)	TMEM 43
ARVD6	AD	(10p12-p14)	?
ARVD7	AD	(10q22)	?
Naxos Disease	AR	(17q21)	JUP (plakoglobin)
ARVD8	AD	(6p24	DSP (desmoplakin)
ARVD9	AD	(12p11)	PKP-2 (plakophilin)
ARVD10	AD	(18q12.1)	DSG-2(desmplein)
ARVD11	AD	(18q12.1)	DSC-2 (desmocollin)
ARVD12	AD	(17q21)	JUP
Carvajal Syndrome	AR	(6p24)	DSP

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Diagnosis of ARVC cannot be made by a single test

Original Task Force Criteria

*McKenna WJ, et al. Br Heart J **1994**;71:215-18*

highly specific

lack of sensitivity

Proposed Modifications

Marcus F, McKenna WJ, et al. Circulation;121(13),2010,1533-41

- Global or regional dysfunction and structural alterations
- Tissue characterisation of walls
- Repolarisation abnormalities
- Depolarisation/conduction abnormalities
- Arrhythmias
- Family history

Each group includes major and minor criteria

Global or regional dysfunction or structural alterations

Original Task Force Criteria

Major

- Severe dilatation& reduction of RV EF with no or mild LV involvement
- Localised RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)
- Severe segmental RV dilatation

Minor

- Mild global RV dilatation and/or reduced EF with normal LV
- Mild segmental RV dilatation
- Regional RV hypokinesia

Modified Task Force Criteria

Major (by 2D Echo)

- Regional RV akinesia, dyskinesia or aneurysm **and** 1 of the following:
  - -PLAX RVOT≥32mm (≥19mm/m^2)
  - -PSAX RVOT≥36mm (≥21mm/m^2)
  - -or Fractional Area Change ≤33%

Minor (By 2D Echo)

- Regional RV akinesia, dyskinesia or aneurysm and 1 of the following:
  - -PLAX RVOT ≥ 29 <32mm (≥16mm/m^2 - 19mm/m^2)
  - -PSAX RVOT ≥ 32 <36mm (≥18mm/m^2 - 21mm/m^2)
  - -or FAC >33% ≤40%

Global or regional dysfunction or structural alterations

Original Task Force Criteria

Major

- Severe dilatation& reduction of RV EF with no or mild LV involvement
- Localised RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)
- Severe segmental RV dilatation

Minor

- Mild global RV dilatation and/or reduced EF with normal LV
- Mild segmental RV dilatation
- Regional RV hypokinesia

Modified Task Force Criteria

Major (by CMR)

- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
- **and** 1 of the following:
  - -Ratio of RV end-diastolic volume to
  - -BSA ≥110mL/m^2 (M) or ≥100mL/m^2 (F)
  - -or RV EF <40%

Minor (by CMR)

- Regional RV akinesia, dyskinesia or dyssynchronous RV contraction
- **and** 1 of the following:
  - -Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (M)
  - -or ≥90 to <100mL/m^2 (F)
  - -or RV EF ≥40% <45%

Modified Task Force Criteria

Repolarisation abnormalities

Major

TWI in right precordial leads (V1,V2 & V3) or beyond in individuals >14y
(in the absence of RBBB)

Minor

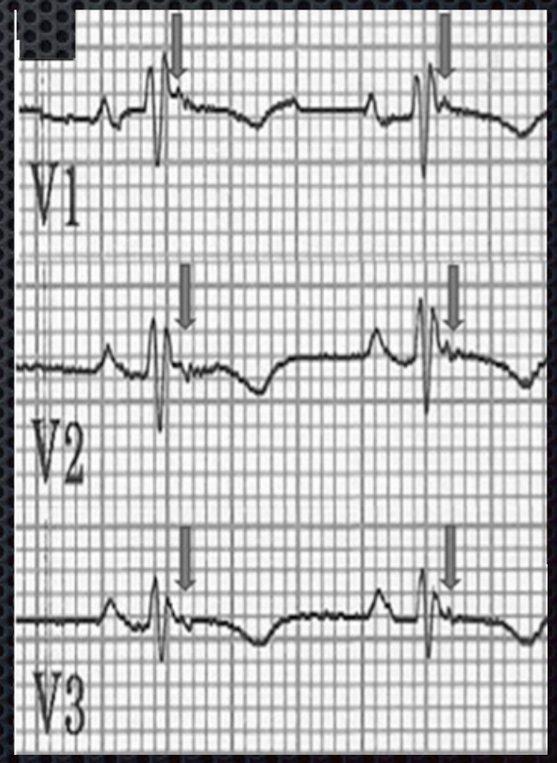
TWI in leads V1,V2 in individuals >14y or in V4, V5 or V6
(in the absence of RBBB)
Inverted T-waves in leads V1, V2, V3 V4 in individuals >14y

Depolarisation / conduction abnormalities

Major

Epsilon wave in V1-V3

ε



Minor

Late potentials by SAECG in >1 or 3 parameters in the absence of QRS≥110ms
Terminal activation duration of QRS 55ms (nadir of the S-wave to the end of QRS) in V1-3

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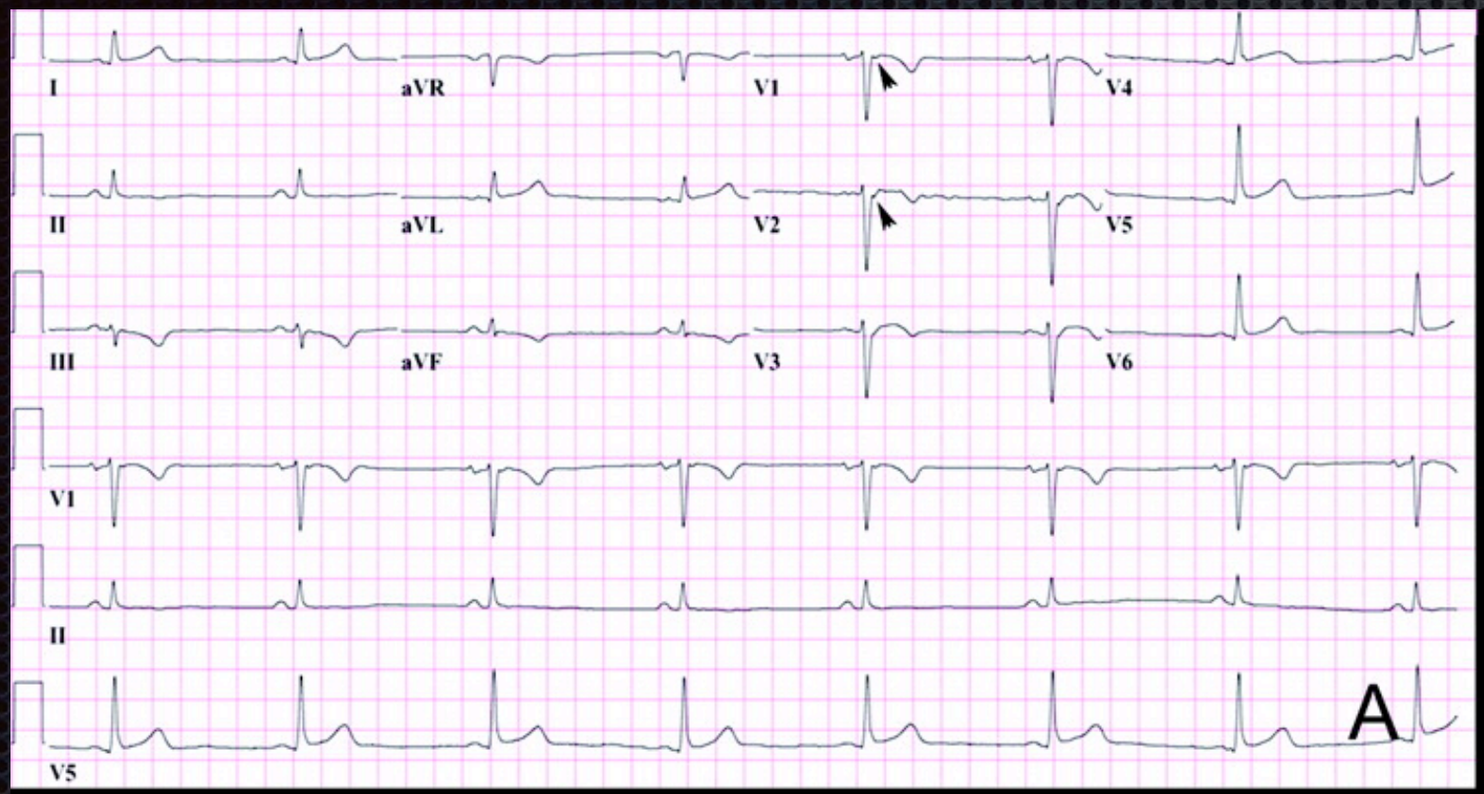
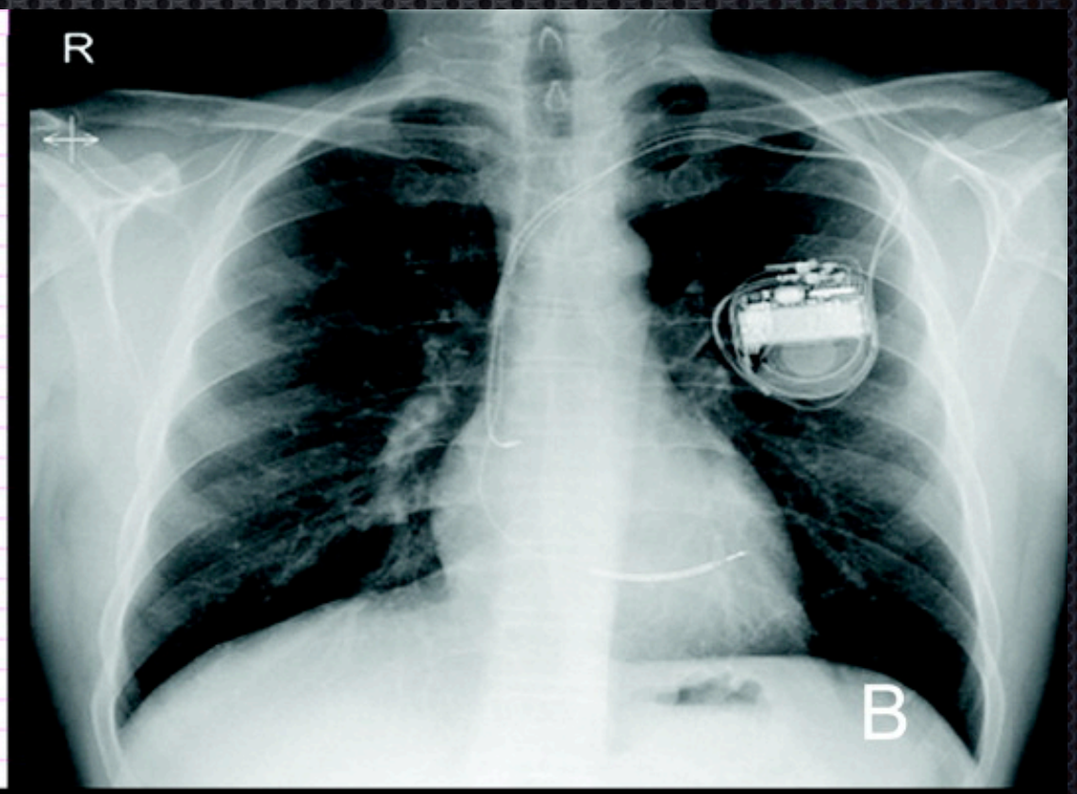
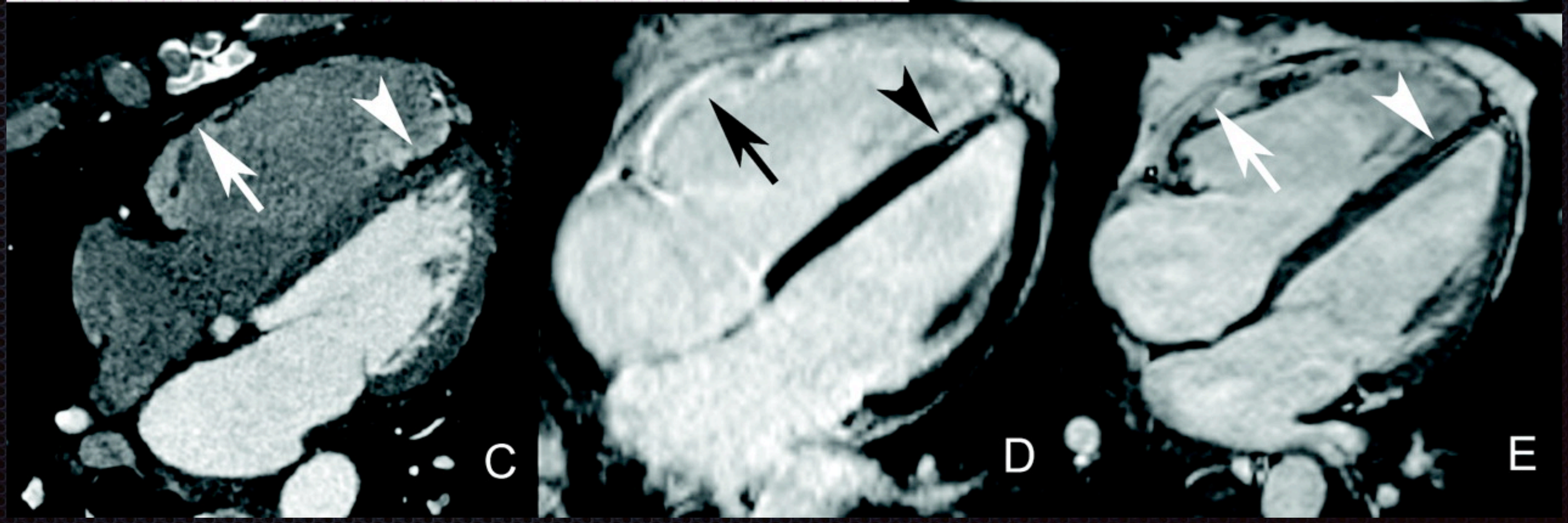
ECG with typical signs for ARVC:

