Flash news: Are all patients with degenerative mitral regurgitation the same?

Risk of arrhythmias and sudden death

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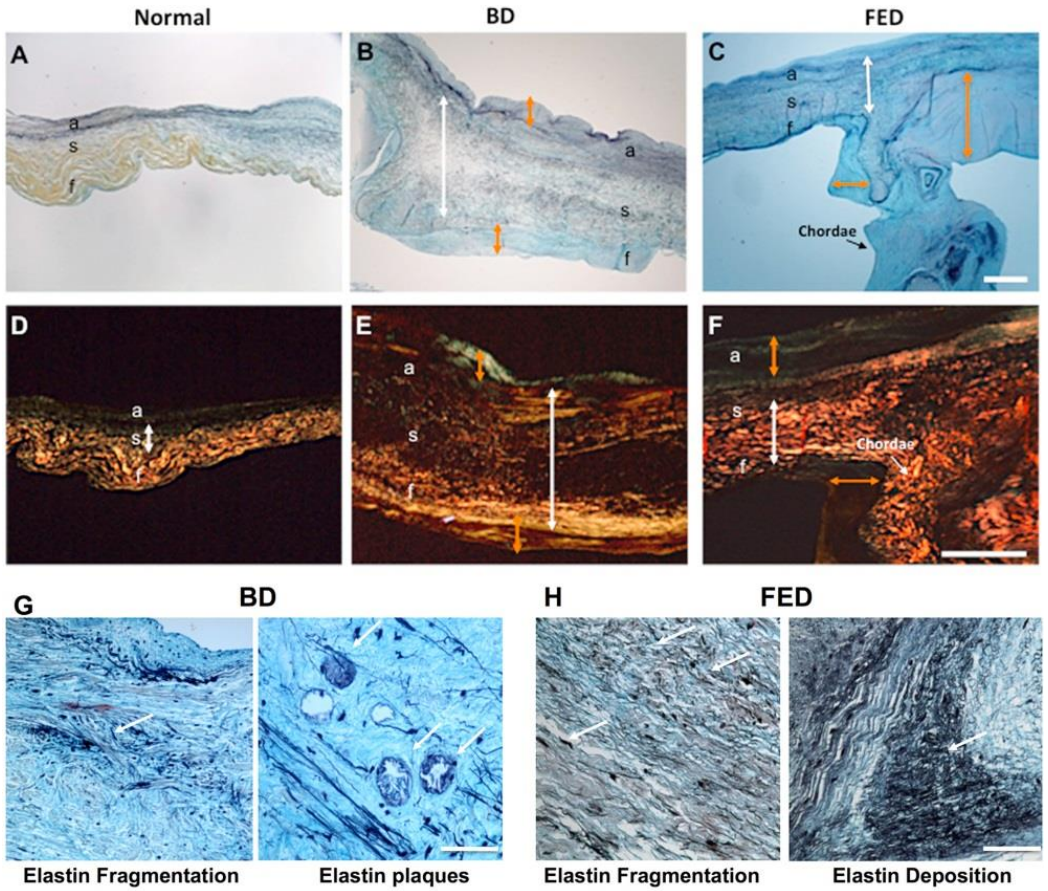
The NICE Topic Adviser on Heart Valve Disease

Are all patients with degenerative mitral regurgitation the same?

BD & **FED** are 2 distinct entities regarding microscopic pathology

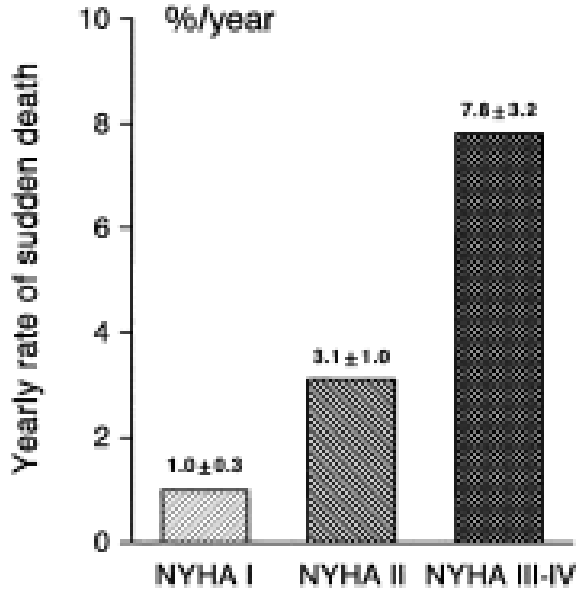
Arrhythmia and SCD risk factors differ with the type of degenerative MR

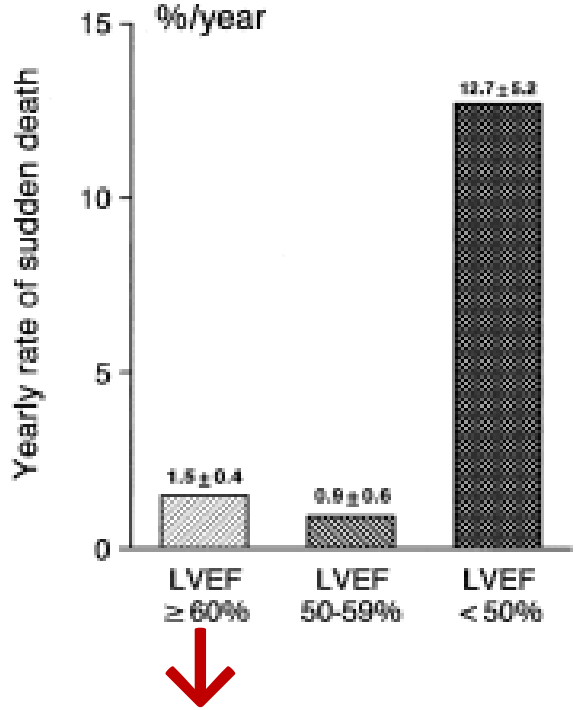


Hjortnaes et al (Levine, Carpentier), Semin Thoracic Surg 2016

Risk of SCD in severe MR due to flail MV leaflet (*FED)

