PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
Centro Congressi
di Confindustria
Auditorium
della Tecnica

9ª Edizione

30 Settembre
1 Ottobre
2022

Cardiomiopatia dilatativa non ischemica

ECG:MARKERS DIAGNOSTICI E PROGNOSTICI

Dott.ssa Crescenzi Cinzia
Policlinico Casilino Roma

Dilated Cardiomyopathy

- DCM is one of the most common cardiomyopathies; prevalence between **1:250 and 1:2500**
- Up to **50%** have a **positive familial history** and ca. **40%** have an **identifiable genetic cause**
- SCD may be the initial manifestation of DCM in previously asymptomatic individuals.
- The **'arrhythmogenic DCM' phenotype**, in overlaps with the current concept of arrhythmogenic cardiomyopathy, can occur in up to **one-third** of DCM patients
- The arrhythmic stratification in this population remains extremely challenging. Recent data suggest that **both genetic and cardiac magnetic resonance findings** can contribute to risk stratification

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ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1815

REVIEW

The electrocardiogram in the diagnosis and management of patients with dilated cardiomyopathy

Gherardo Finocchiaro[1]*, Marco Merlo[2], Nabeel Sheikh[1], Giulia De Angelis[2], Michael Papadakis[3], Iacopo Olivotto[4], Claudio Rapezzi[5,6], Gerald Carr-White[1], Sanjay Sharma[3], Luisa Mestroni[7], and Gianfranco Sinagra[2]

- ECG is rarely normal in DCM; ECG **abnormalities** reported in **more than 80% of cases**

- Historically, ECG in DCM has been considered *non-specific*. Advances **in *genotype-phenotype*-functional correlations** have improved understanding of **specific ECG patterns** typical of certain genetic or acquired forms of DCM

Table 1 Main electrocardiographic features in dilated cardiomyopathy

ECG feature	No.	Males (%)	Mean LVEF (%)	Prevalence (%)
LVH[a]				17–69
Roberts *et al.*, 1987[3]	152	72	–	39
Momiyama *et al.*, 1994[4]	45	–	–	69
Merlo *et al.*, 2019[5]	414	71	32	17
LA enlargement				17–51
Roberts *et al.*, 1987[3]	152	72	–	35
Wilensky *et al.*, 1988[6]	56	82	–	51
Kamiyama *et al.*, 1997[7]	41	71	–	51
Merlo *et al.*, 2019[5]	414	71	32	17
LBBB				23–28
Grimm *et al.*, 2003[8]	343	78	31	28
Merlo *et al.*, 2019[5]	414	71	32	23
Abnormal Q waves				26–36
Wilensky *et al.*, 1988[6]	56	82	–	36
Merlo *et al.*, 2019[5]	414	71	32	26
AF				3–25
Roberts *et al.*, 1987[3]	152	72	–	25
Wilensky *et al.*, 1988[6]	56	82	–	14
Aleksova *et al.*, 2010[9]	539	73	30	10
Merlo *et al.*, 2019[5]	414	71	32	3
First degree AV block				10–23
Hamby *et al.*, 1868[10]	60	–	–	18
Roberts *et al.*, 1987[3]	152	72	–	23
Merlo *et al.*, 2019[5]	414	71	32	10
Inferior T-wave inversion				
Merlo *et al.*, 2019[5]	414	71	32	14
Anterolateral T-wave inversion				
Merlo *et al.*, 2019[5]	414	71	32	13
RBBB				2–6
Roberts *et al.*, 1987[3]	152	72	–	6
Wilensky *et al.*, 1988[6]	56	82	–	6
Merlo *et al.*, 2019[5]	414	71	32	2
RA enlargement				3–6
Roberts *et al.*, 1987[3]	152	72	–	6
Wilensky *et al.*, 1988[6]	56	82	–	3
Merlo *et al.*, 2019[5]	414	71	32	4

AF, atrial fibrillation; AV, atrio-ventricular; LA, left atrial; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RA, right atrial; RBBB, right bundle branch block.
[a]Based on Sokolow–Lyon or Cornell voltage criteria.