Negative T-waves and epsilon waves







Modified Task Force Criteria

Tissue characterisation of wall

Major

- Residual myocytes <60% by morphometric analysis (or <50% if estimate), ***with fibrous replacement of the RV free wall*** in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

Minor

- Residual myocytes 60&-75% by morphometric analysis (or 50%-65% if estimated), ***with fibrous replacement of the RV free wall*** in ≥1 sample

Arrhythmias

Major

- NSVT or sustained VT of LBBB morphology with superior axis (negative or indeterminate QRS in II, III, aVF and positive in aVL

Minor

- NSVT or sustained VT of LBBB morphology with inferior axis (positive in II, III, aVF and negative in aVL
- 500 ventricular extrasystoles / 24h (Holter)

Modified Task Force Criteria

Family History

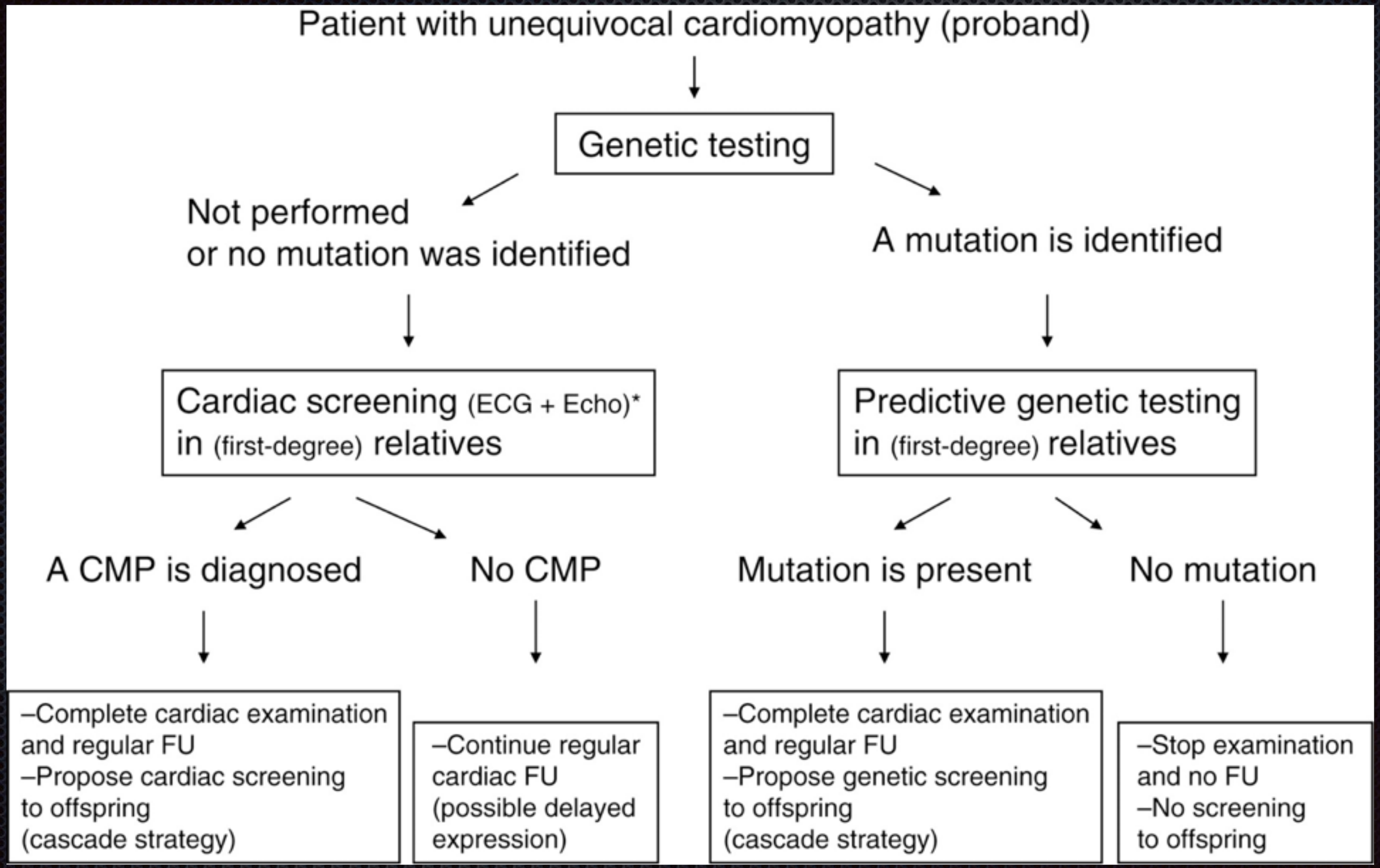
Major

- ARVC confirmed in a first-degree relative who meets current Task Force criteria
- ARVC confirmed at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation categorised as associated or probably associated with ARCV in the patient under evaluation

Minor

- History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current criteria
- Premature SD (<35y) due to suspected ARVC in a first-degree relative
- ARVC confirmed pathologically or by current Task Force Criteria

Organization of family screening



Charon et al. Eur Heart J. 2010

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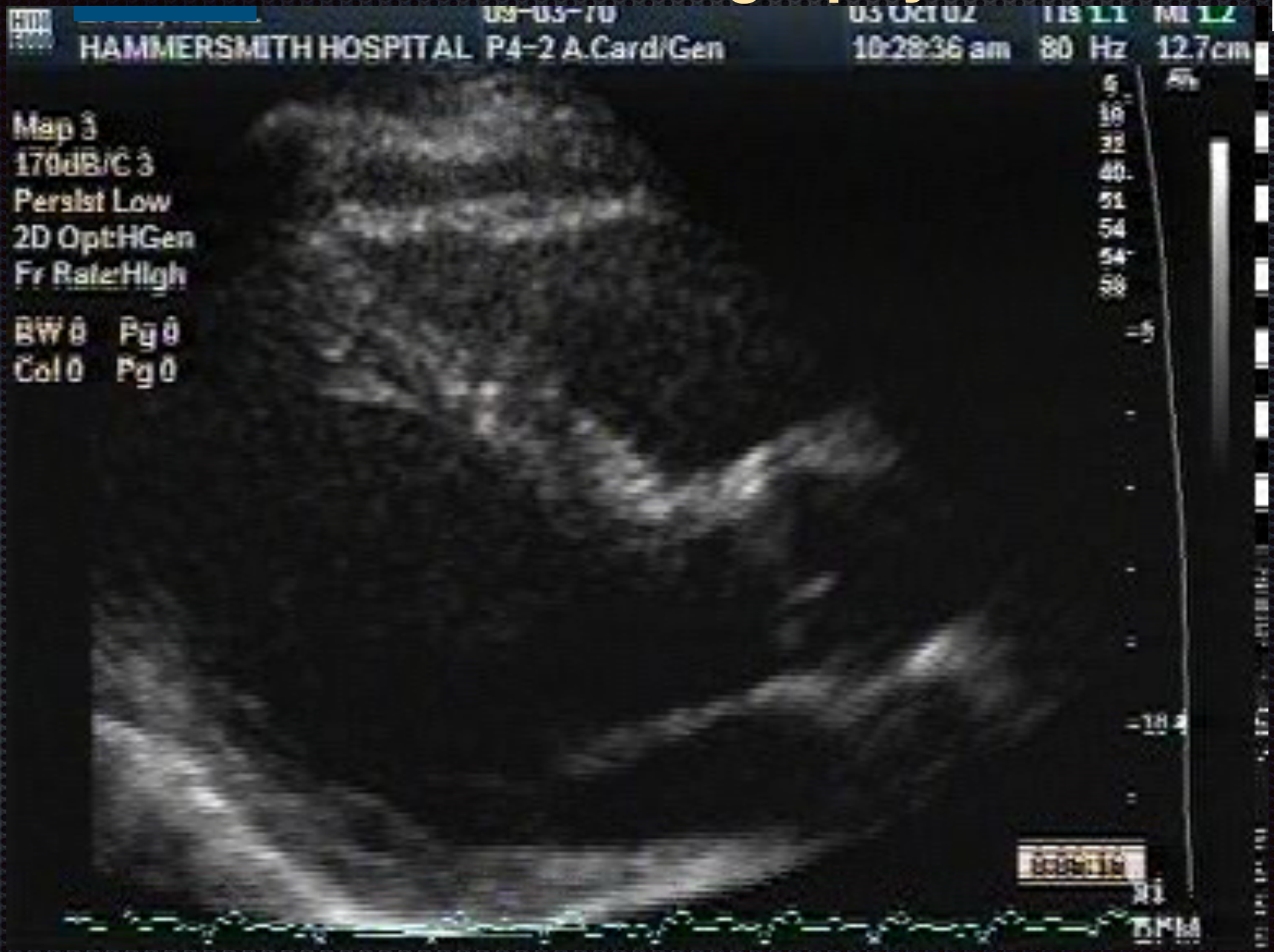
Revised Task Force Criteria

Definite	Borderline	Possible
2 major	1 major + 1 minor	1 major
1 major + 2 minor	3 minor	2 minor
4 minor		

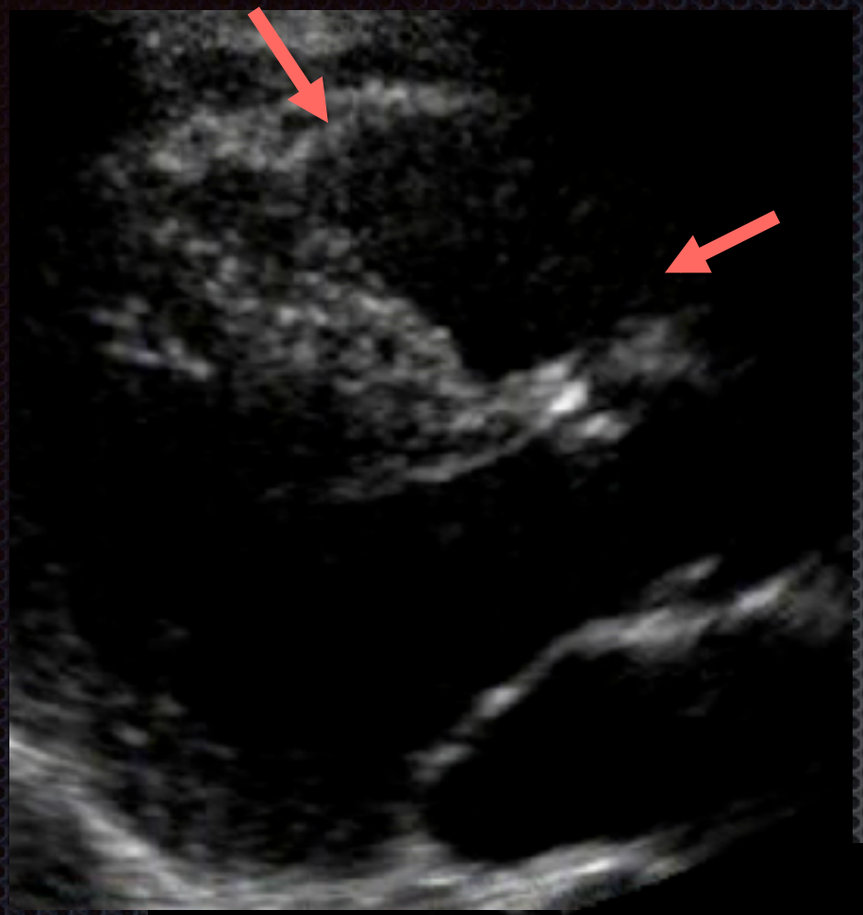
Marcus F, McKenna WJ, et al. Circulation;121(13),2010,1533-41