symptoms / EF drop





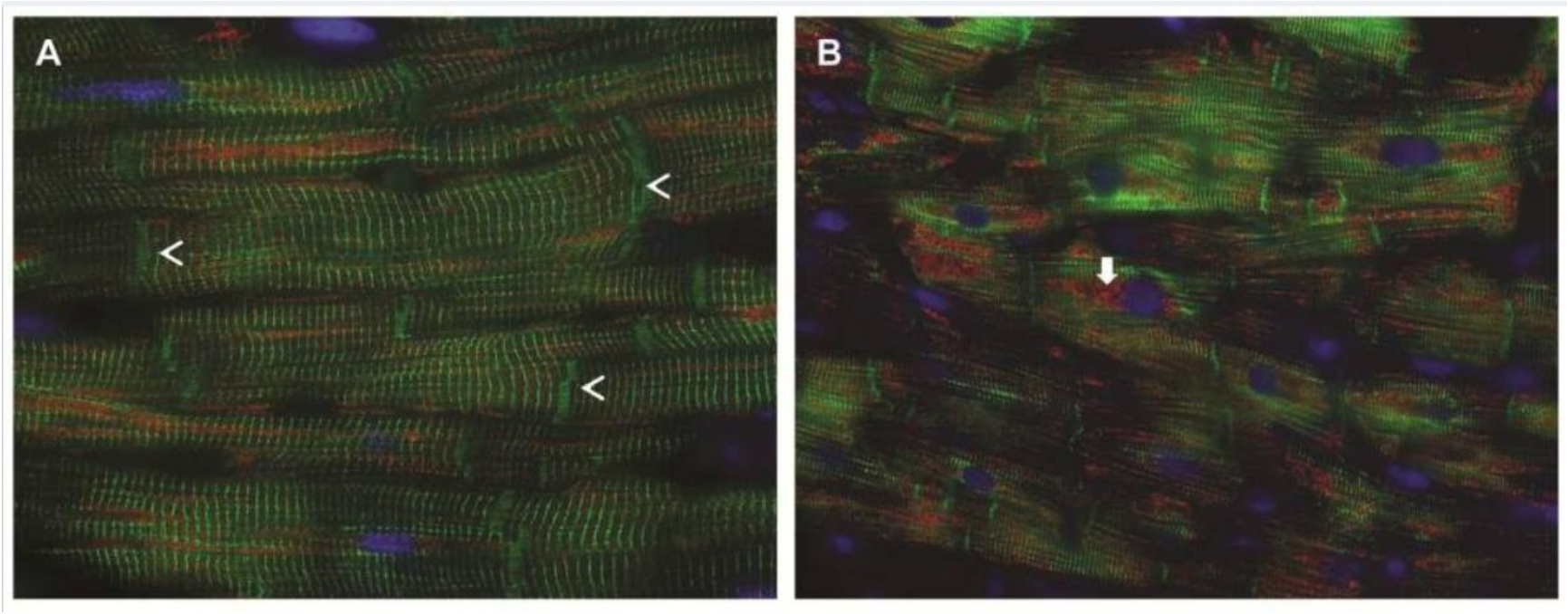
not negligible

Grigioni et al, JACC 1999

Normal heart **vs** Severe MR with LVEF > 60%

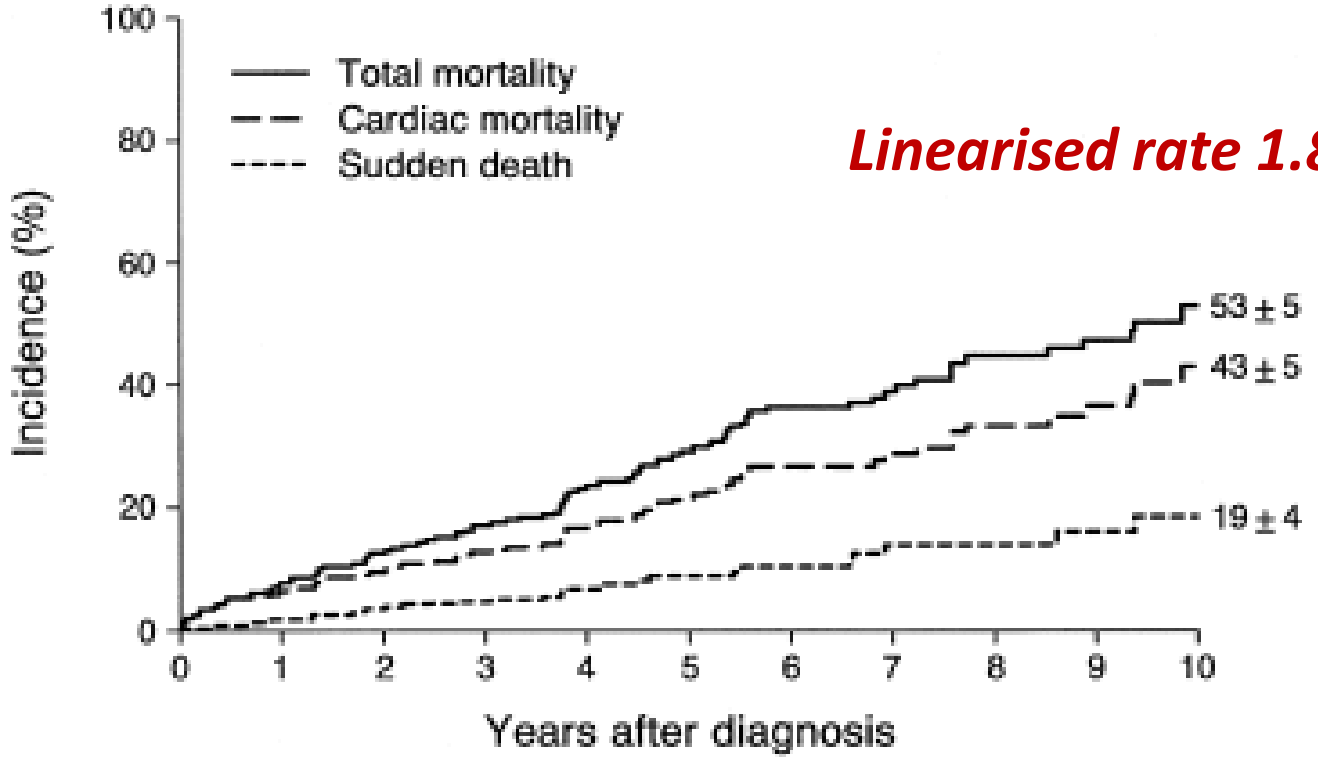
desmin disruption / reduction / aggregation

disruption of desmin-mitochondrial architecture



Ahmed et al, J Thorac Cardiovasc Surg, 2016

SCD in severe MR due to flail MV leaflet (*FED)



Linearised rate 1.8 per year

348 patients (age 67 +/- 12 years)

Grigioni et al. JACC, 1999

MVP Sudden Cardiac Arrest

almost half have no significant MR → unrelated to volume overload / HF

Table 3 Comparison of SCA patients with and without MVP

Characteristic	With MVP (n = 17)	Without MVP (n = 712)	*P*
Age (y)	60.9 ± 16.4	69.7 ± 14.7	.02
Sex: male	12 (70.6)	459 (64.5)	.60
Race: white	14 (82.4)	599 (84.7)	.73
Body mass index (kg/m^2)	27.0 ± 5.8	30.3 ± 9.1	.18
Hypertension	7 (41.2)	561 (78.9)	.001
Diabetes	1 (5.9)	330 (46.4)	.001
Known CAD	5 (29.4)	467 (65.6)	< .0001
Chronic kidney disease	2 (11.8)	250 (35.2)	.04
LVEF (%)	54.2 ± 14.7	48.1 ± 16.9	.14
LVEF ≤35%	1 (6.7)	196 (28.5)	.08
Left atrial diameter (mm)	45.0 ± 8.7	44.9 ± 10.1	.98
LV diameter (mm)	54.7 ± 7.3	51.8 ± 10.6	.38
Moderate or severe MR	10 (58.8)	170 (23.9)	.02
β-Blockers	9 (52.9)	404 (59.0)	.62
ACE inhibitors	4 (23.5)	338 (49.3)	.05
ARBs	1 (5.9)	65 (9.5)	1.0
Antiarrhythmic drugs	2 (11.7)	219 (32.0)	.11
Antiplatelets	7 (41.2)	510 (74.4)	.002
Lipid-lowering drugs	2 (11.7)	337 (49.2)	.002
QT-prolonging drugs	5 (29.4)	334 (48.7)	.11
QTc interval (ms)	429.3 ± 33.1	459.0 ± 40.6	.35

Narayanan et al. Heart Rhythm, 2016

“Malignant” MVP

0.7% of unexplained OHCA

young

mainly women

bi-leaflet prolapse

(Barlow Disease)

mild-moderate MR

ST – T changes

No ischaemia

No channelopathy

Table 1 Demographics of OHCA Cohort (n = 24)

Demographic	OHCA Cohort	Bileaflet MVP	No MVP	p Value*
n	24/1,200 (2%)‖	10/24 (42%)	14/24 (58%)	—
Age at sentinel event (yrs)	32 ± 15 (median 33.5; range: 5–60)	33 ± 16 (median 34.7; range: 5–60)	32 ± 14 (median 29.4; range: 14–51)	0.84†
Women	16 (67%)	9/10 (90%)	7/14 (50%)	0.04
QTc interval (ms)	430 ± 25	434 ± 22	428 ± 28	0.52§
Cardiac arrest as sentinel event	22/24 (92%)	8/10 (80%)	14/14 (100%)	0.16‡
Activity at time of cardiac arrest	17 wakeful rest, 7 acute emotional or physical stress, 0 sleep	8 wakeful rest, 2 acute emotional or physical stress, 0 sleep	9 wakeful rest, 5 acute emotional or physical stress, 0 sleep	0.65‡
ICD implantation	24/24 (100%)	10/10 (100%)	14/14 (100%)	—
Follow-up after ICD placement (yrs)	3.8 ± 4.1 (median 1.8; range: 0.1–11.9)	7.2 ± 3.5 (median 7.3; range: 2.4–11.9)	1.4 – 2.5 (median 0.7; range: 0.1–5.9)	0.0003†
Patients with appropriate ICD therapies	13/24 (54%)	8/10 (80%)	5/14 (36%)	0.04‡
Genetic testing for channelopathies¶	20/24 (83%)	9/10 (90%)	11/14 (79%)	0.61‡
LQTS types 1, 2, and 3	17/24 (71%)	9/10 (90%)	8/14 (57%)	0.18‡
Isolated testing for *SCN5A* gene mutation	2/24 (8%)	0/10 (0%)	2/14 (14%)	0.49‡
RYR2 gene mutation test	7/24 (29%)	2/10 (20%)	5/14 (36%)	0.65‡
LVEF at presentation	60.3 ± 1.6	60.5 ± 3.1	60.2 ± 1.7	0.92§
No. with abnormal RV size or function	0	0	0	—
RVSP by Doppler echocardiographic estimation (mm Hg)	28.7 ± 5.6 (range: 19–41)	28.6 ± 6.0 (range: 23–41)	28.7 ± 5.6 (range: 19–41)	0.95§
Mitral valve regurgitation	18/24 (75%)	10/10 (70%)	8/14 (57%)	0.02‡
Mild	13/24 (54%)	5/10 (50%)	8/14 (57%)	1.00‡
Moderate	4/24 (17%)	4/10 (40%)	0/14 (0%)	0.02‡
Severe	1/24 (4%)	1/10 (10%)	0/14 (0%)	0.42‡
ST-T repolarization changes#	16/23 (70%)	8/9 (89%)	8/14 (57%)	0.17‡
Inverted/biphasic T wave	12/23 (52%)	7/9 (78%)	4/14 (29%)	0.04‡
J wave	5/23 (22%)	1/9 (11%)	4/14 (29%)	0.62‡
ST-segment depression > 1 mm	1/23 (4%)	1/9 (11%)	0/14 (0%)	0.39‡

Sriram et al. JACC, 2013

Mayo EP team

Variable VE morphology / origin

not supporting traction theory / focal fibrosis relationship

automatic not reentry mechanism

Table 2 Relationship of Ventricular Ectopic Activity With Bileaflet MVP in OHCA Survivors With Ambulatory Holter Monitoring (n = 19)

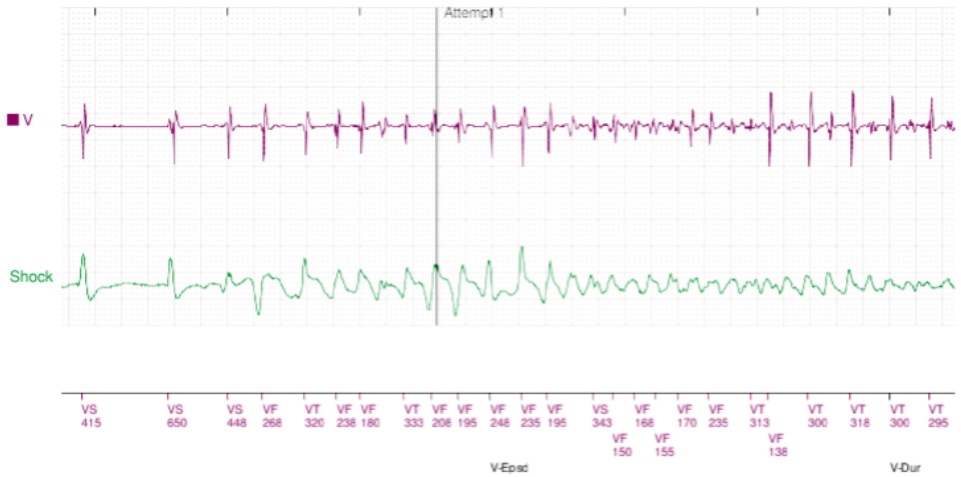
Variable	Bileaflet MVP (n = 9)	No MVP (n = 10)	p Value*
PVCs	9/9 (100%)	7/7 (100%)	—
Ventricular ectopic activity burden (PVCs/h)	67 (35–690)	23 (1–258)	0.002†
NSVT/sustained VT	7/9 (78%)	1/10 (10%)	0.006‡
Polymorphic VT	4/9 (44%)	1/10 (10%)	0.14‡
Episodes of NSVT per h	0.3 (0–7.4)	0 (0–0.1)	0.003†
Bigeminal PVCs	9/9 (100%)	1/10 (10%)	<0.0001†
Bigeminal PVCs per h	0.4 (0.05–67.6)	0 (0–0.3)	0.0003†
Ventricular couplets per h	3.0 (0.3–26.5)	0.04 (0–1.6)	0.0015†
Alternating papillary muscle/outflow tract PVCs§	7/9 (78%)	2/10 (20%)	0.02‡
Other sites of PVC origin			
RV free wall	1/9 (11%)	1/10 (10%)	
RV midcavity	2/9 (22%)	1/10 (10%)	
LV midcavity	2/9 (22%)	1/10 (10%)	
Fascicle/papillary muscle alone	0/9 (0%)	1/10 (10%)	
Multiform PVCs	1/9 (11%)	0/10 (0%)	