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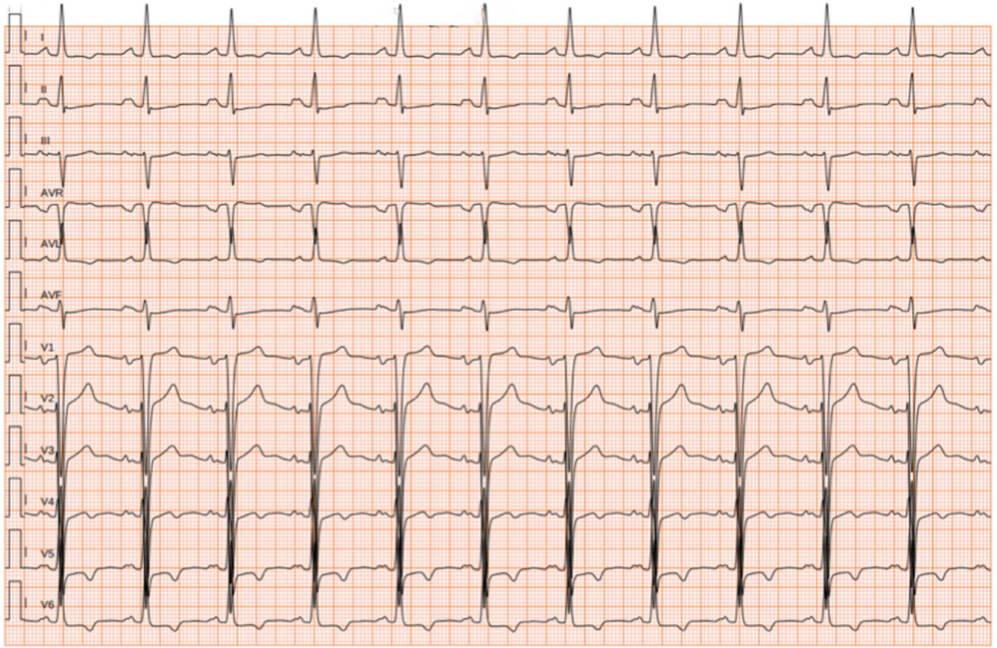
Left Ventricular Hypertrophy (LVH)



- **Sokolow-Lyon criteria**: R in V5 or V6 + S in V1 >35 mm
- **Cornell criteria**:
  - R in aVL and S in V3 >28 mm (men)
  - R in aVL and S in V3 >20 mm (women)

ECG feature	No.	Males (%)	Mean LVEF (%)	Prevalence (%)
LVH[a]				17–69
Roberts *et al.*, 1987[3]	152	72	–	39
Momiyama *et al.*, 1994[4]	45	–	–	69
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- LVH has been frequently described in pts with DCM
- Hypertensive aetiology should be excluded
- LVH in DCM could be expression of possibile hypertrophic cardiomyopathy discovered in dilatative-hypocinetic phase

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Left Ventricular Hypertrophy (LVH)

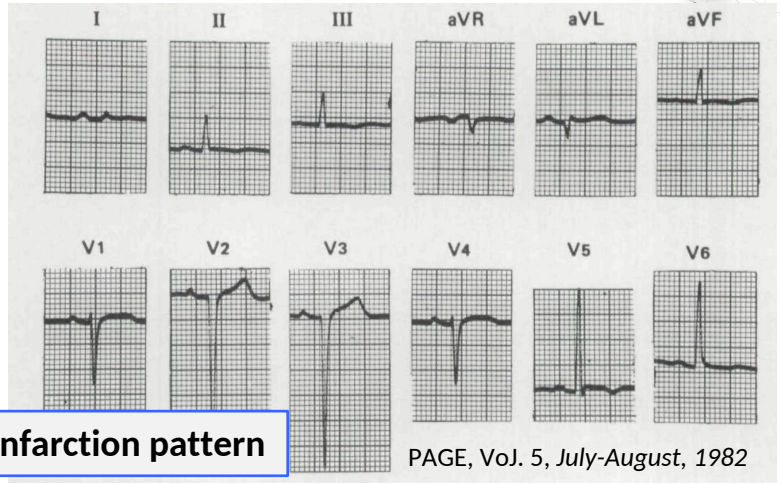
ELECTROCARDIOGRAPHY

Edited by S. Serge Barold

A Specific ECG Triad Associated with Congestive Heart Failure

ARY L. GOLDBERGER
From the Cardiology Division, Med
University of California, San Diego

- SV1 or SV2 + RV5 or RV6 ≥ 3.5 mV
- Total QRS amplitude in each of the limb leads ≤ 0.8 mV
- Poor precordial R wave progression (R/S ratio < 1 in V4)



Pseudo-infarction pattern

PAGE, VoJ. 5, *July-August, 1982*

Electrocardiographic Left Ventricular Hypertrophy Is Independently Associated With Better Long-Term Outcomes in Dilated Cardiomyopathy Patients

Circulation Reports
Circ Rep 2019; **1**: 248–254
doi:10.1253/circrep.CR-19-0025

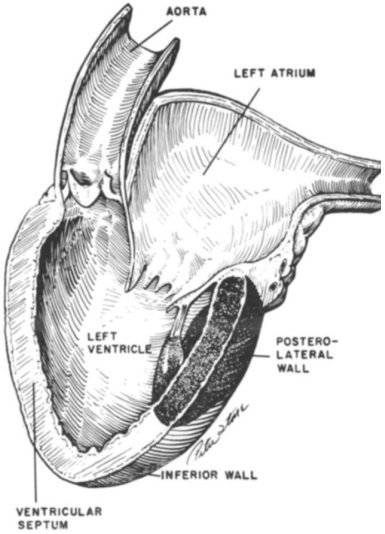
Shouji Matsushima, MD, PhD; Hidetaka Kaku, MD; Nobuyuki Enzan, MD; Tomomi Ide, MD, PhD; Taiki Higo, MD; Miyuki Tsuchihashi-Makaya, PhD; Hiroyuki Tsutsui, MD, PhD