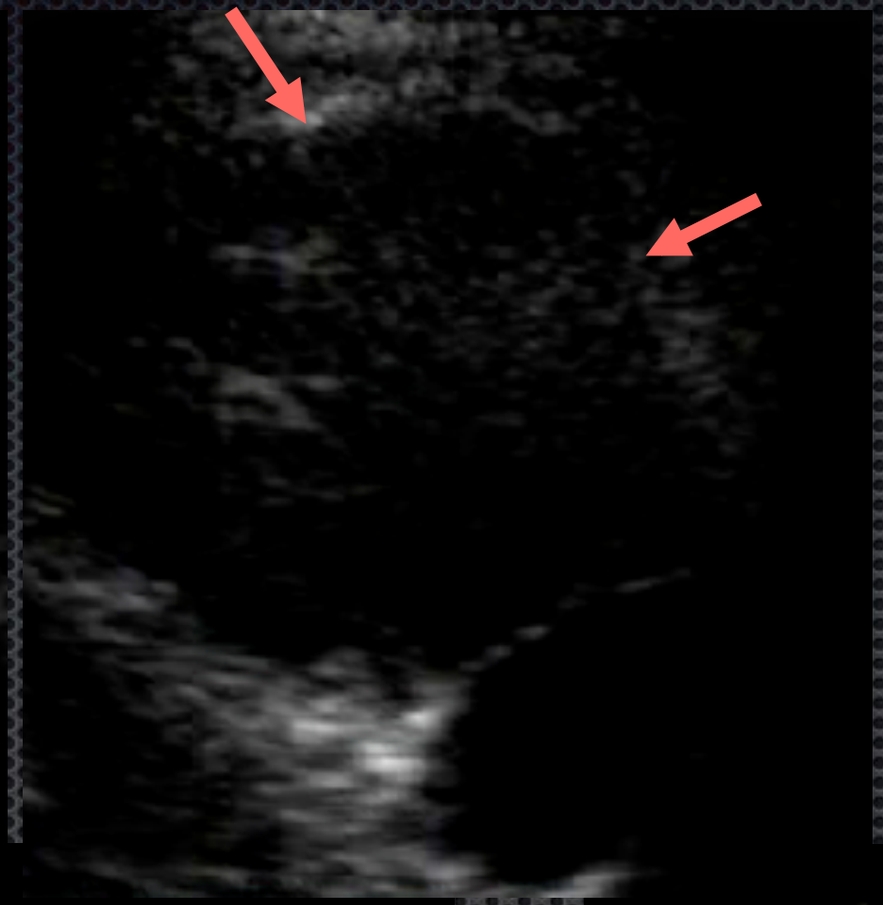
Echocardiography

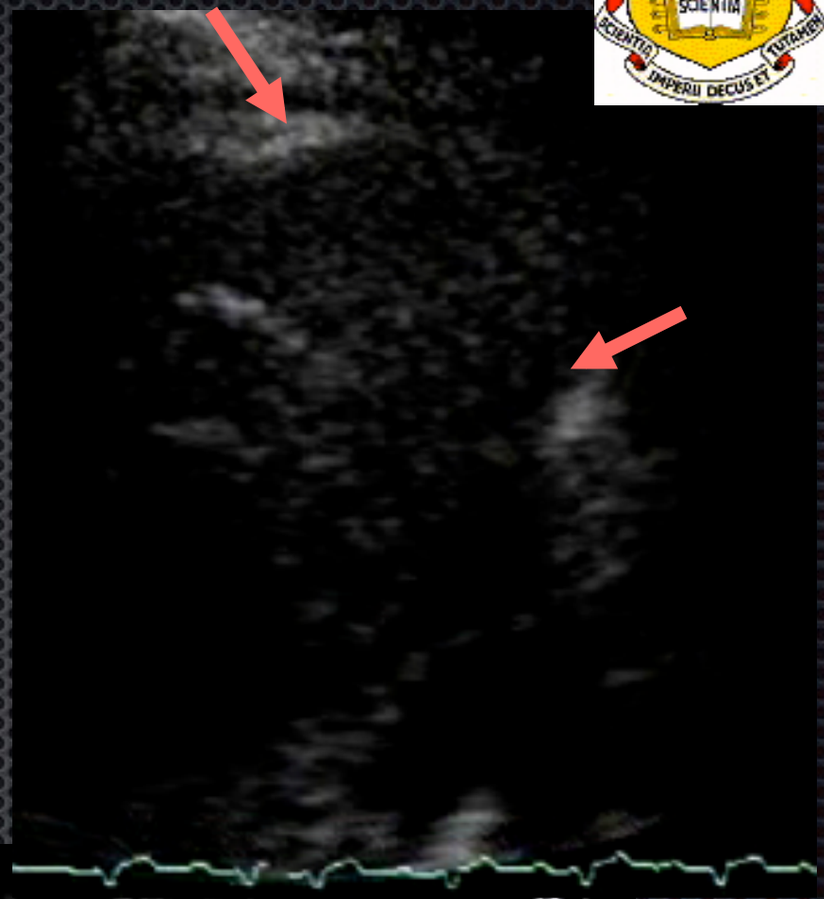


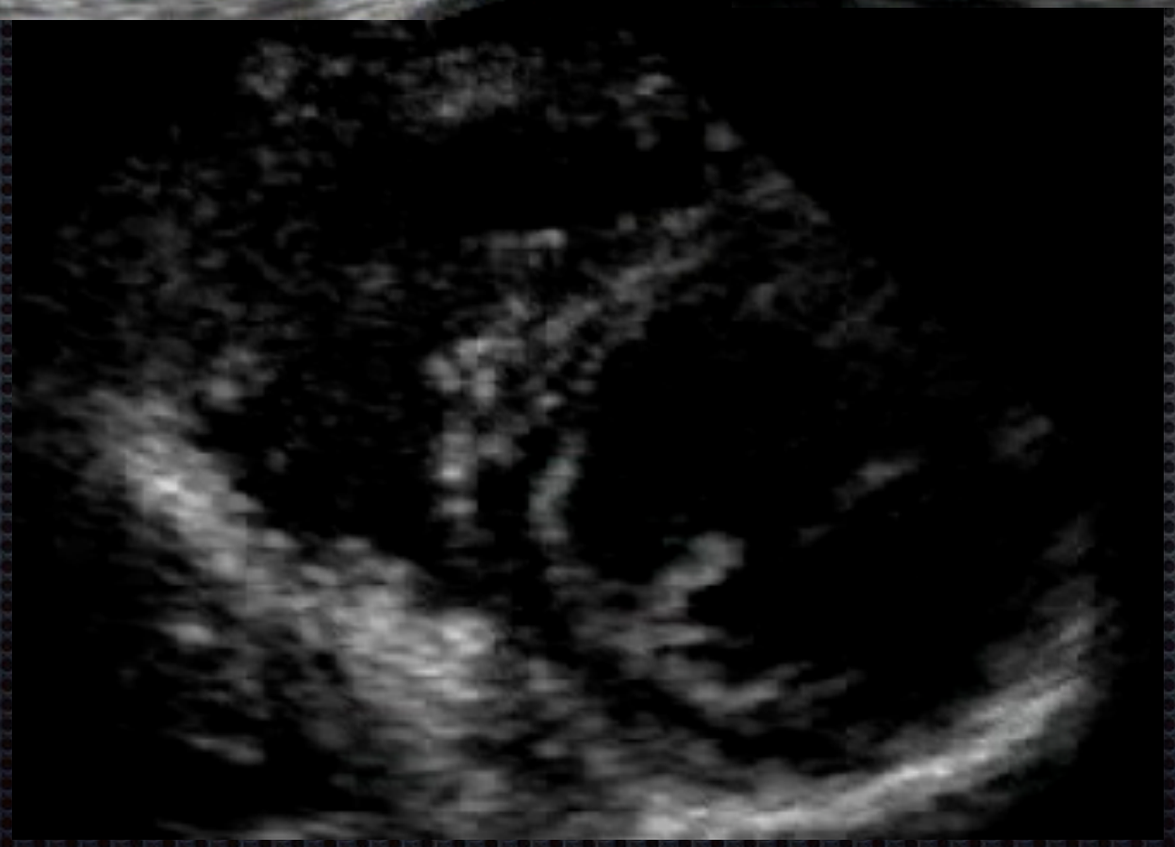
RV dilatation (>32mm)