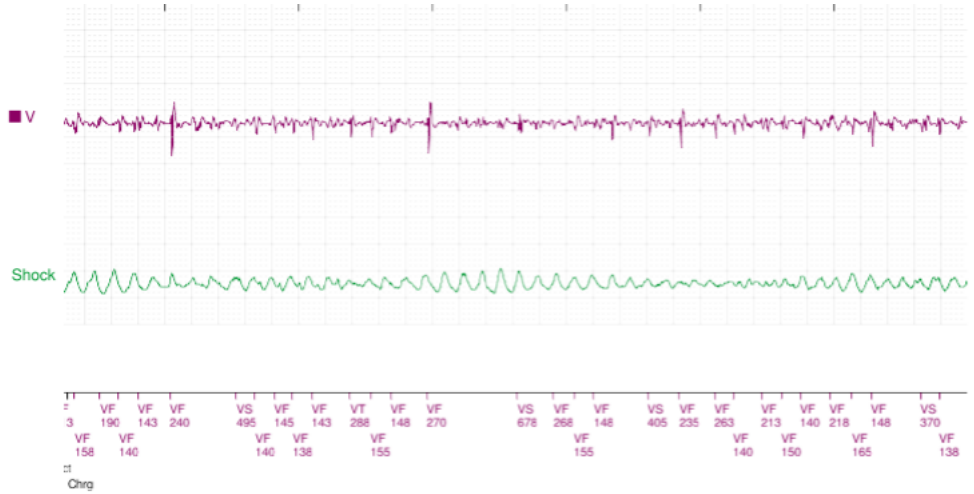
Sriram et al. JACC, 2013

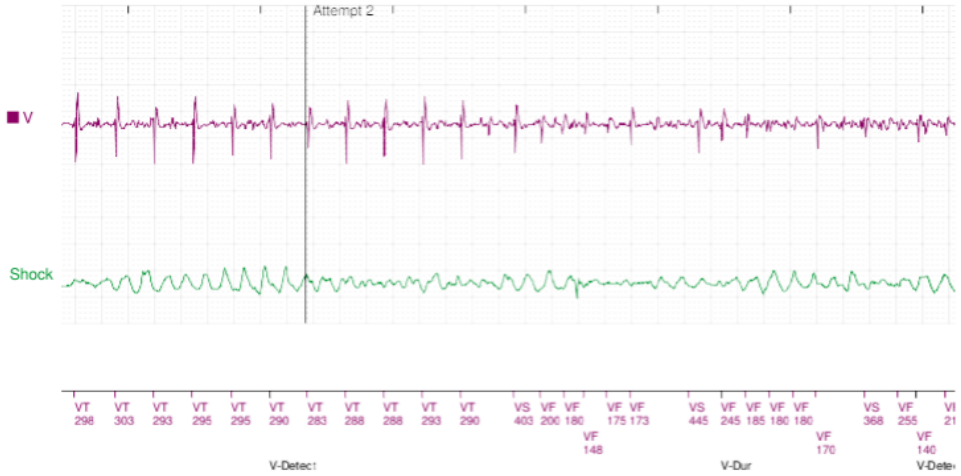
Typical case

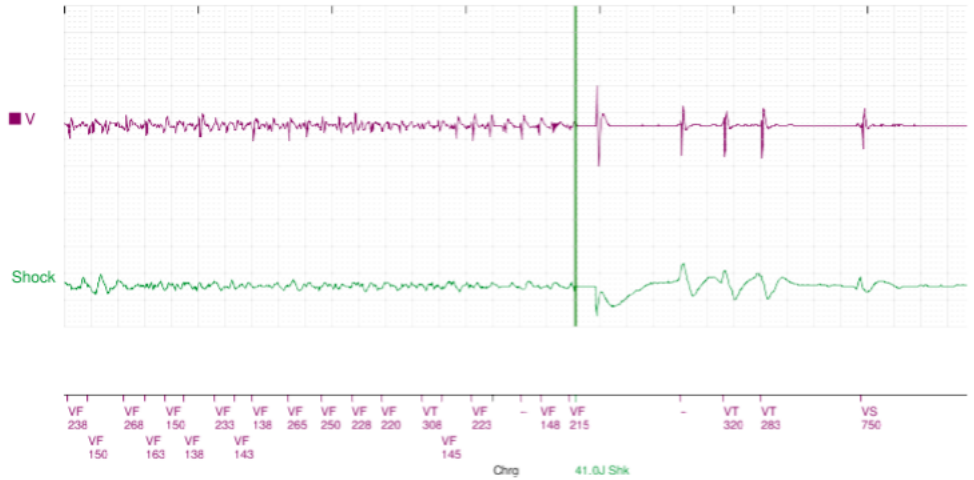
ICD implantation for out of hospital cardiac arrest