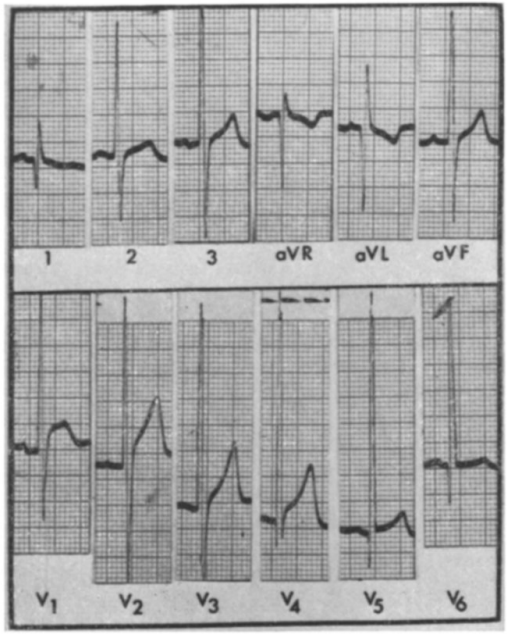
Q Waves

The Distinctive Electrocardiogram of Duchenne's Progressive Muscular Dystrophy*

An Electrocardiographic-Pathologic Correlative Study

Perloff et al American Journal of Medicine 1967





ECG feature	No.	Males (%)	Mean LVEF (%)	Prevalence (%)
Abnormal Q waves				26–36
Wilensky *et al.*, 1988[6]	56	82	–	36
Merlo *et al.*, 2019[5]	414	71	32	26

- **Pathological** Q-wave: **duration ≥40 ms** or an absolute **depth of >3 mm** or an **amplitude ≥25% of the ensuing R wave**.
- Abnormal Q waves have been described in the anterior, lateral and inferior leads ranging from 7% to 36% in DCM
- **Inferolateral Q waves** should raise **suspicion of muscular dystrophy (13%** of pts with **DMD)**

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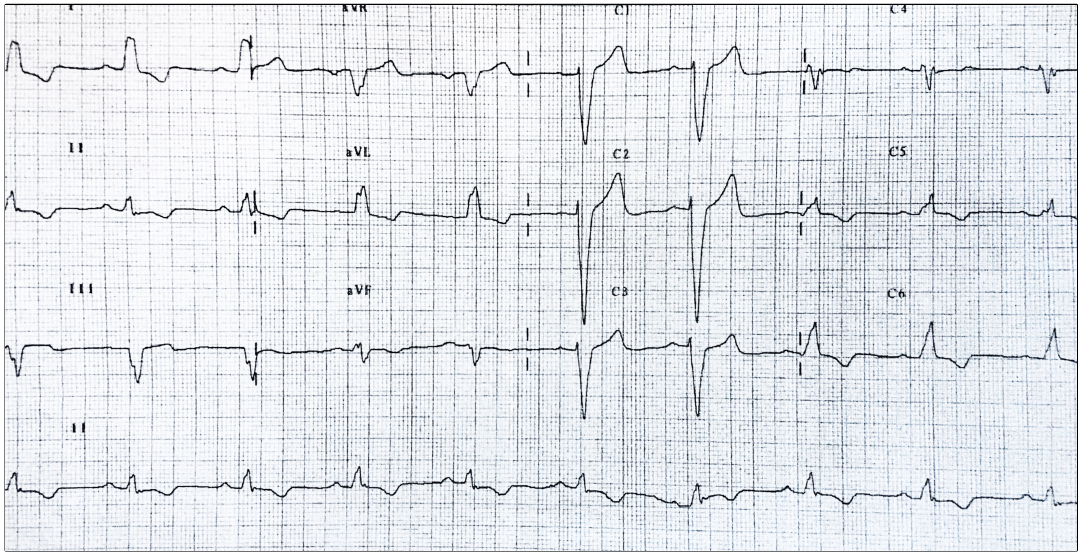
Left Bundle Branch Block (LBBB)



True BBS: QRS duration ≥140 ms (130 ms in women)
QS or rS pattern in V1-V2 and mid-QRS notching or slurring in ≥2 of leads V1, V2, V5, V6, I, aVL.