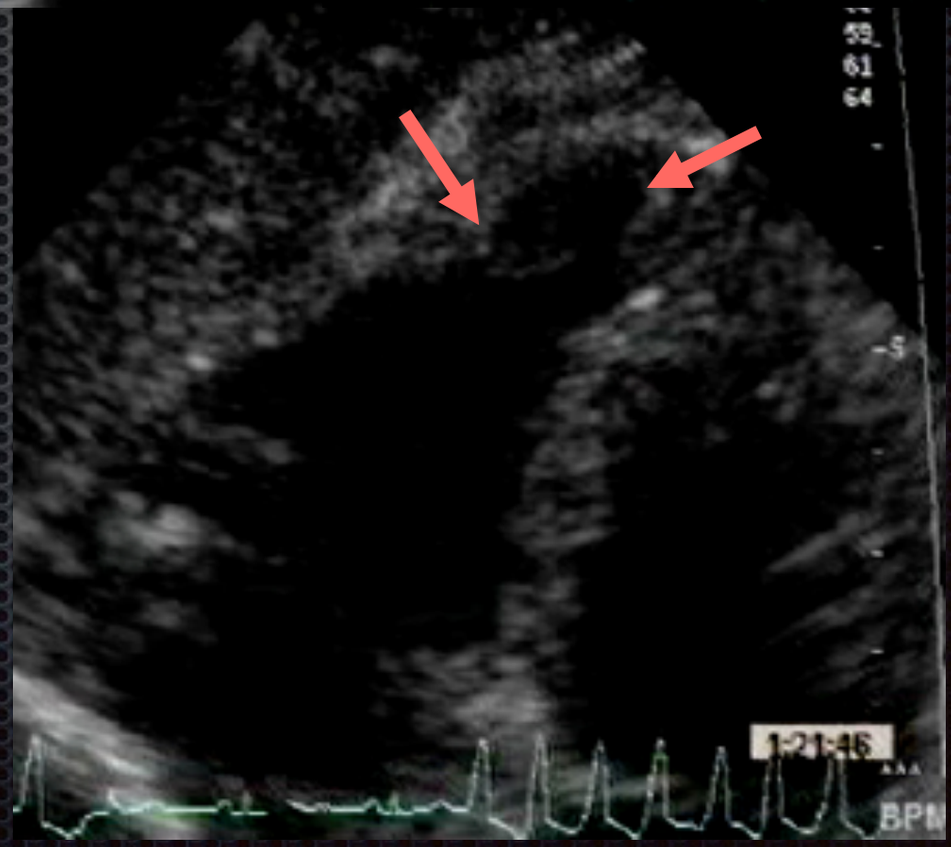
Triangle of Dysplasia

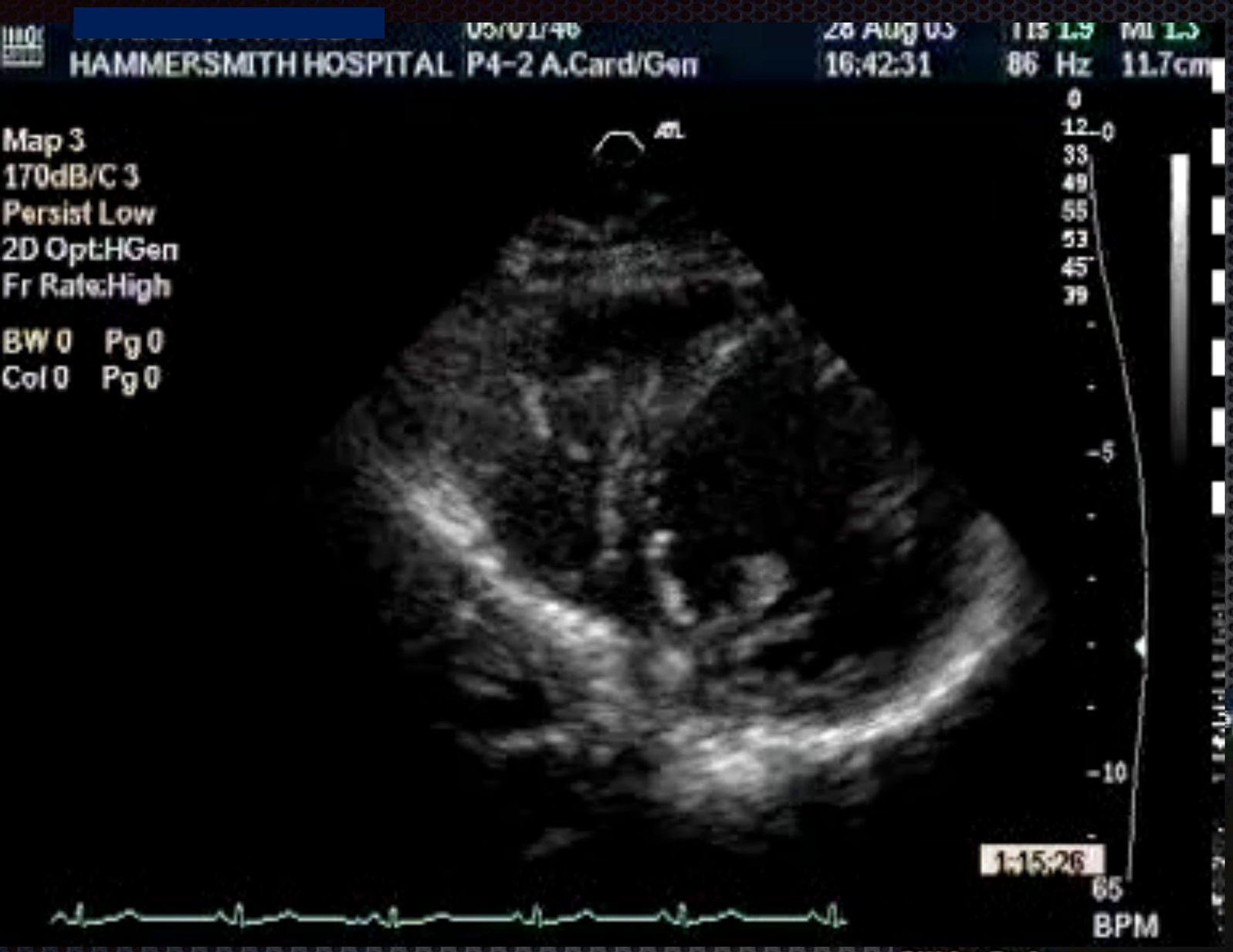


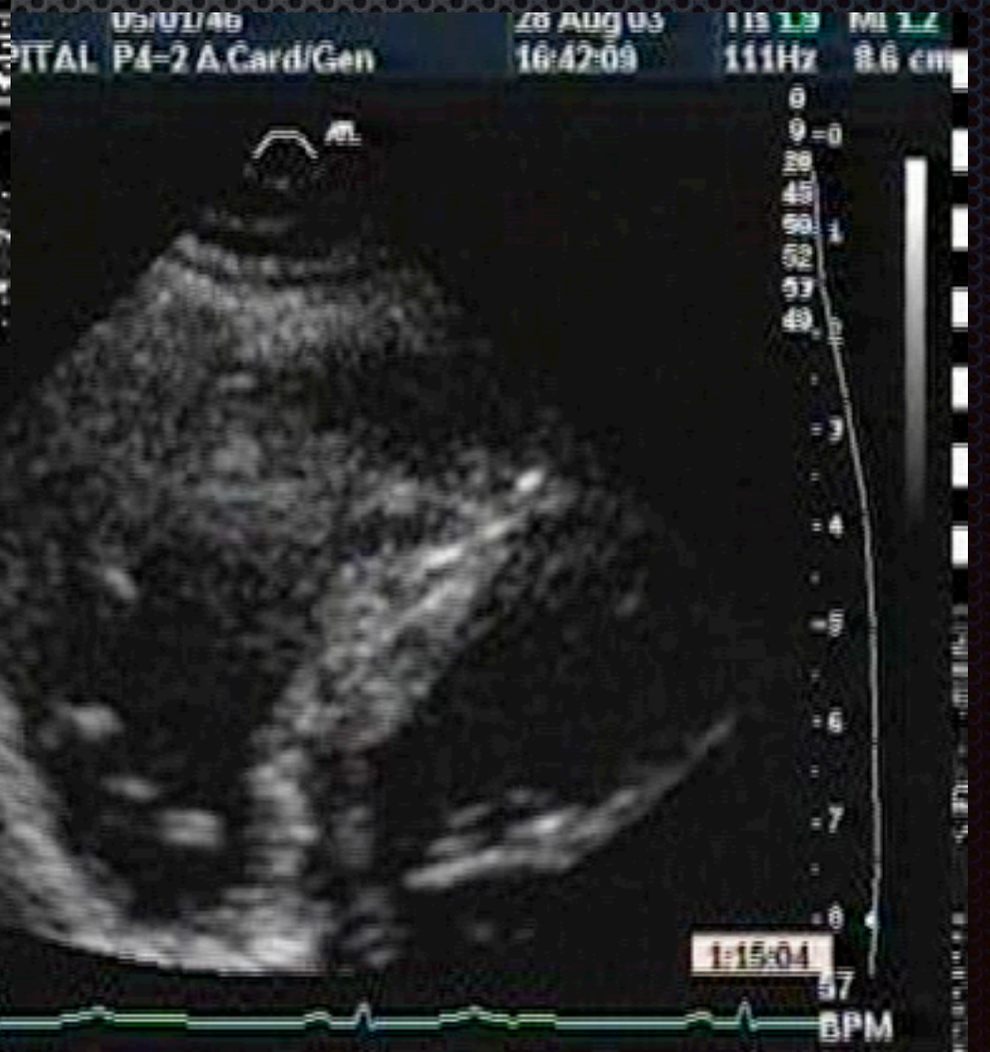












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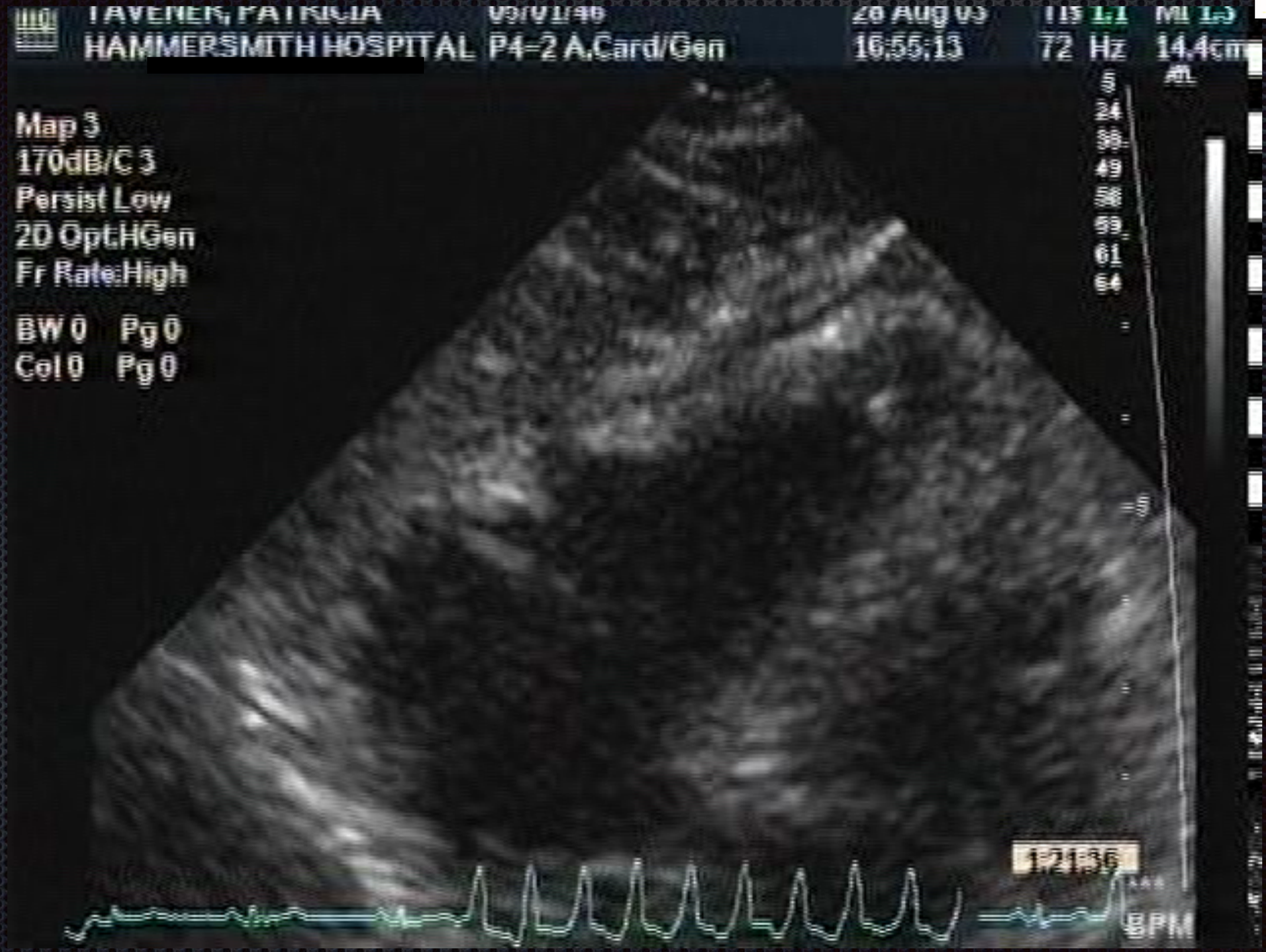