ICD shock (x3) a few months later for polymorphic VT degenerating in VF

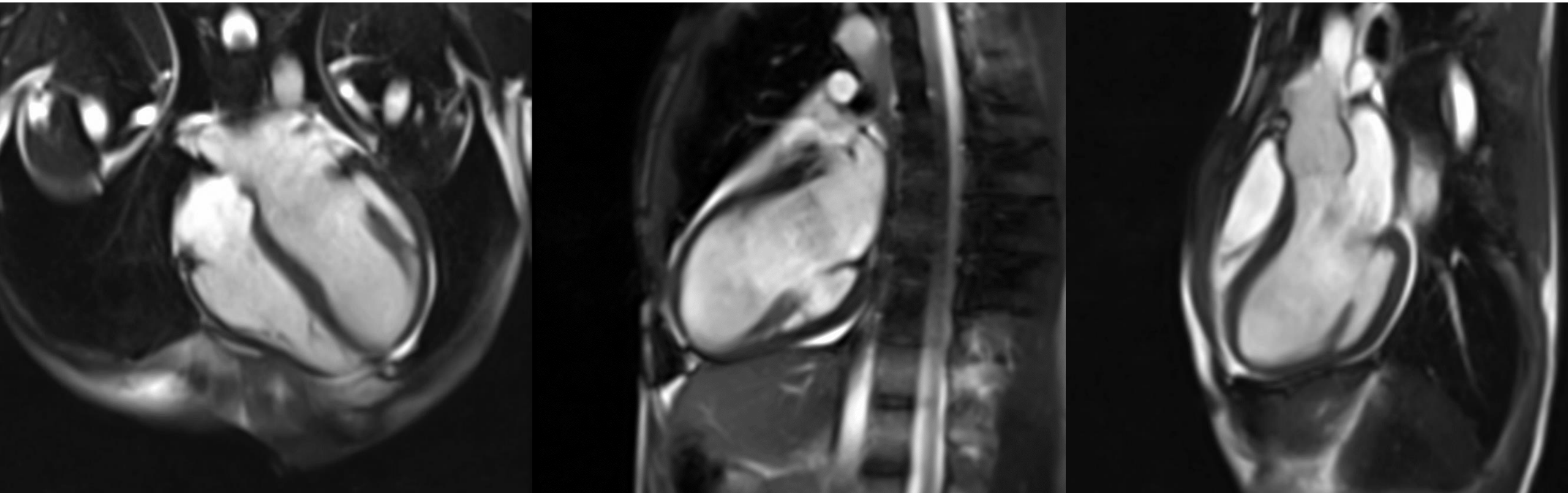




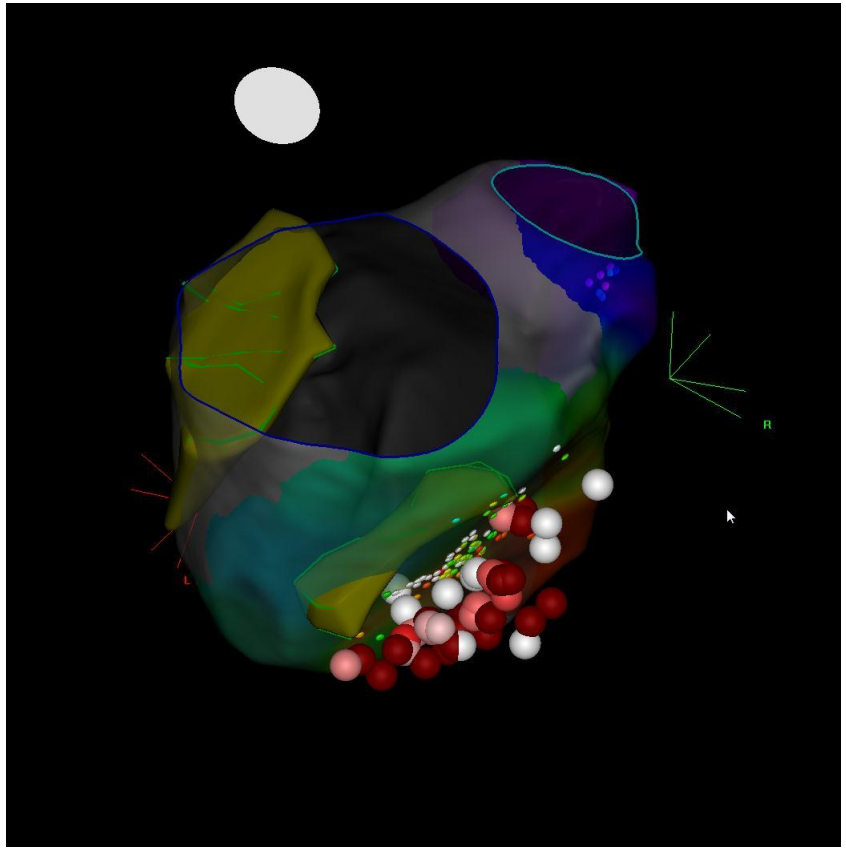


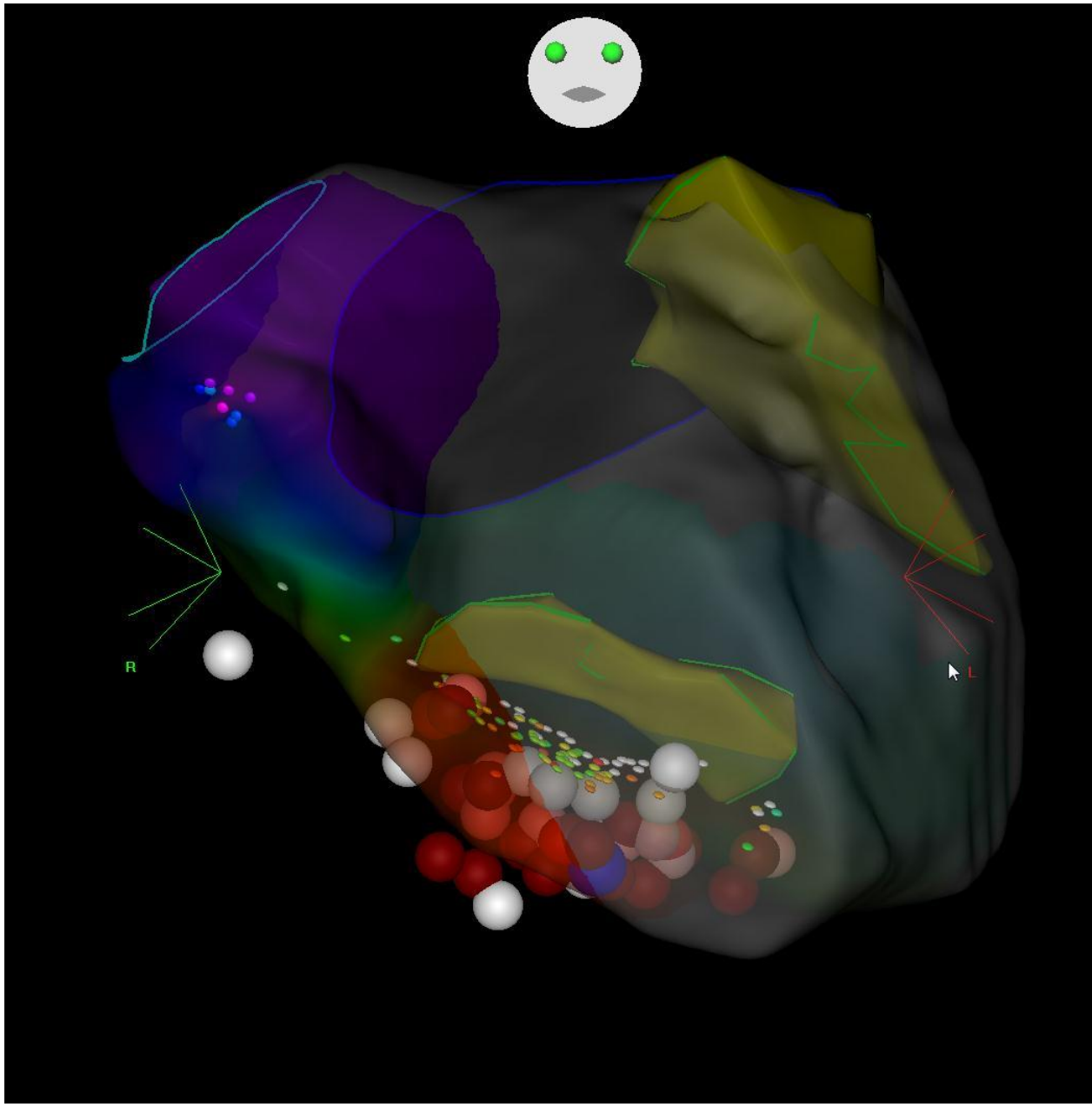


MRI: myopathic LV & bi-leaflet MVP

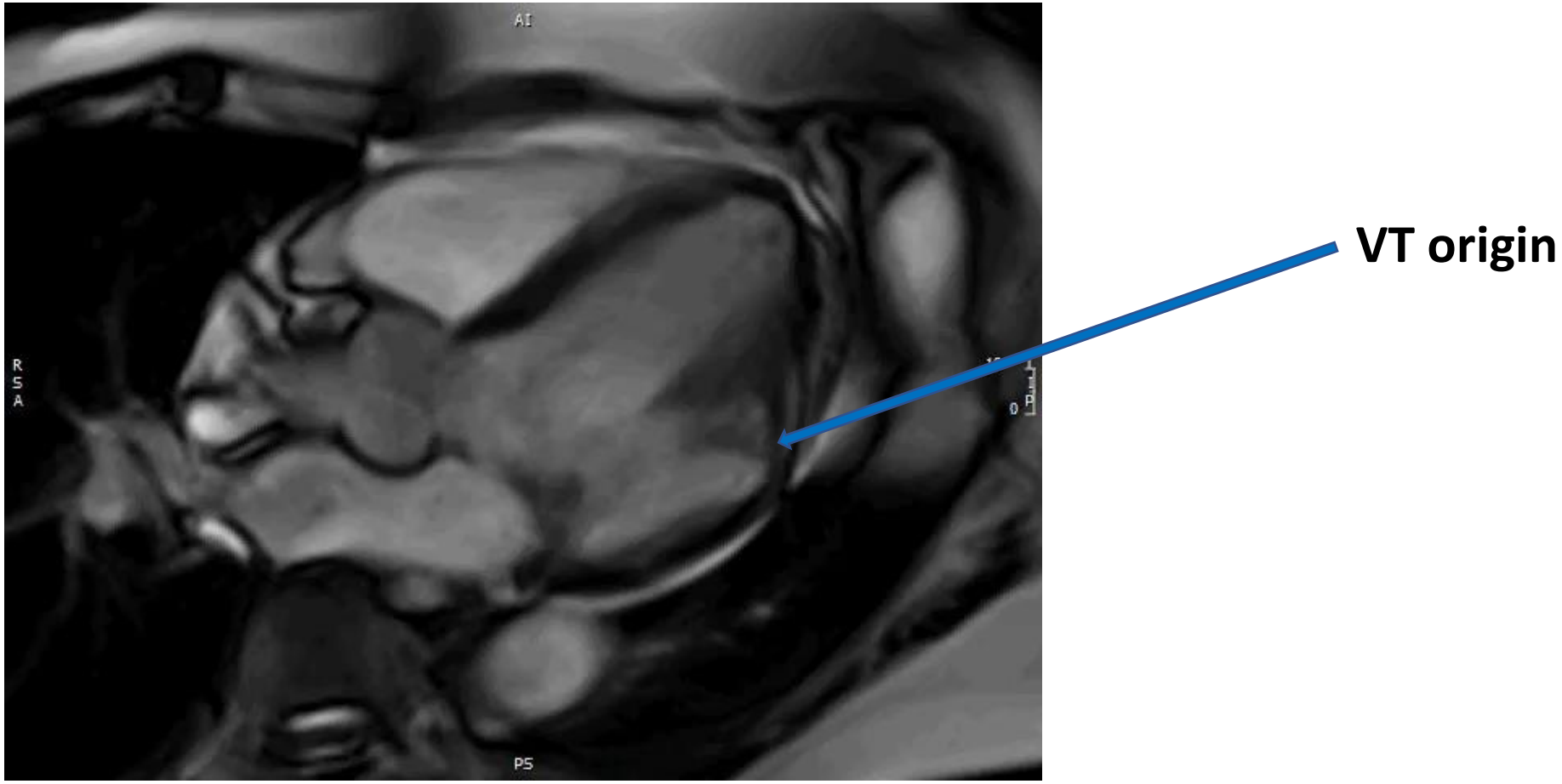


CARTO mapping for VT ablation
based on CT imaging integration
basal posterior wall
beneath the papillary muscle and the subvalvular apparatus of the mitral valve
only 1% VEs on 24 h ECG following ablation





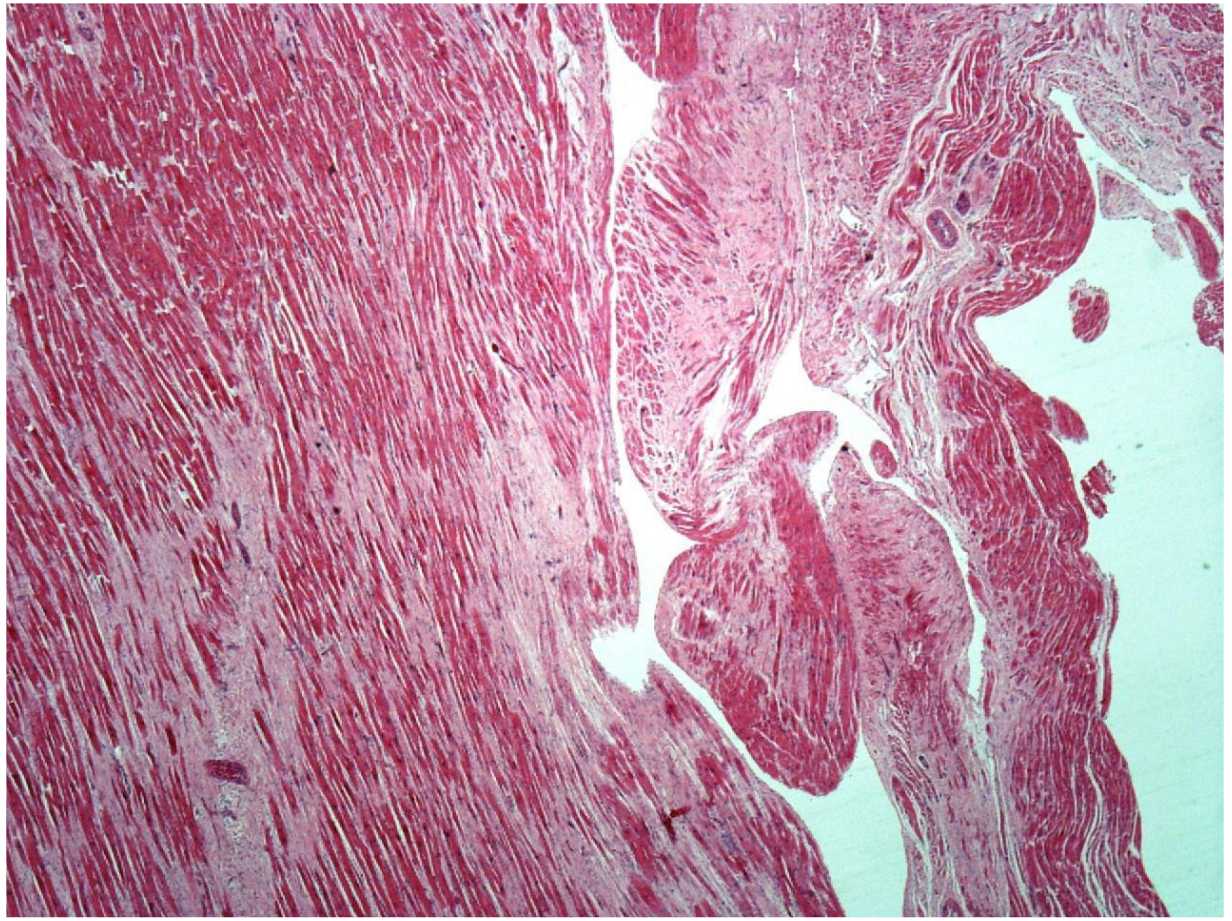
Myocardial origin of automatic VT with high VF potential