ECG feature	No.	Males (%)	Mean LVEF (%)	Prevalence (%)
LBBB				23–28
Grimm *et al.*, 2003[8]	343	78	31	28
Merlo *et al.*, 2019[5]	414	71	32	23

- LBBB is considered **the most common** characteristics in DCM (≈one third of pts with DCM)
- LBBB **may precede** the development of structural changes in the heart
- **The new onset of LBBB** is significantly related to **prognosis** in pts with DCM

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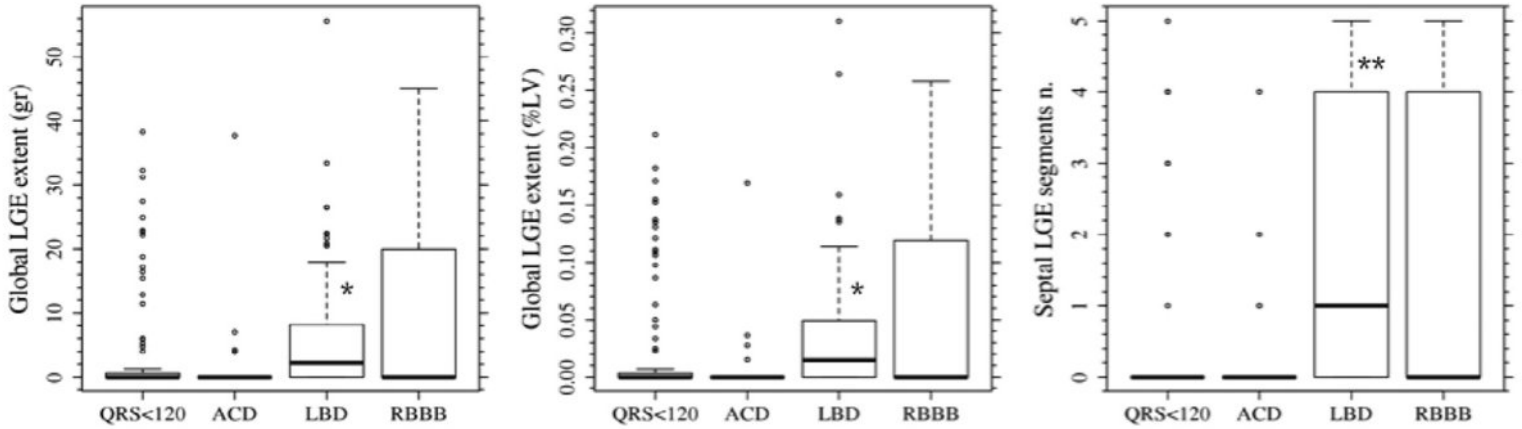
Left Bundle Branch Block (LBBB)

Magnetic Resonance Imaging Correlates of Left Bundle Branch Disease in Patients With Nonischemic Cardiomyopathy

Chrysanthos Grigoratos, MD[a,b,*], Riccardo Liga, MD[c], Elena Bennati, MD[d], Andrea Barison, MD[a,b], Giancarlo Todiere, MD[a], Giovanni Donato Aquaro, MD[a], Matteo Dell'Omodarme, MD[e], Michele Emdin, MD[a,b], and Pier Giorgio Masci, MD[f]

LBBB could be the expression of **septal fibrosis ...**



**p < 0.005
**p < 0.001

ACD = aspecific conduction defect;
LBD = left bundle disease (EAS or LBBB)
RBBB = Right bundle branch block

Am J Cardiol 2018;121:370–376

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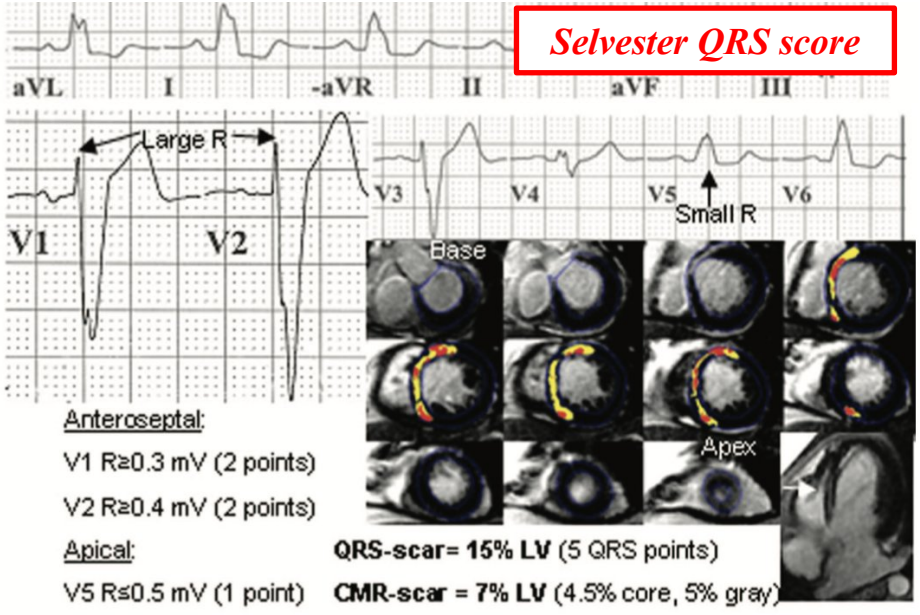
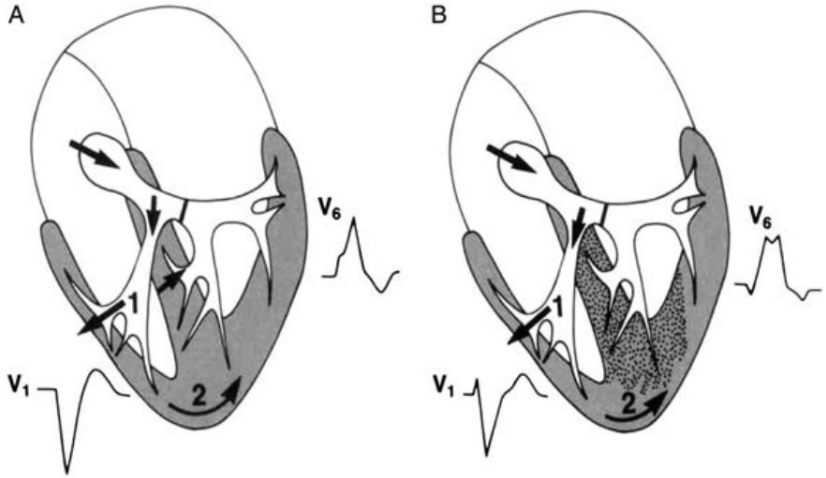
Left Bundle Branch Block (LBBB)