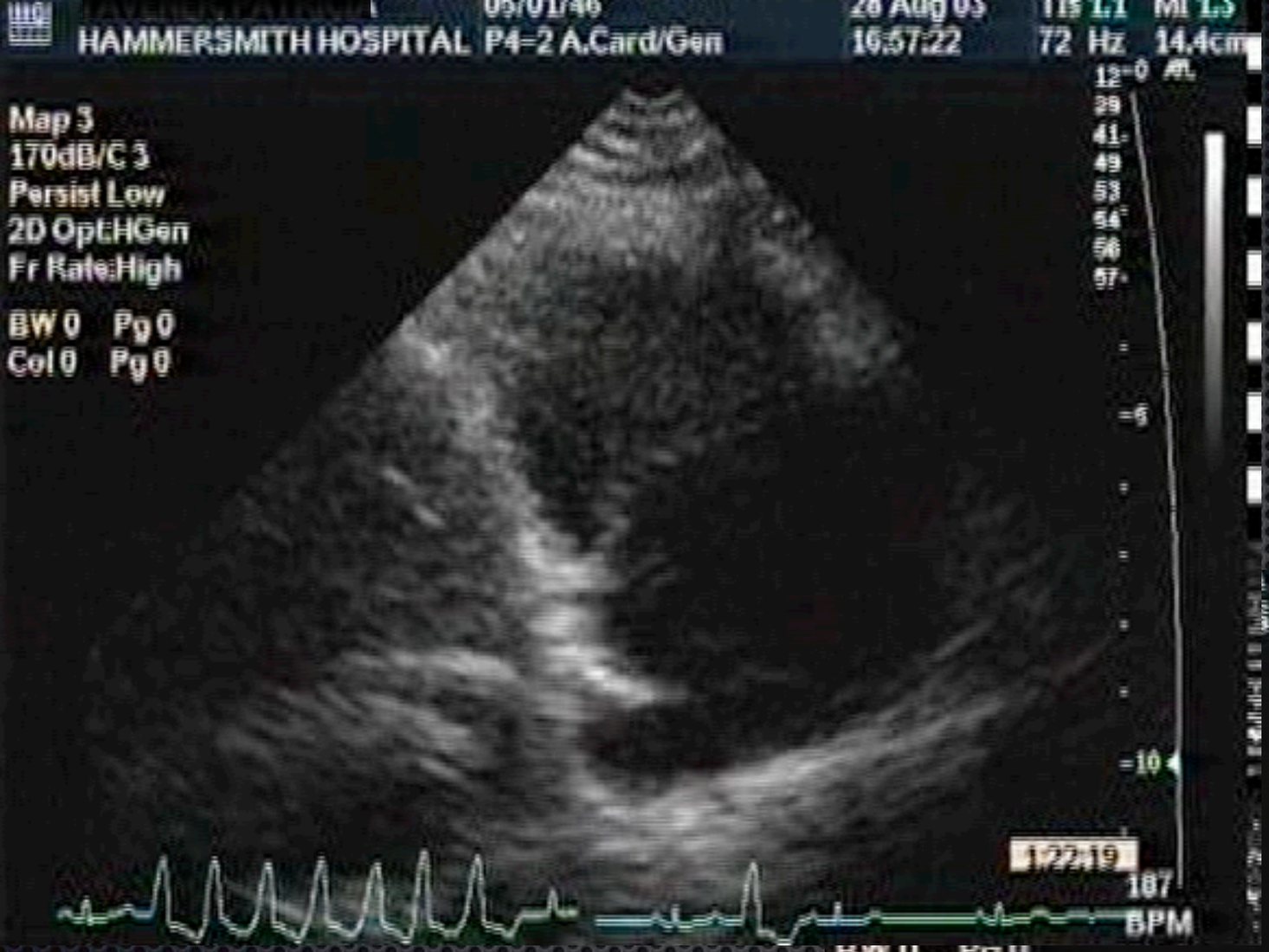

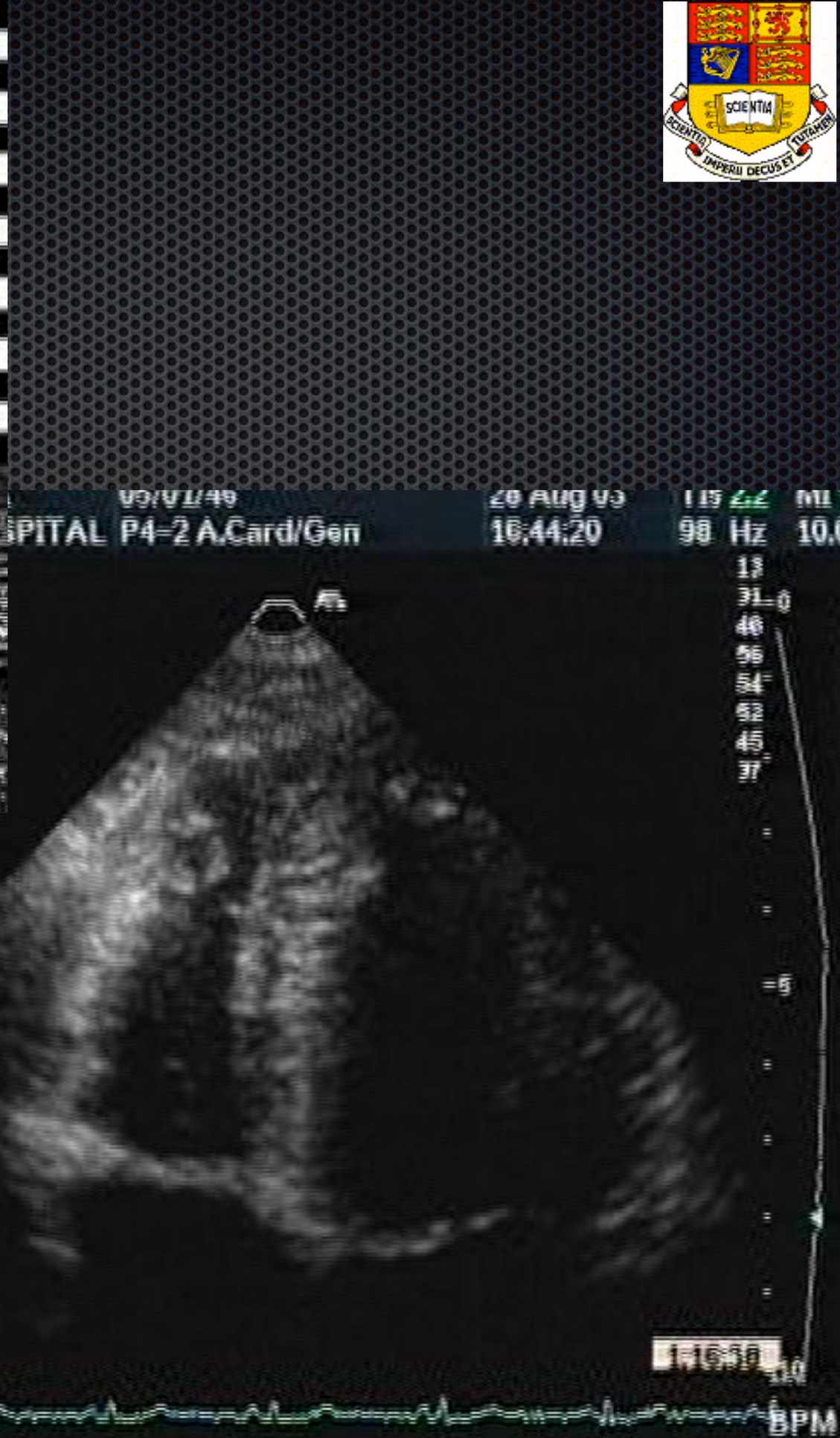

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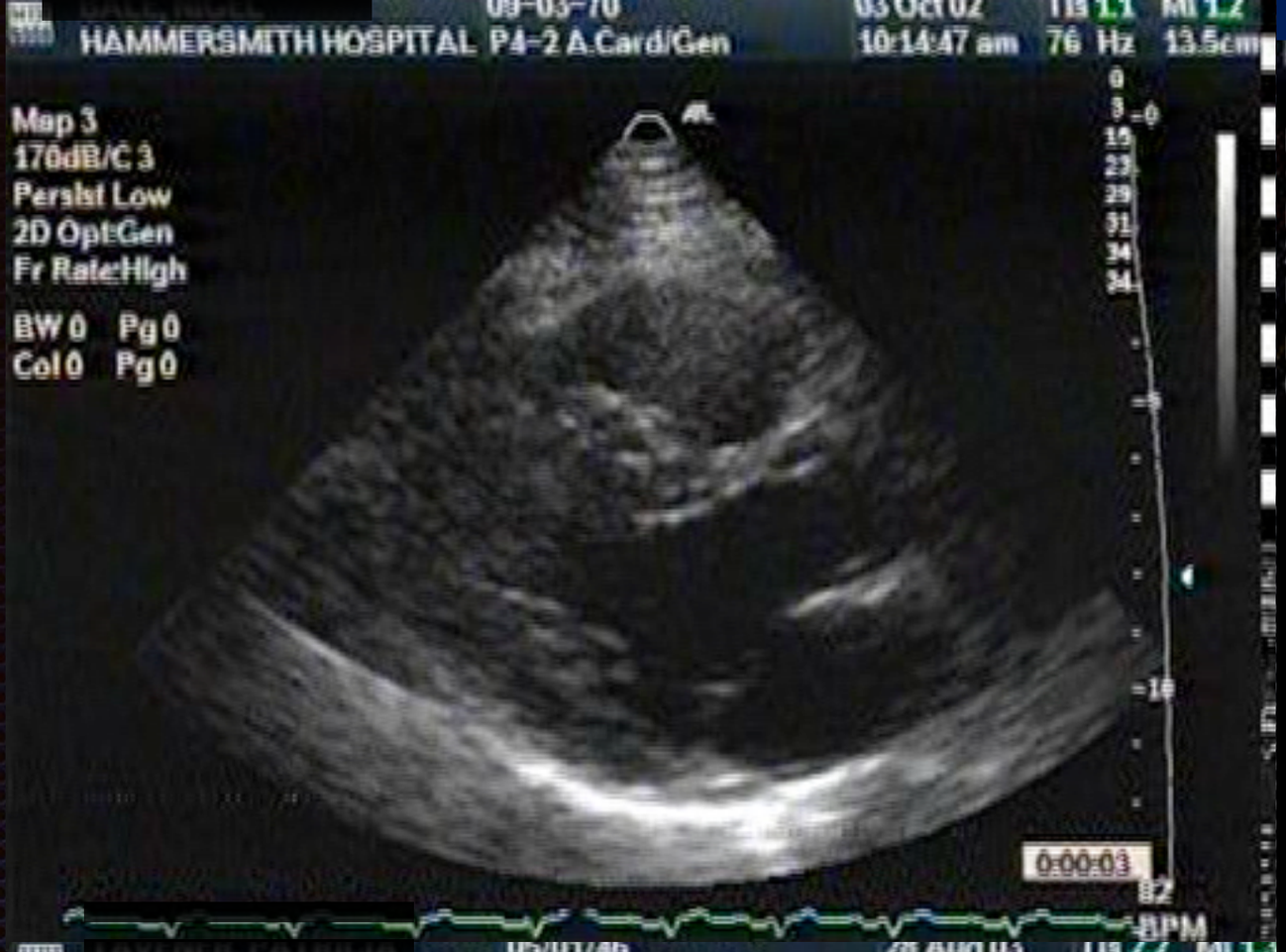