Pathology evidence

68 consecutive cases with MVP as “cause of death” (SCD reference centre)
no evidence of CAD
all were Barlow valves

Ventricular fibrosis
microscopic
diffuse
80.9%
89.1% LV only
10.9% RV as well

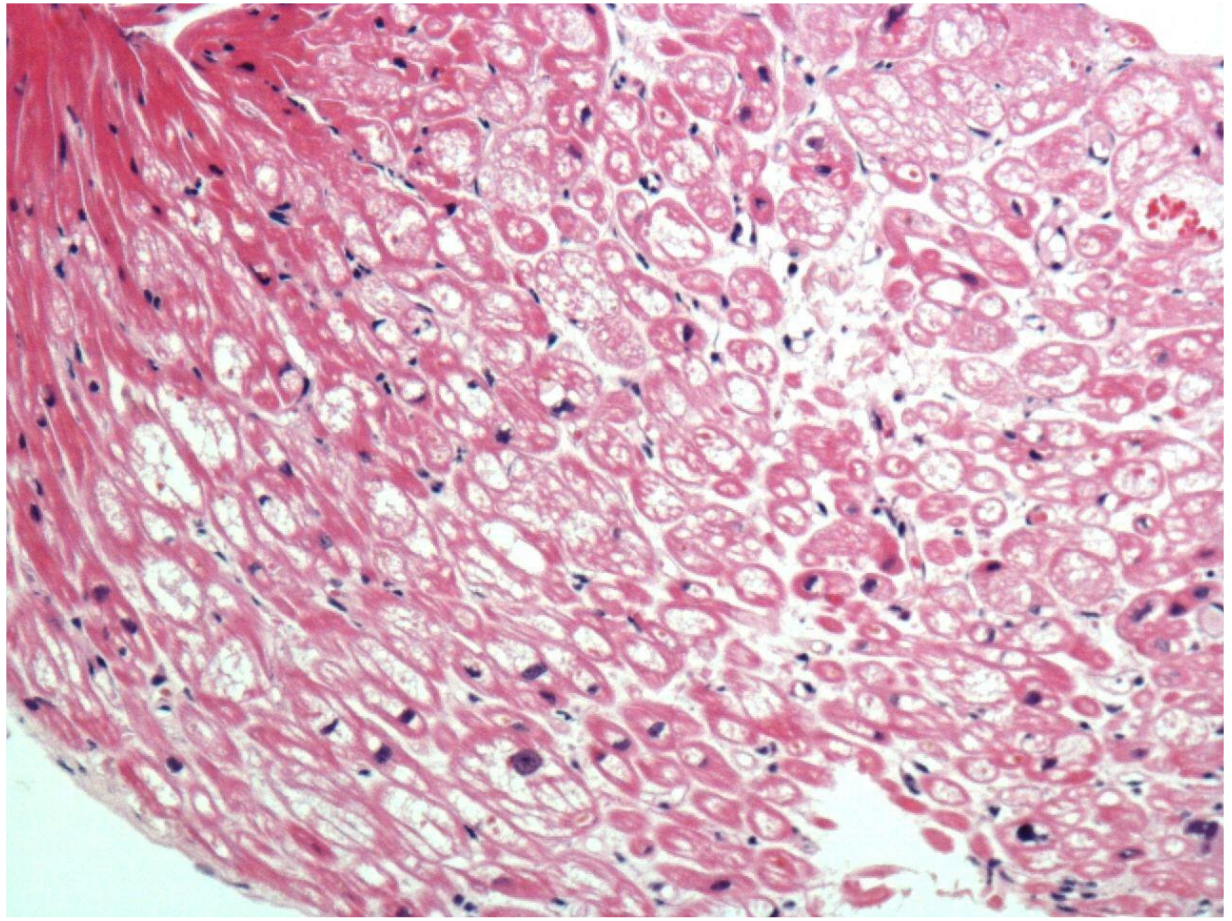


Garbi, Lancellotti, Sheppard, OpenHeart 2018

Barlow Cardiomyopathy

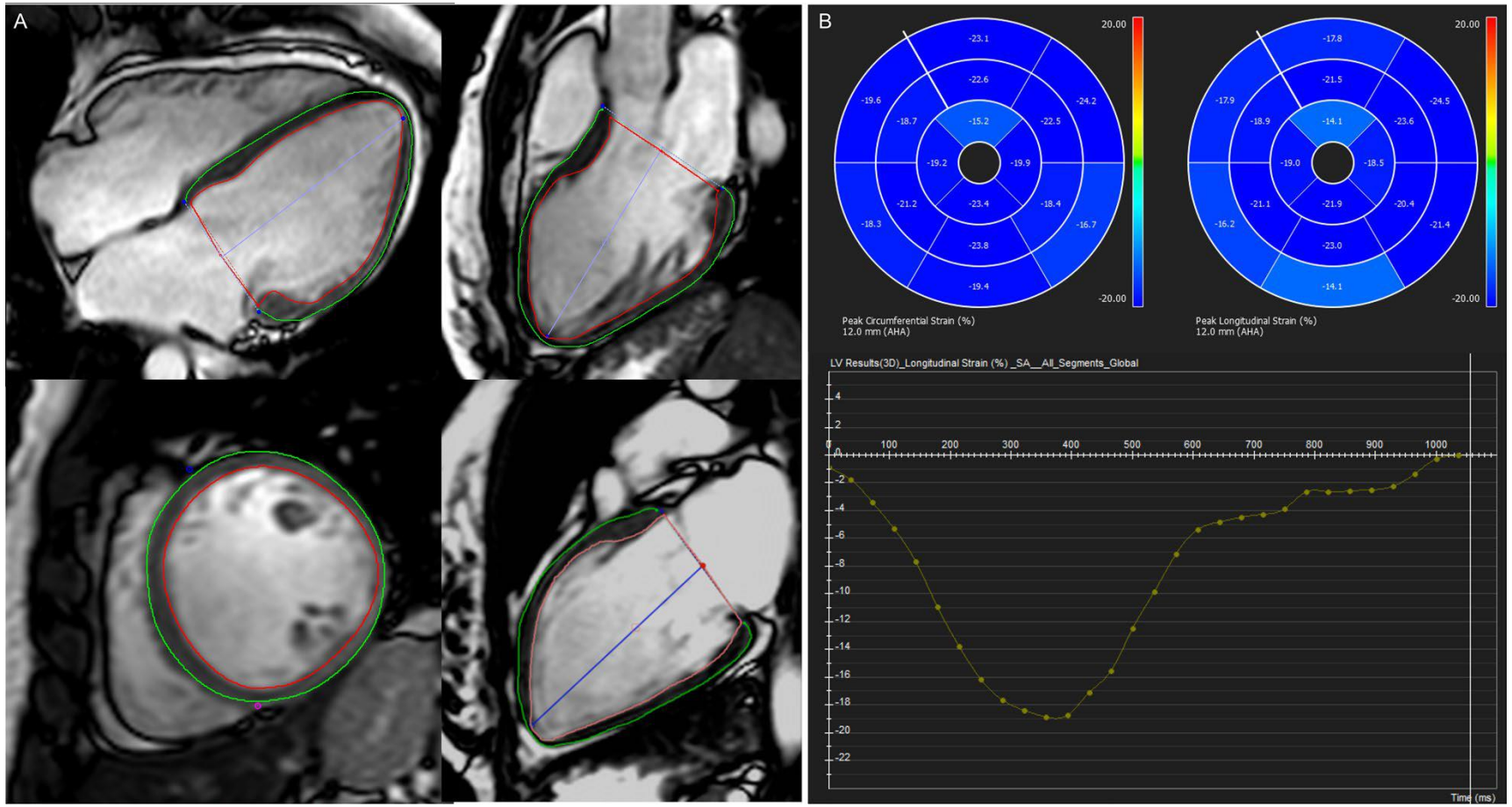
Myocyte degeneration
cytoplasmic vacuolation