ECG Quantification of Myocardial Scar in Cardiomyopathy Patients With or Without Conduction Defects

Correlation With Cardiac Magnetic Resonance and Arrhythmogenesis

David G. Strauss, BA; Ronald H. Selvester, MD; João A.C. Lima, MD; Håkan Arheden, MD, PhD; Julie M. Miller, MD; Gary Gerstenblith, MD; Eduardo Marbán, MD, PhD; Robert G. Weiss, MD; Gordon F. Tomaselli, MD; Galen S. Wagner, MD; Katherine C. Wu, MD





Wellens HJ, Europace 2012; 14: 619-620

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QRS duration

European Heart Journal (2009) 30, 2011–2018
doi:10.1093/eurheartj/ehp293

CLINICAL RESEARCH
Heart failure/cardiomyopathy

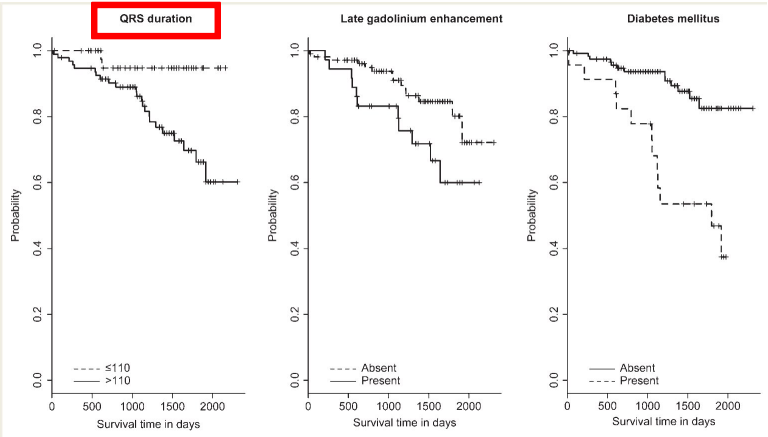
Electrocardiographic and cardiac magnetic resonance imaging parameters as predictors of a worse outcome in patients with idiopathic dilated cardiomyopathy

Vinzenz Hombach[1]*, Nico Merkle[1], Jan Torzewski[1], Johann M. Kraus[2], Markus Kunze[1], Oliver Zimmermann[1], Hans A. Kestler[2†], and Jochen Wöhrle[1†]

- **Prognostic value of clinical, ECG (QRS and QTc) and CMR** findings of 141 pts with idiopathic DCM
- The primary endpoint: **cardiac death or sudden death** in 25 (**18%**)
- **LGE** in 36 (**26%**). Pts with **LGE** had more often a **QRS >110 ms** than pts without LGE (80.6 vs. 61.9%, **P = 0.034**)

Table 3 Univariate and multivariable analyses for predictors of primary endpoint

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Diabetes	4.38 (1.98–9.66)	<0.001	3.19 (1.40–7.29)	0.006
QRS >110 ms	5.43 (1.28–23.1)	0.022	4.64 (1.04–20.78)	0.045
QTc >440 ms	1.57 (0.71–3.5)	0.261		
LVEDVI	1.00 (1.00–1.01)	0.238		
RVEDVI	1.01 (1.00–1.02)	0.003	1.01 (1.00–1.02)	0.006
CI	0.45 (0.25–0.83)	0.010	0.35 (0.19–0.65)	<0.001
LVEF	0.95 (0.92–0.99)	0.013		
RVEF	0.97 (0.95–0.99)	0.022		
LGE	2.26 (1.03–4.99)	0.043		



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QRS fragmentation (1)

Fragmented QRS Is Associated with All-Cause Mortality and Ventricular Arrhythmias in Patient with Idiopathic Dilated Cardiomyopathy *Ann Noninvasive Electrocardiol 2011*

Jing Sha, Ph.D., Shu Zhang, M.D., Min Tang, M.D., Keping Chen, M.D., Xinran Zhao, M.D., and Fangzheng Wang, M.D.