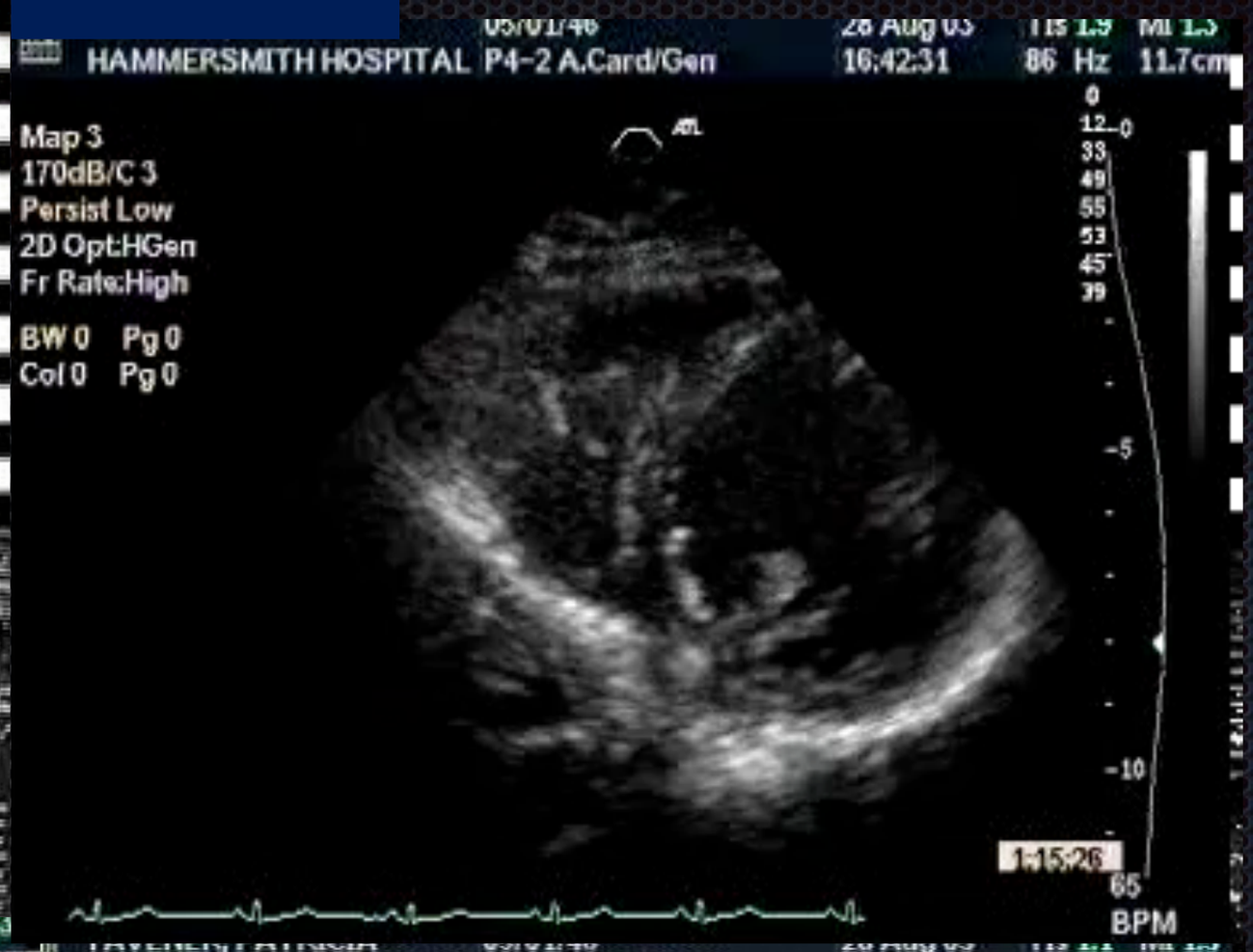

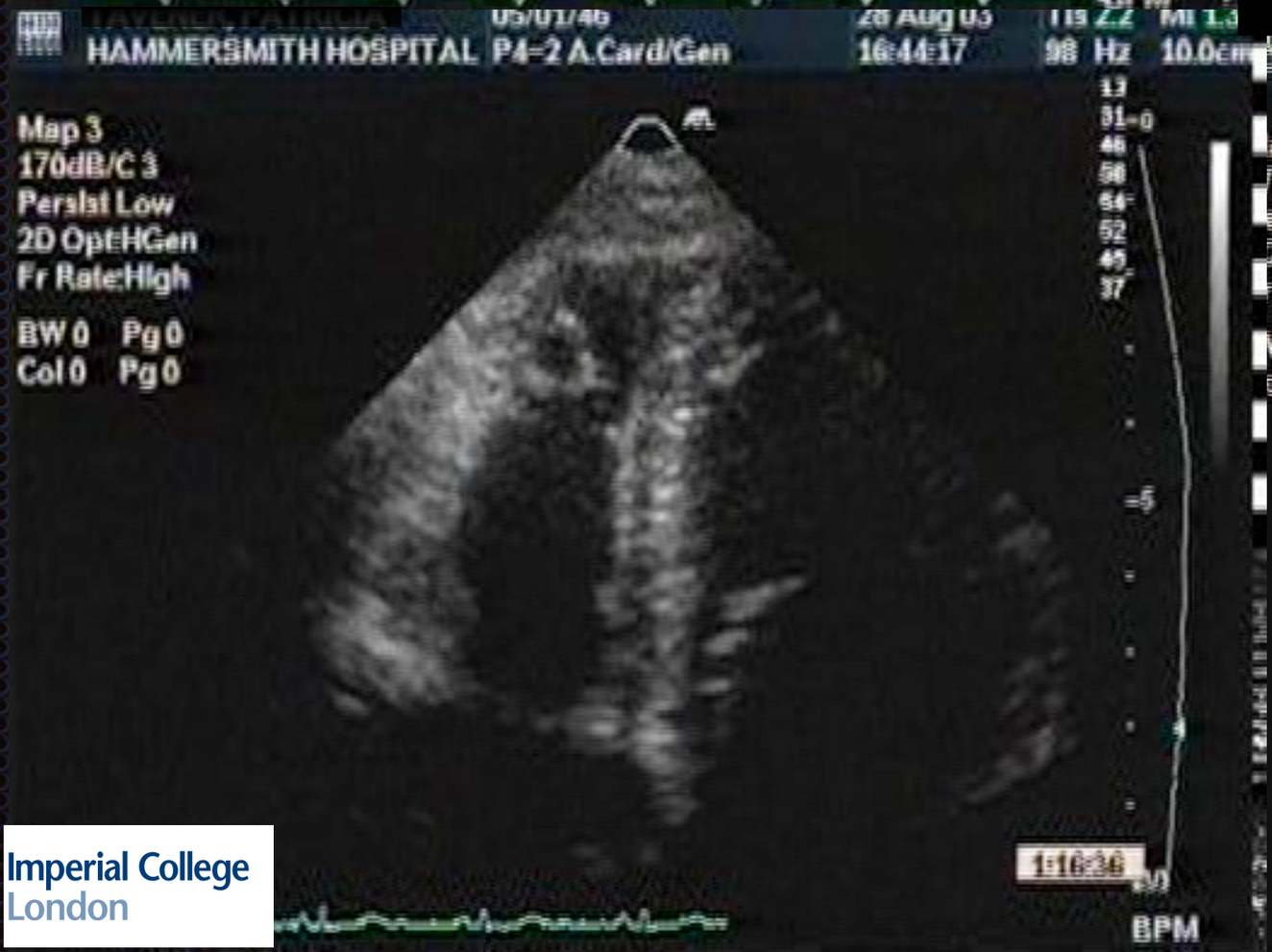

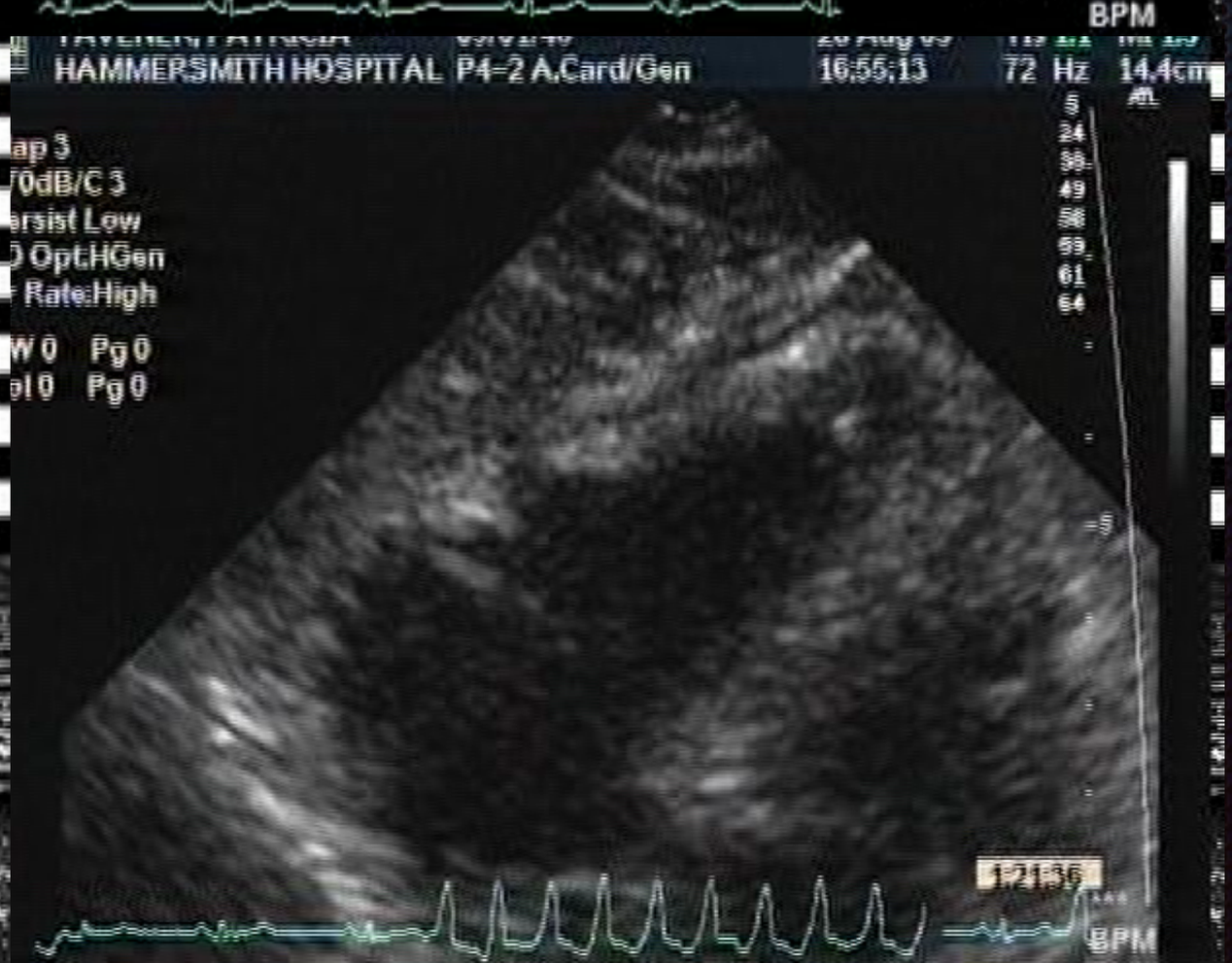

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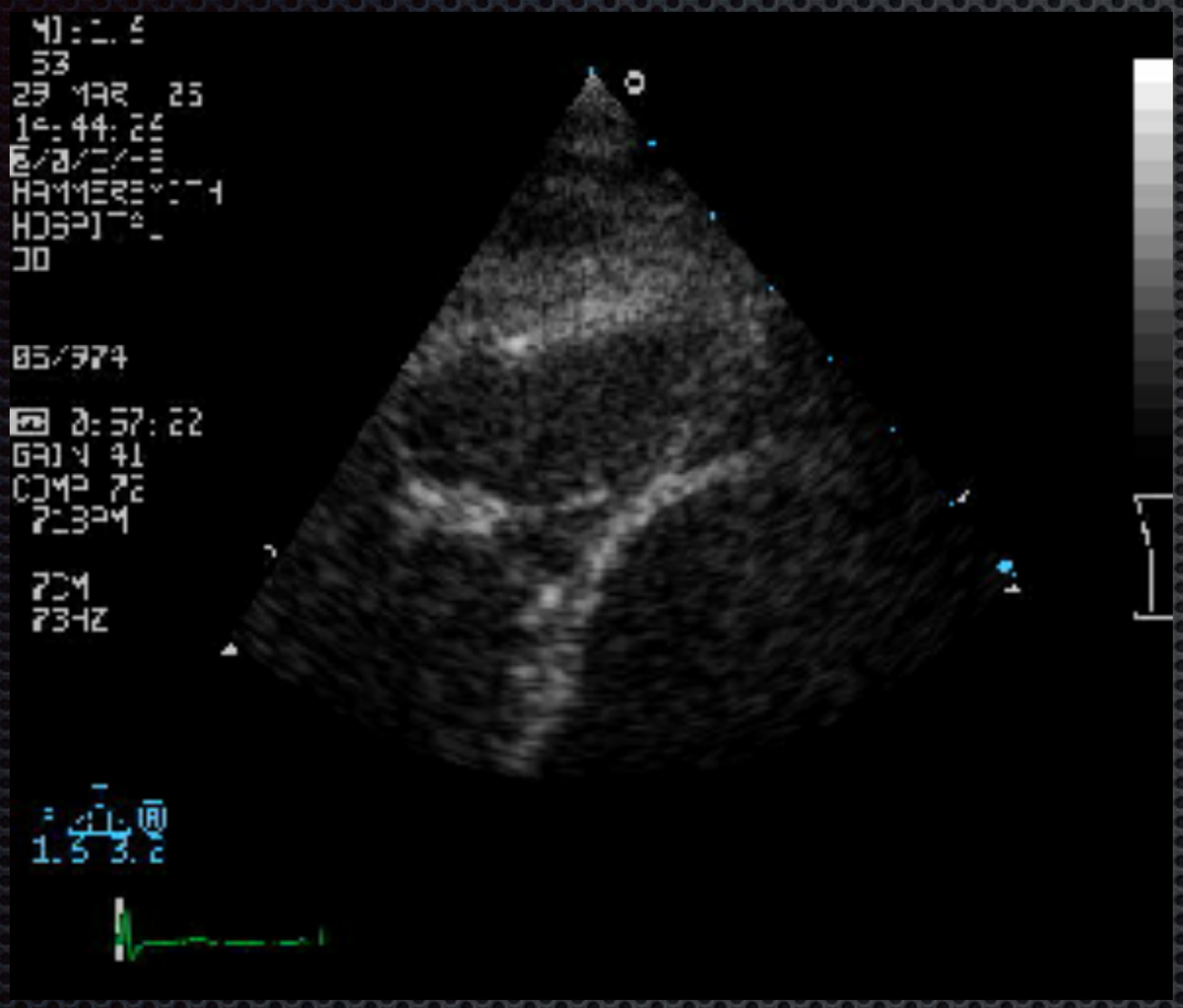
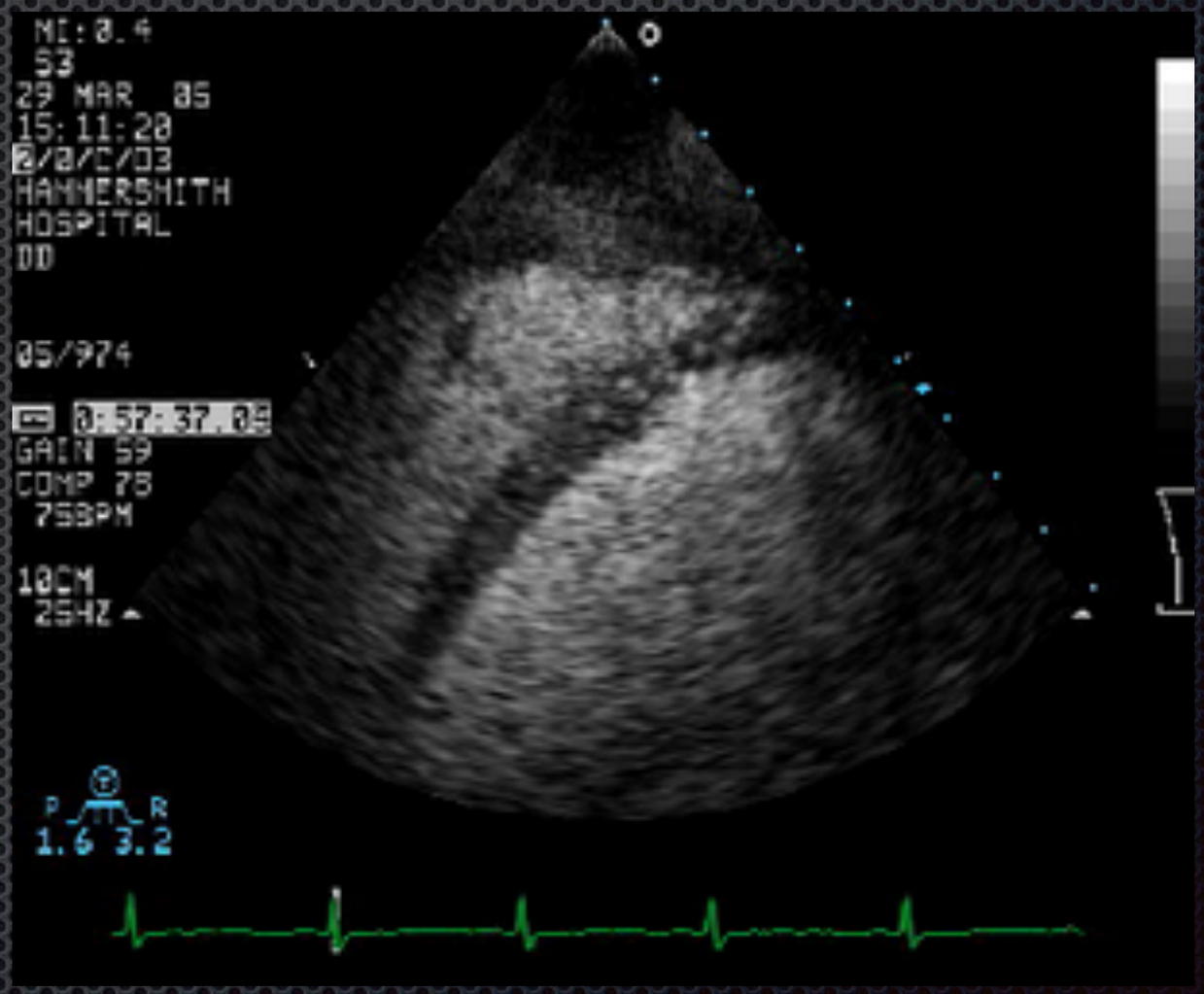
?? RV Dysfunction