Distinct cardiomyopathy



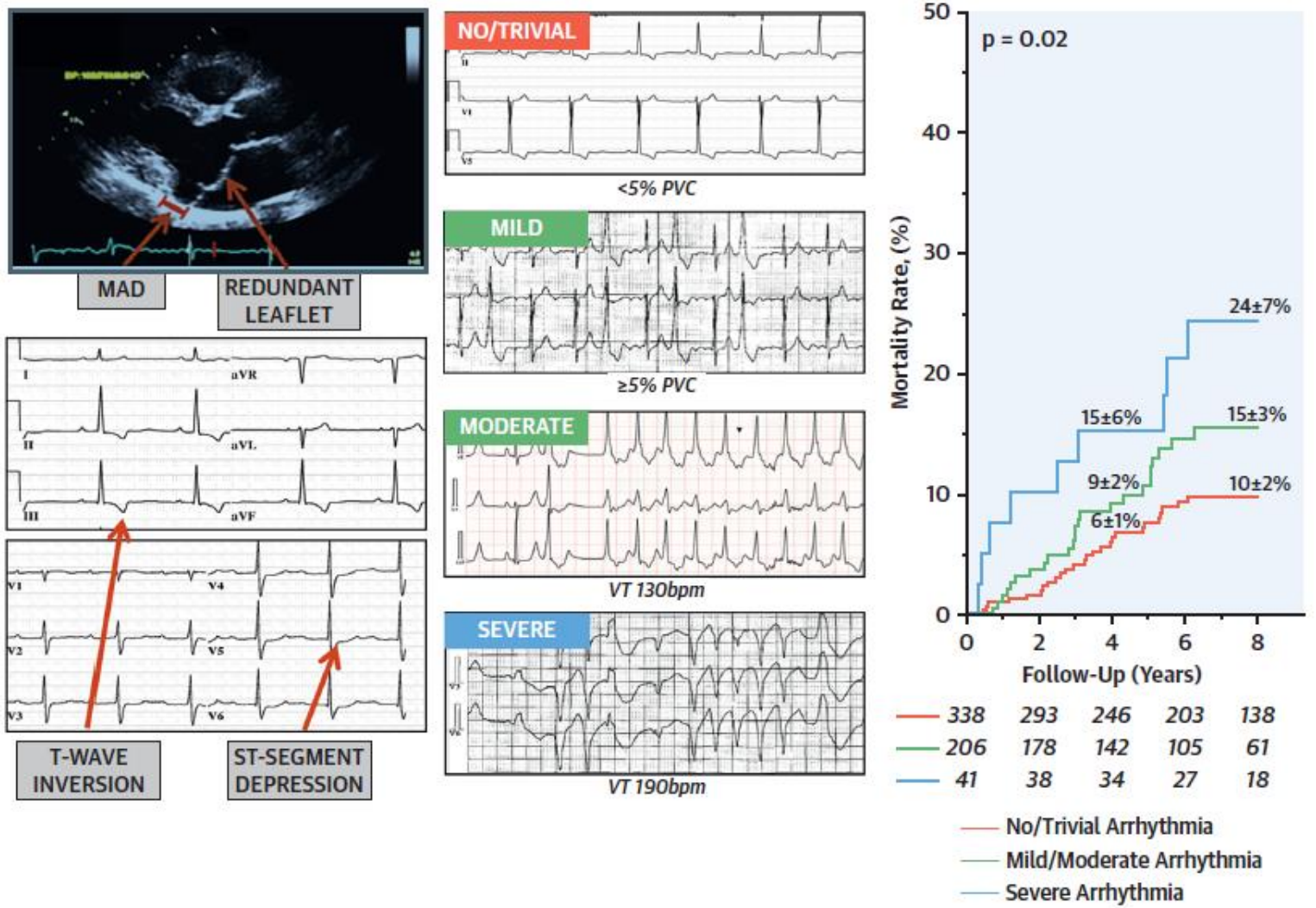
Garbi et al. OpenHeart 2018

Disease of the myocardium as well as of the valve



Daza et al. J Cardiovasc Magn Reson, 2021

Presentation and outcome of arrhythmic MVP



Essayagh […] Enriquez-Sarano, JACC 2020

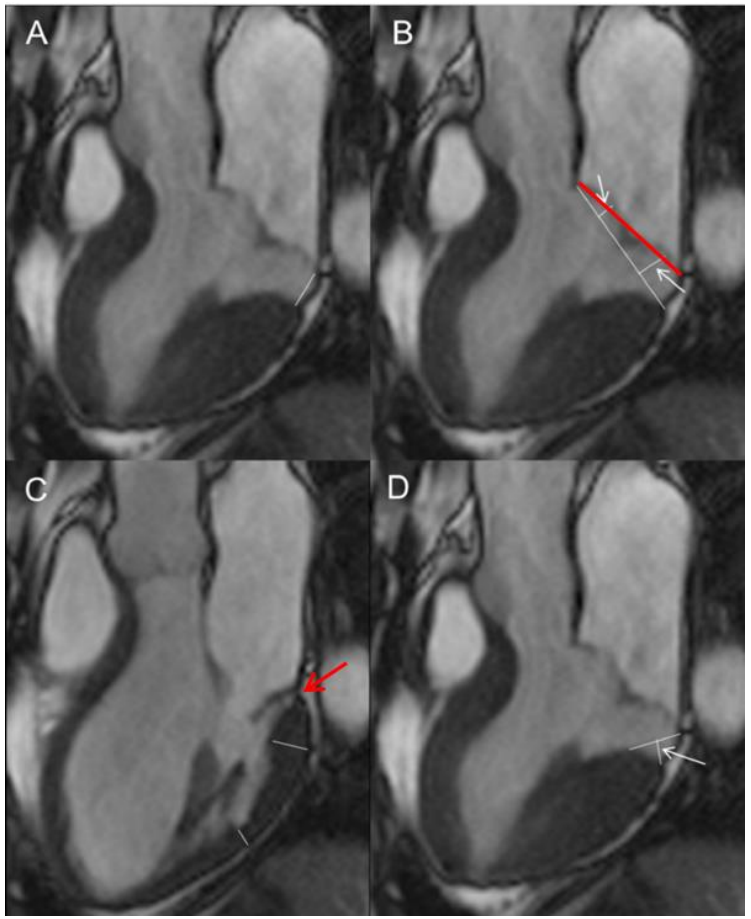
All roads lead to Rome

	Overall Population (N = 595)	No Arrhythmia (n = 338)	Ventricular Arrhythmia (n = 257)	p Value
Clinical characteristics				
Age, yrs	65 ± 16	63 ± 17	68 ± 15	0.0001
Female	278 (47)	178 (53)	100 (39)	0.0008
BMI, kg/m^2	25 ± 5	25 ± 5	26 ± 5	0.0008
HR, beats/min	68 ± 14	67 ± 14	68 ± 15	0.40
Atrial fibrillation	107 (18)	53 (16)	54 (21)	0.09
Hypertension	227 (38)	119 (35)	108 (42)	0.09
Diabetes	43 (7)	23 (7)	20 (8)	0.60
Dyslipidemia	242 (41)	133 (39)	109 (42)	0.50
CAD history	135 (23)	65 (19)	70 (27)	0.02
Congestive heart failure history	46 (8)	19 (6)	27 (11)	0.03
Charlson Index	0.84 ± 1.10	0.78 ± 1.06	0.92 ± 1.14	0.10
Symptoms				
Syncope history	66 (11)	43 (13)	23 (9)	0.10
Chest pain	110 (18)	69 (20)	41 (16)	0.20
Palpitation	213 (36)	122 (36)	91 (35)	0.90
Dyspnea	210 (35)	114 (34)	96 (37)	0.40
Edema	53 (9)	28 (8)	25 (10)	0.50
Echocardiographic variables				
Bileaflet	280 (47)	141 (42)	139 (55)	0.003
Posterior	232 (39)	139 (41)	93 (36)	0.03
Flail leaflet	60 (10)	30 (9)	30 (12)	0.30
* MAD	186 (31)	74 (21)	112 (44)	<0.0001
MAD length, mm	7.5 ± 2.8	6.6 ± 2.4	8.0 ± 3.0	0.001
Mitral leaflets length, mm				<0.0001
Anterior	22.7 ± 4.4	21.5 ± 4.0	24.1 ± 4.6	
Posterior	15.4 ± 4.2	14.1 ± 3.7	17.0 ± 4.1	
Mitral leaflets proximal thickness, mm				<0.0001
Anterior	2.3 ± 1.2	2.1 ± 0.7	2.6 ± 1.7	
Posterior	2.3 ± 0.9	2.1 ± 0.8	2.5 ± 1.0	
Mitral leaflet redundancy	283 (48)	132 (40)	151 (60)	<0.0001
LVEDD, mm	52 ± 7	50 ± 6	54 ± 7	<0.0001
Indexed LVEDD, mm/m^2	28 ± 4	27 ± 4	28 ± 4	0.005
LVESD, mm	33 ± 6	32 ± 5	35 ± 6	<0.0001
Indexed LVESD, mm/m^2	18 ± 3	17 ± 3	18 ± 3	0.004
LVEF	62 ± 7	63 ± 6	62 ± 8	0.03
LAVI, ml/m^2	44 ± 21	38 ± 17	52 ± 24	<0.0001
MR				<0.0001
No/trivial	215 (36)	159 (47)	56 (22)	
Mild	47 (8)	25 (7)	22 (9)	
Moderate	167 (28)	79 (23)	88 (34)	
Severe	166 (28)	75 (22)	91 (35)	

Garbi, Garweg
JACC, 2020

Why MAD obsession?

MAD presence & length was associated with arrhythmic MVP



Over-estimated
Over-reported
Over-measured

Mara et al. (Basso / Padova) Circulation-I, 2016

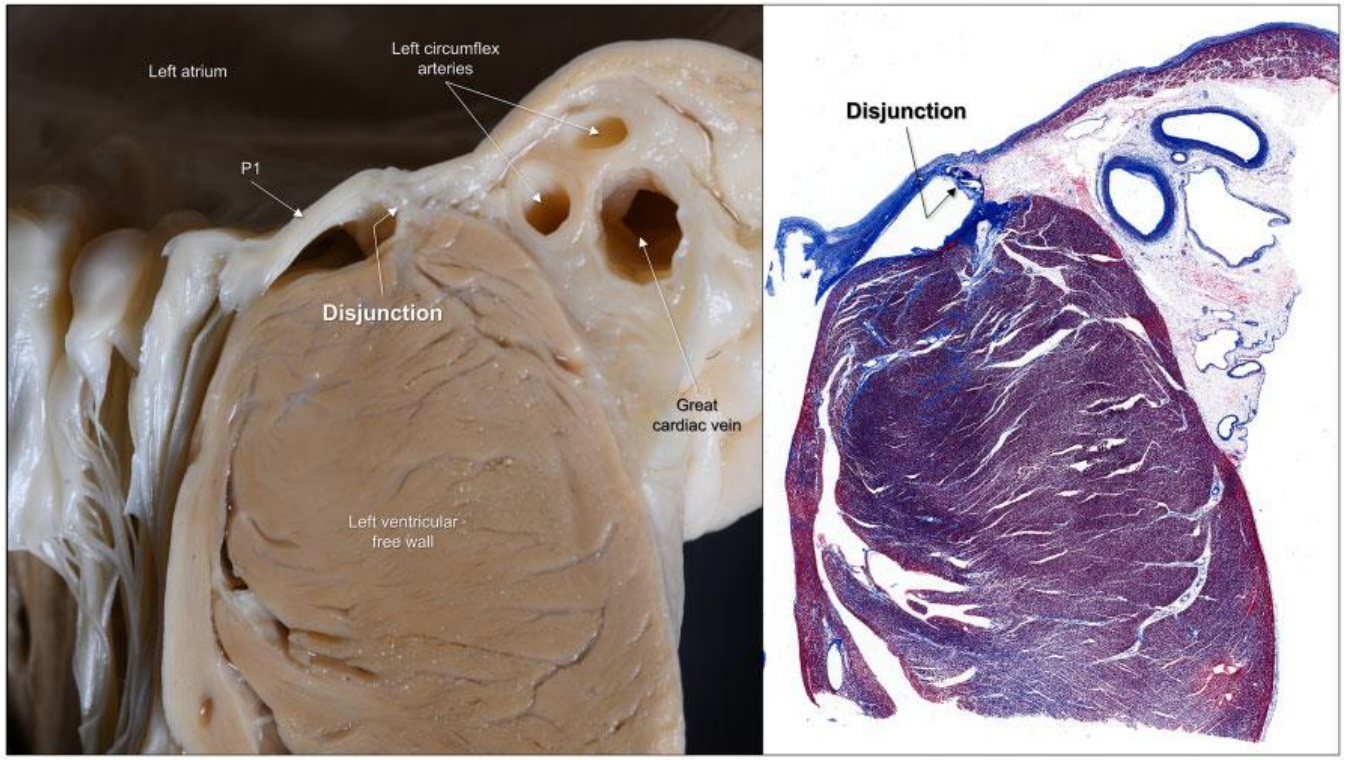
First described by **Henle** in **1876** on pathology studies

as a normal variant

Henle J. Handbuch der systematischen Anatomie des Menschen. 1876. Germany. p14–20.