Prognostic implications of fragmented QRS and its relationship with delayed contrast-enhanced cardiovascular magnetic resonance imaging in patients with non-ischemic dilated cardiomyopathy *Int J Cardiol 2013 Aug 20;167(4):1417-22*

Min-Soo Ahn [a], Jin-Bae Kim [b,*], Boyoung Joung [c], Moon-Hyoung Lee [c], Sung-Soon Kim [c]

Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy *Heart Rhythm 2010 Jan;7(1):74-80*

Mithilesh Kumar Das, MD, Waddah Maskoun, MD, Changyu Shen, PhD,* Mark A. Michael, MD, Hussam Suradi, MD, Mona Desai, BS, Roopa Subbarao, MD, Deepak Bhakta, MD

QRS fragmentation (2)

Europace (2012) 14, 1180–1187
doi:10.1093/europace/eur437

CLINICAL RESEARCH
Electrocardiology and Risk Stratification

The J wave and fragmented QRS complexes in inferior leads associated with sudden cardiac death in patients with chronic heart failure

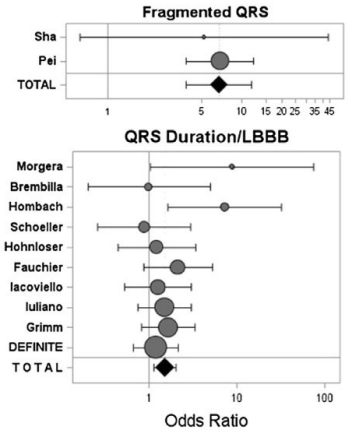
Juanhui Pei[1], Ning Li[1], Yonghong Gao[2], Zengwu Wang[1], Xian Li[1], Yinhui Zhang[1], Jingzhou Chen[1], Ping Zhang[3†], Kejiang Cao[4†], and Jielin Pu[1*]

1570 CHF patients, 572 DCM and 998 ICM

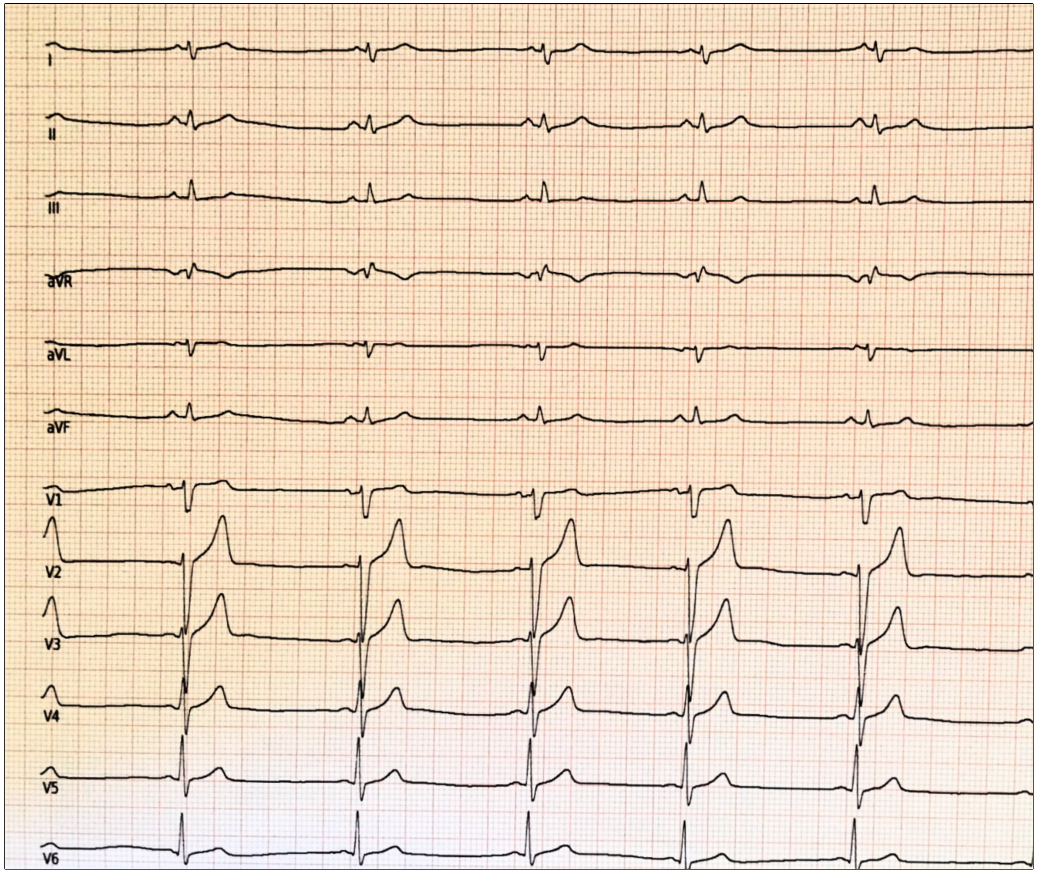
Presence of **J wave or fQRS in the Inferior leads** predicted a **higher risk for SCD in DCM** [HR 4.095; 95% CI 2.132–7.863]