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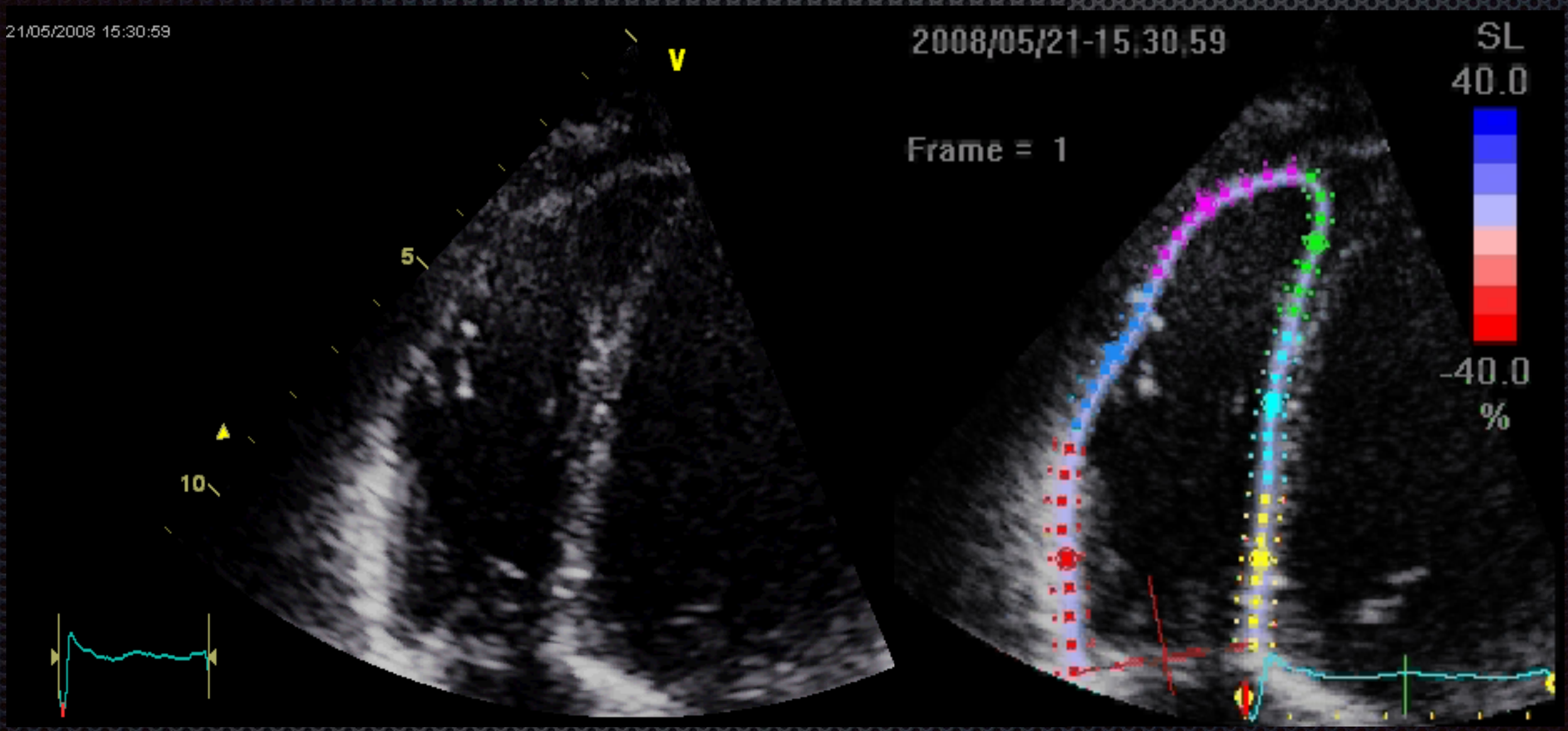
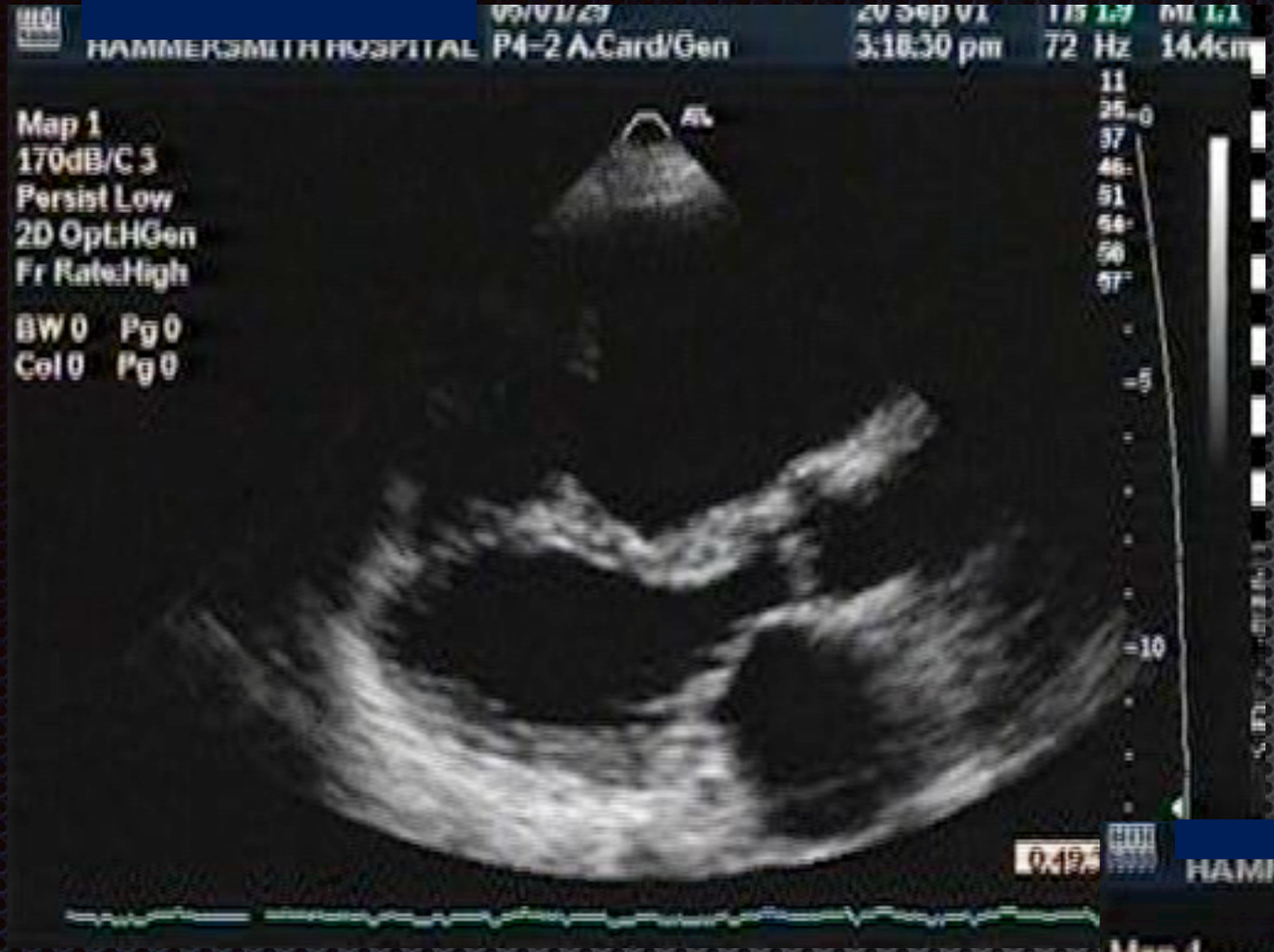
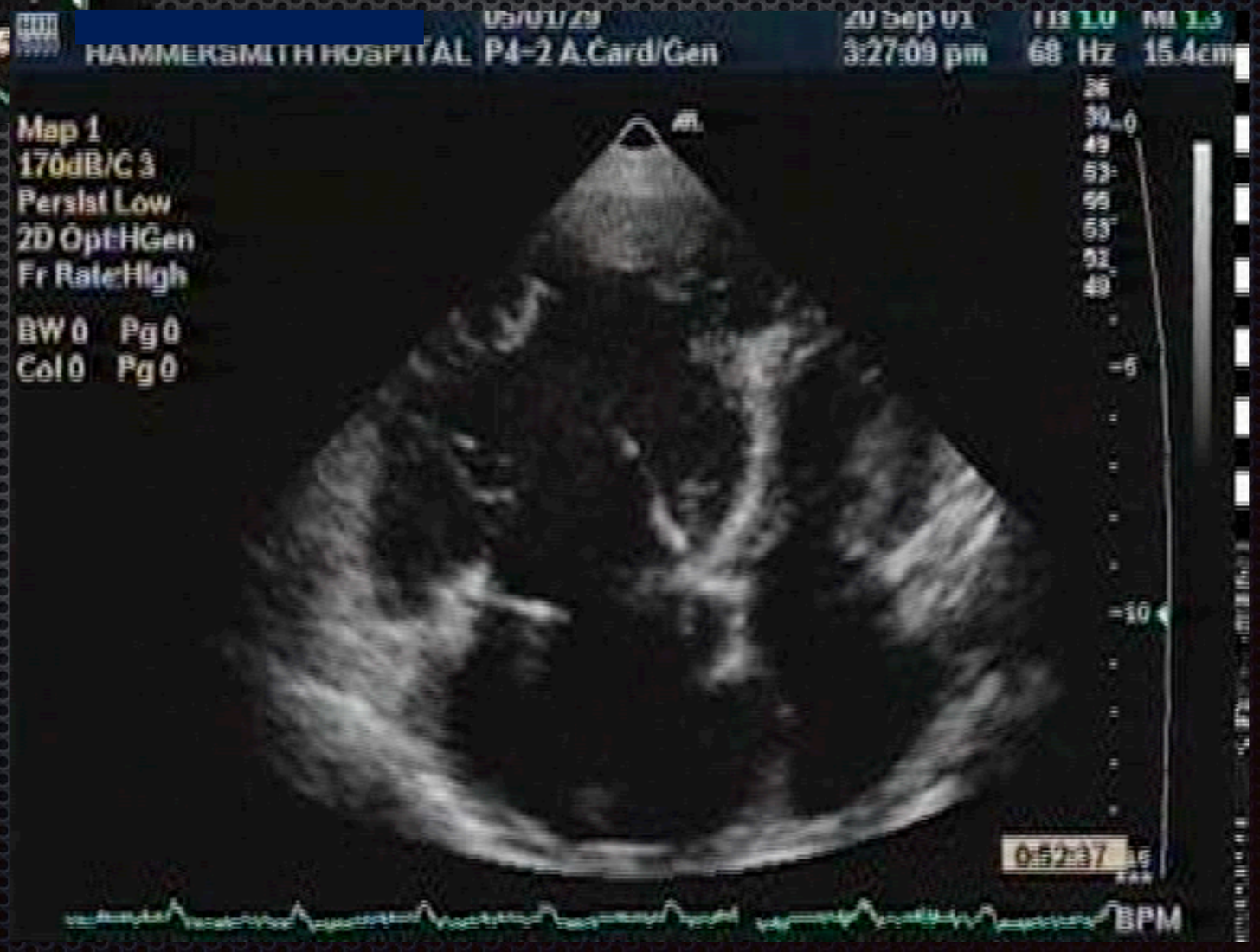
RV speckle Tracking



ARVC





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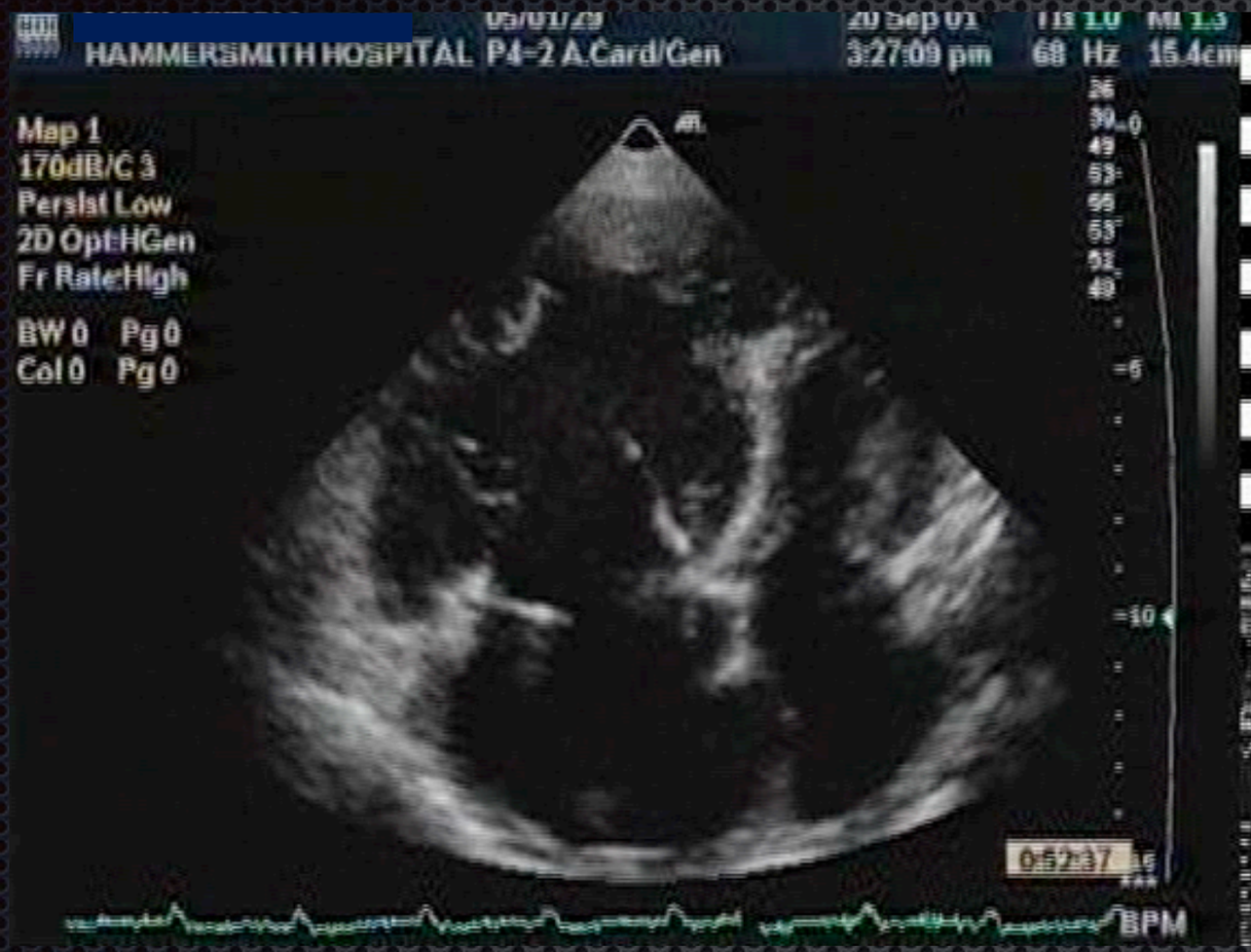
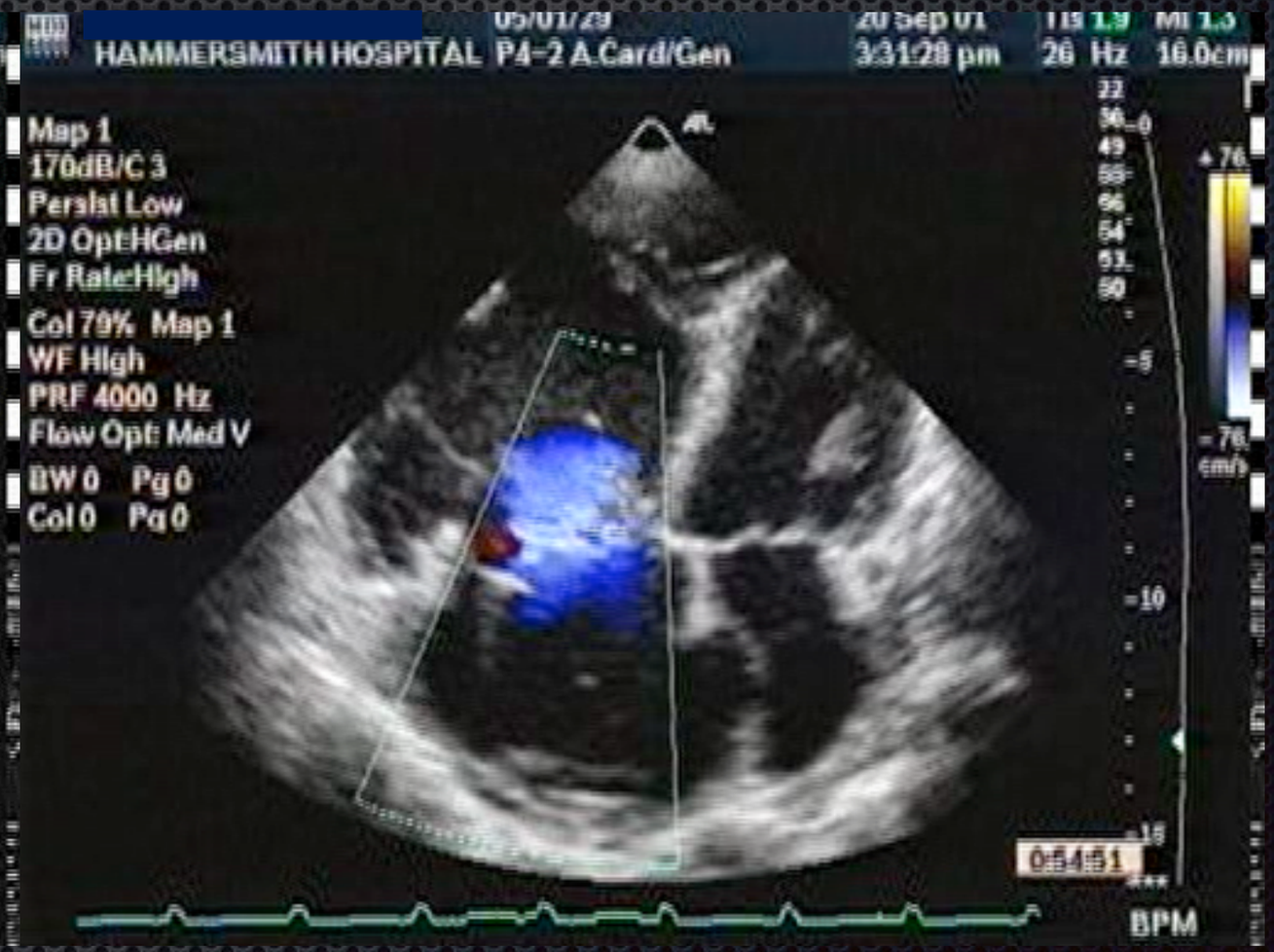
Apical 4-Chamber