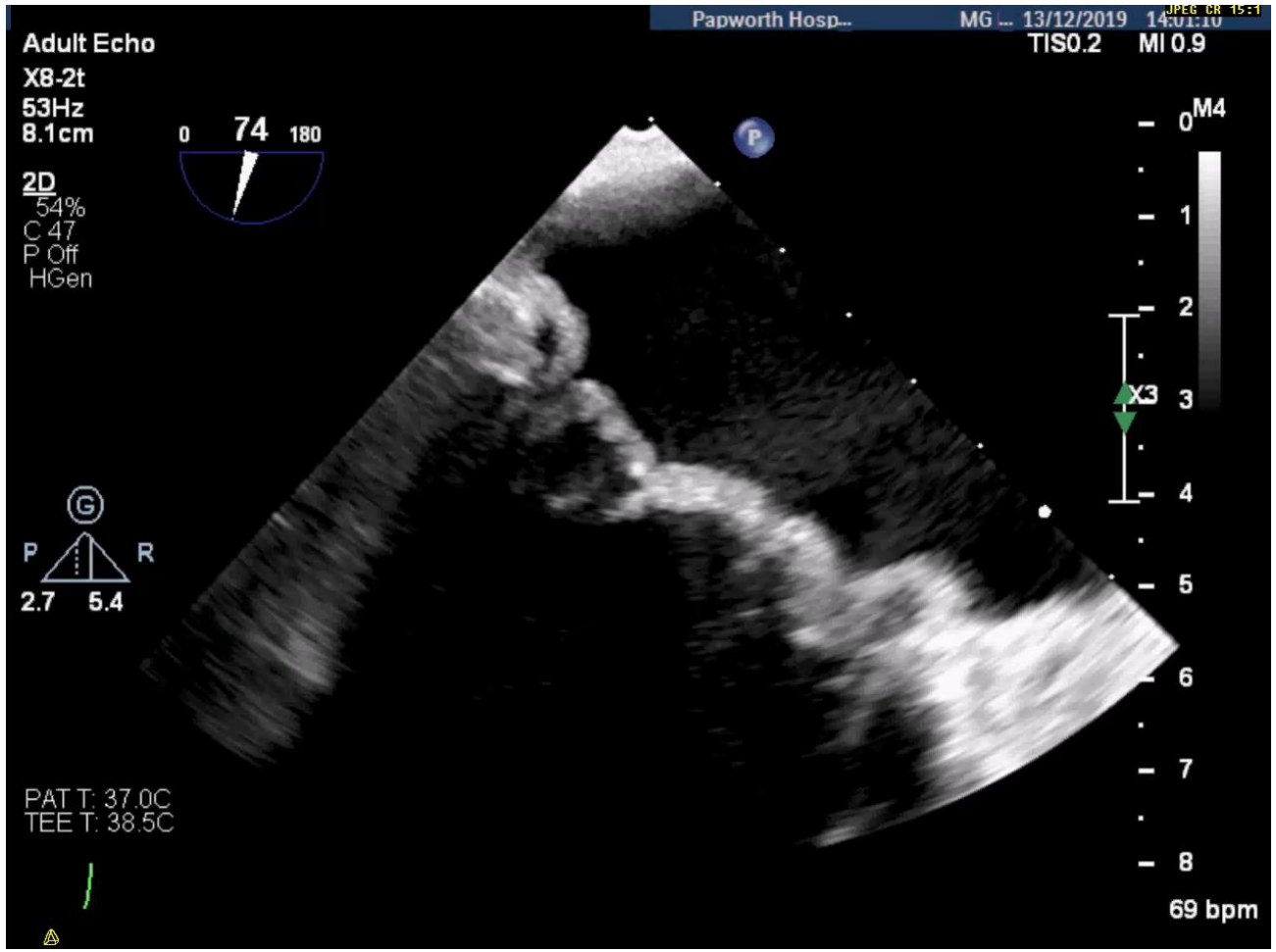
confirmed as normal variant by McAlpine (1975), Angelini (RH Anderson) (1988), Zimmerman (1966)

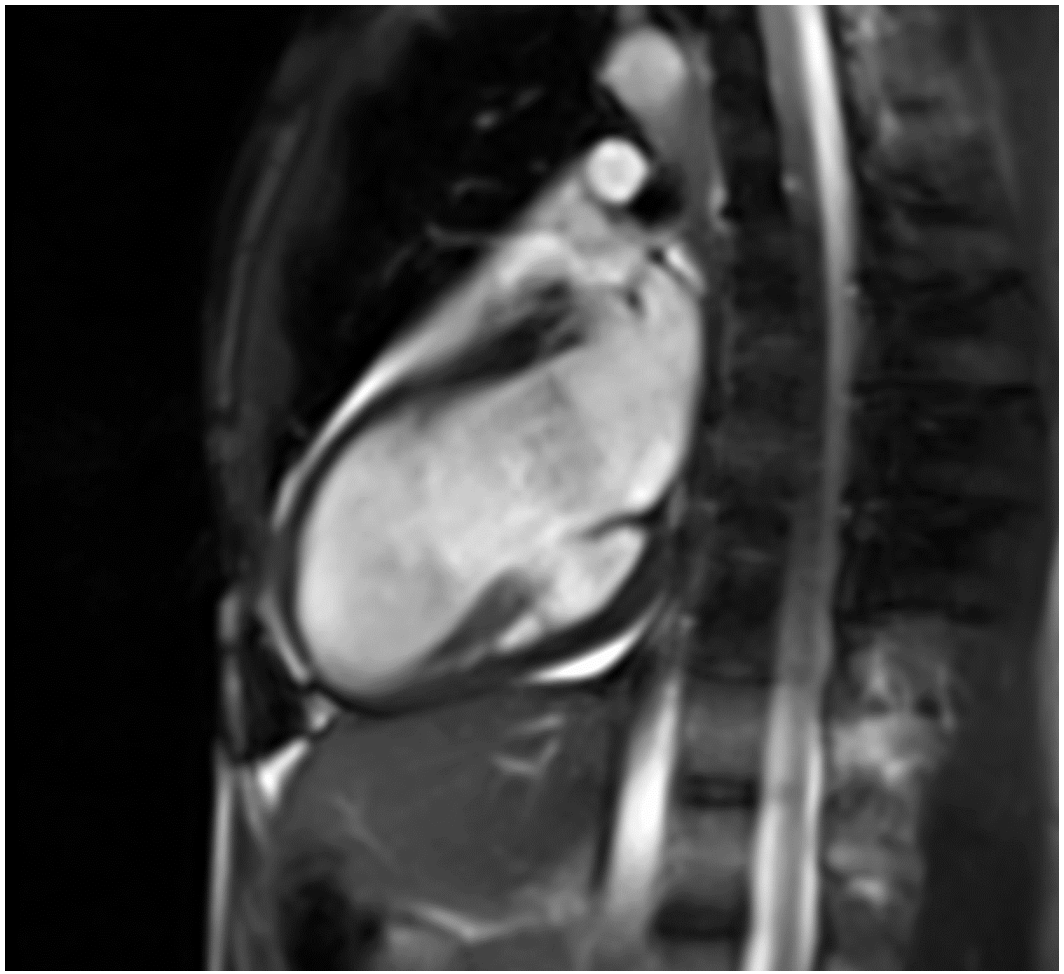
found to be more common and longer in patients with MVP by Hutchins on 900 cases pathology (NEJM,1986)



So, if it's a pathology finding, can we see it on imaging?

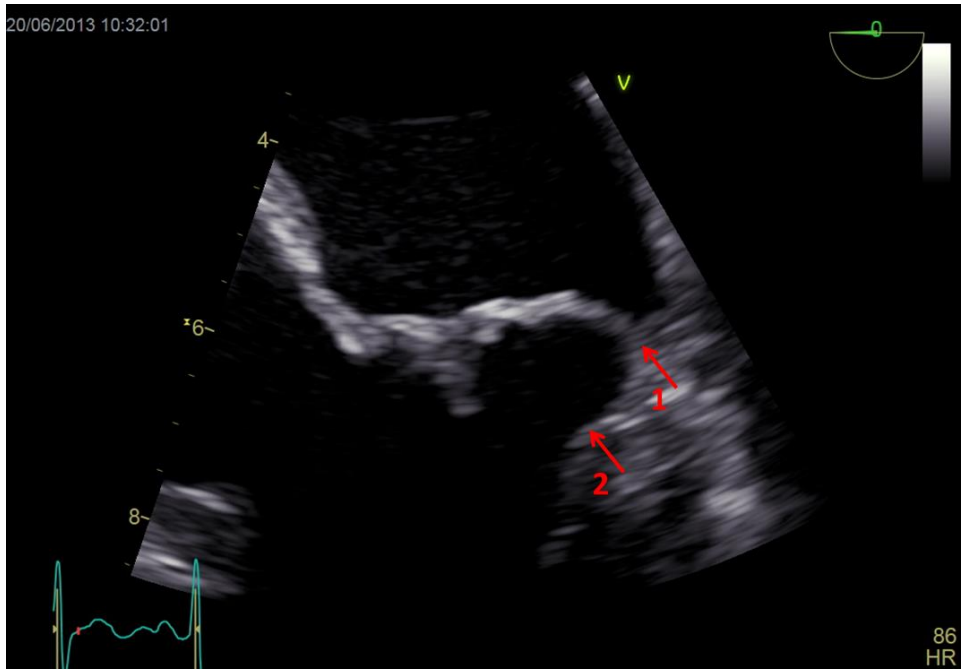
*What we see is **"leaflet atrialisation"** comprising prolapsing leaflet + MAD with limited spatial / temporal resolution & no tissue characterization ability*