Sudden Cardiac Death Risk Stratification in Patients With Nonischemic Dilated Cardiomyopathy

Jeffrey J. Goldberger, MD, MBA,* Haris Subačius, MA,* Taral Patel, MD,* Ryan Cunnane, MD,† Alan H. Kadish, MD‡



Low QRS voltages



Definited as QRS complexes with a **peak-to-peak amplitude <0.5 mV in all peripheral leads**.

LQRSV may be observed in pts with conditions that lead to a diseases characterized by loss of myocytes with replacement fibrosis (ACM, cardiac sarcoidosis, healed myocarditis, or idiopathic NILVS).

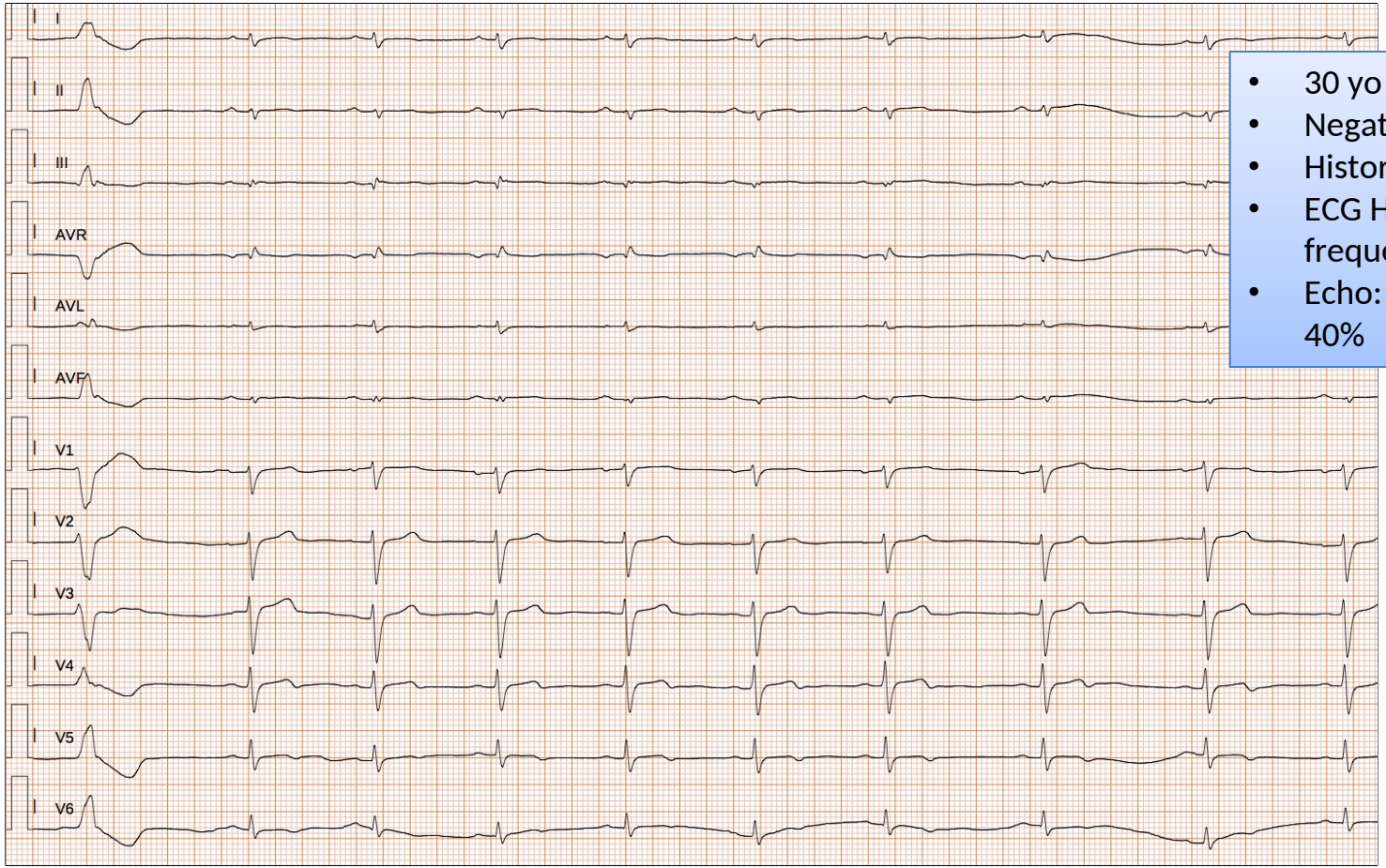
Low QRS voltages are characteristic of ***FLNC***, ***PLN*** **and** ***DSP*** and may precede any echocardiographic changes