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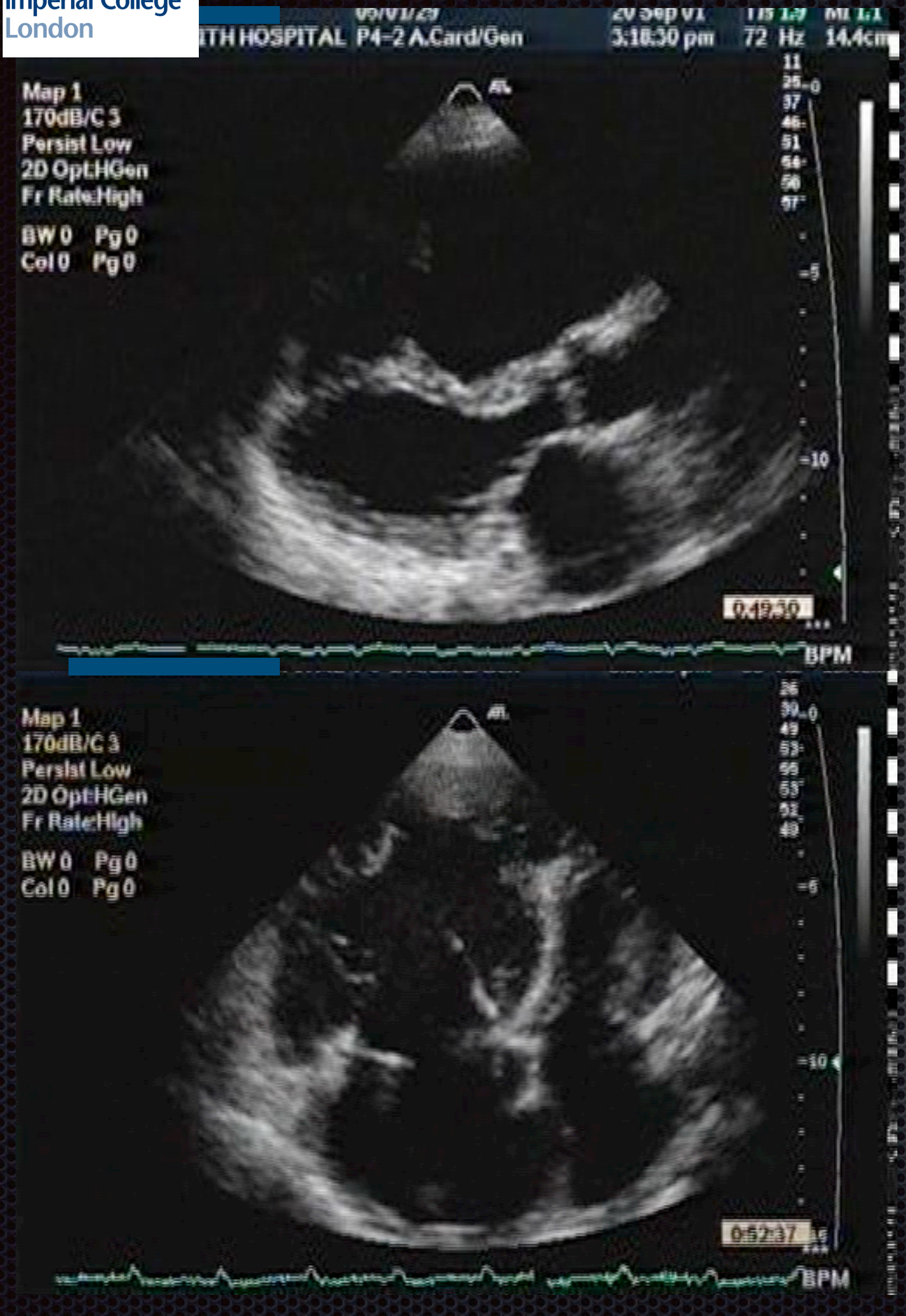
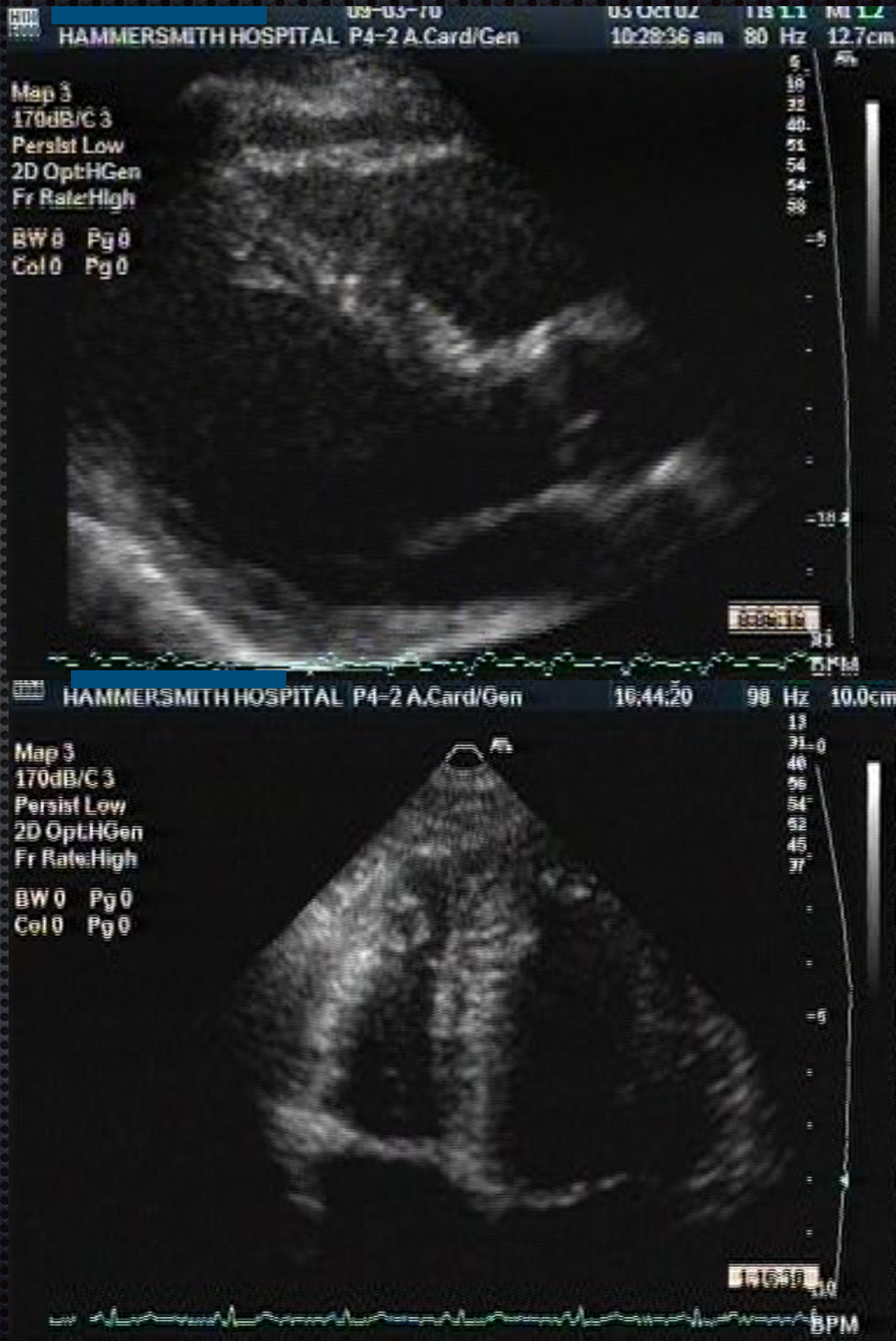




Natural History

Structural alterations

Electrical phenomena

Subclinical Phase
No symptoms
Subtle ECG changes
No structural abnormalities
SD can occur

Overt RV electrical phase
Palpitations, syncope, SD
VE, VT, VF
Structural changes detected

RV failure phase
HF symptoms
VE, VT, VF, SD
RV dilatation-dysfunction

End-stage phase
Biventricular involver
Severe HF symptoms
Transplantation, deat

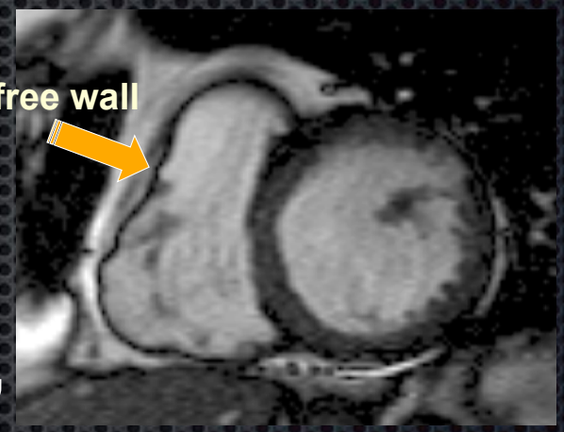
Cardiac Magnetic Resonance Imaging

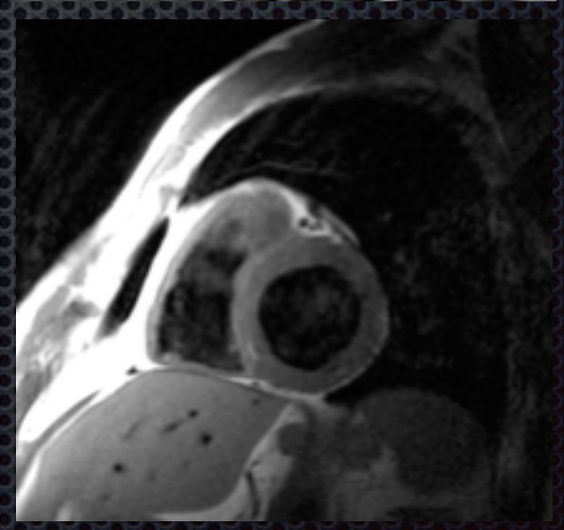
- 1.5 or 3T scanners
- Dedicated phased-array coils with multiple elements
- ECG triggering
- Expert centres

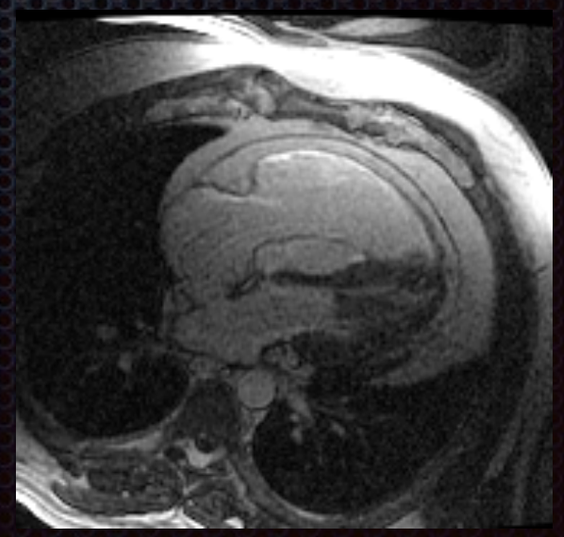
- **Functional:** Dilatation, global/regional function, focal aneurysms (subjective), RV volumes, EF

- **Morphological:** Focal thinning, RVOT enlargement, fatty infiltration with T1 weighted spin echo images (not a task force criterion)

- **Delayed enhancement:** Detection of fibrosis
??prognostic implications not defined
LV involvement







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Summary

- ARVC has a wide spectrum of manifestations
- Electrical abnormalities predominate in early stages
- Overt structural alterations develop progressively

- Diagnosis cannot be made by a single test
- Task Force Criteria have to be implemented to obtain diagnosis

- ARVC is not only a RV disease
- Frequent LV involvement also occurs (arrhythmogenic cardiomyopathy)

- Echocardiography remains the first choice imaging technique for ARVC
- CMR offers invaluable diagnostic and prognostic assistance

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Thank You!

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