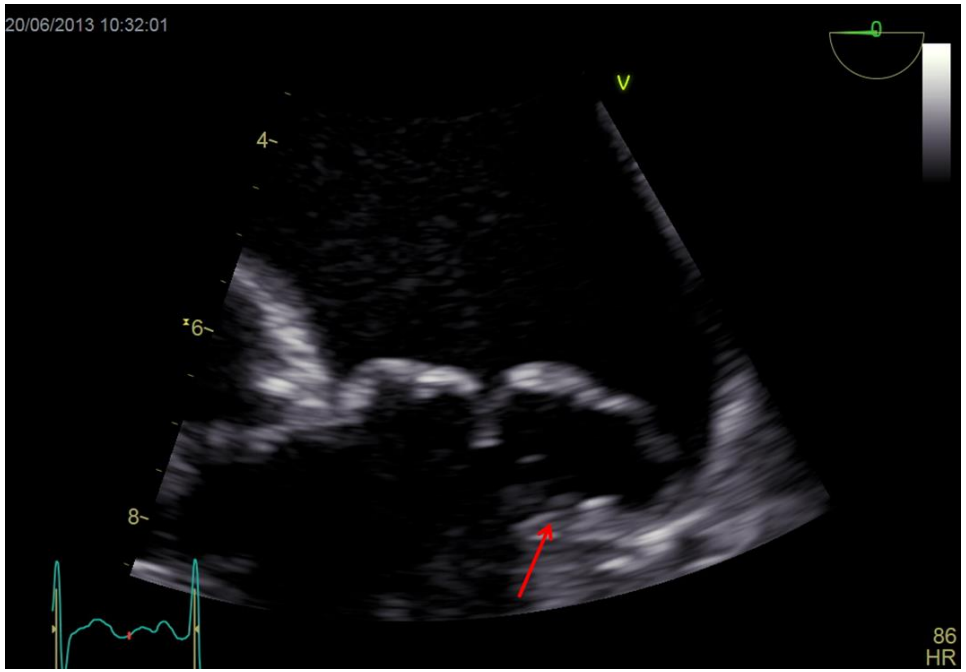




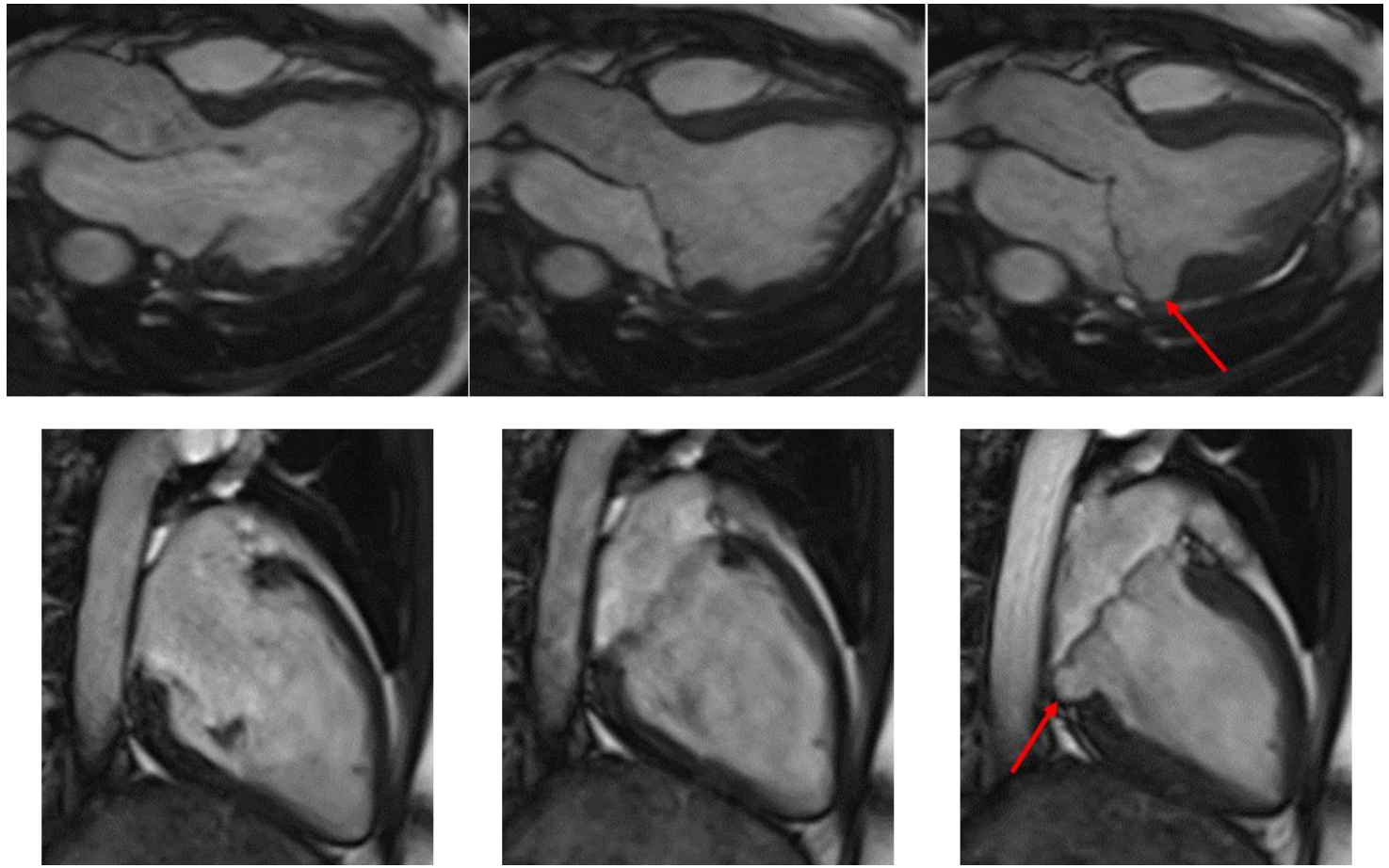
Can we measure **MAD** on imaging?

To measure MAD you have to be able to distinguish MAD from leaflet tissue





What is measured on imaging is “the size of the shadow”



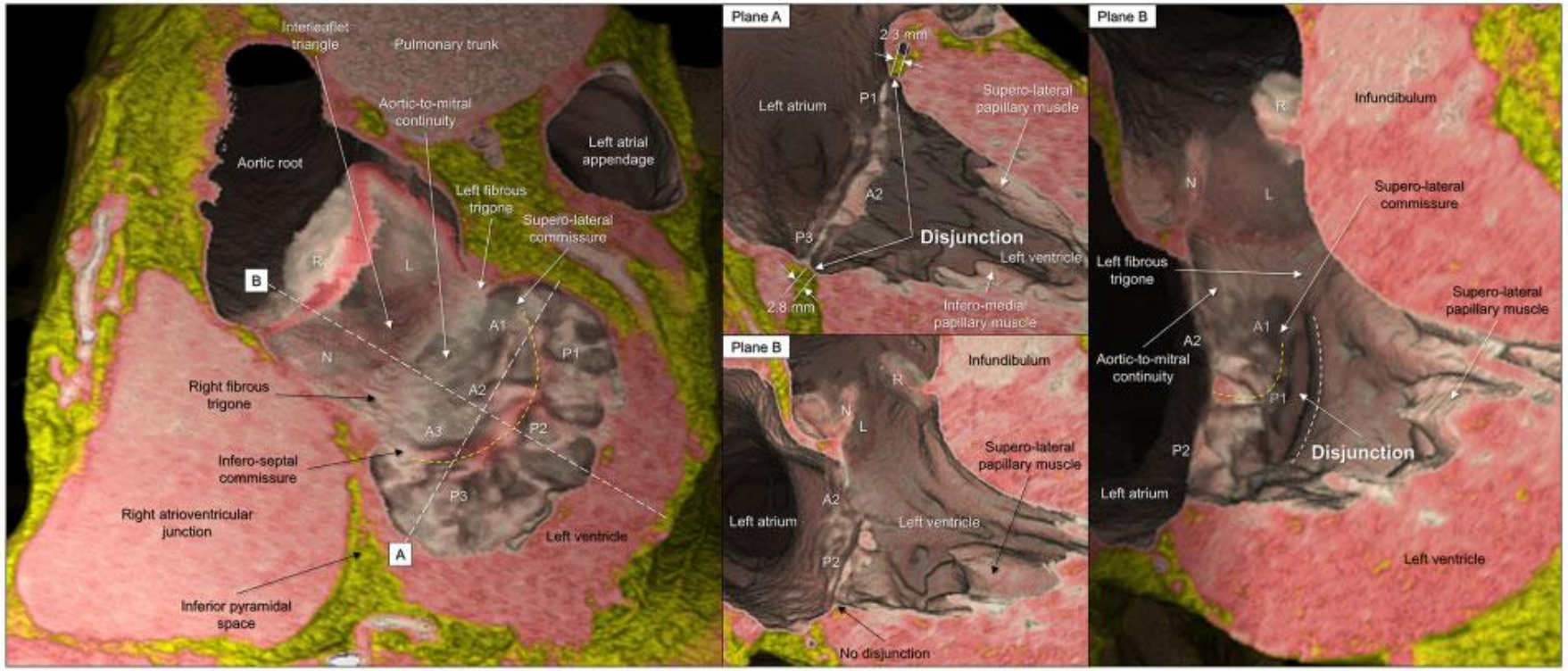
Garbi et al, Heart, 2020

And, regarding association with arrhythmia…

*MAD detection with newer imaging in **96%** of structurally normal hearts*

cardiac CT reconstruction – virtual dissection

An common feature cannot be a factor of risk



Toh, Shumpei Mori, et al, EHJ-CVI, 2021

Are all patients with degenerative MR arrhythmia / SCD the same ?

I. Severe MR, impaired LV, HF or comorbidities (*IHD)
II. No significant MR or comorbidities – true malignant potential