Low QRS voltages

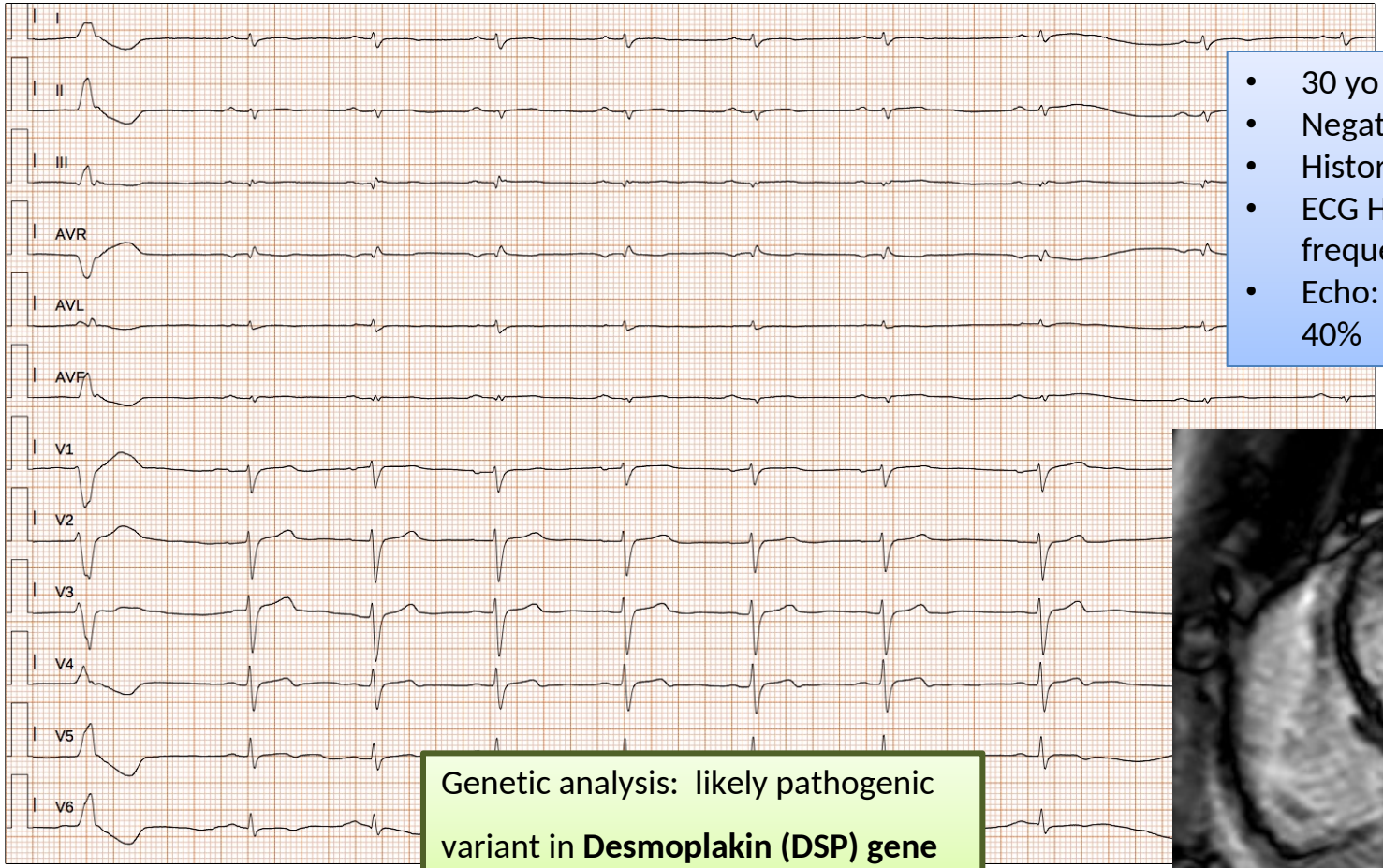
Arrhythmogenic Right Ventricular Cardiomyopathy: Characterization of Left Ventricular Phenotype and Differential Diagnosis With Dilated Cardiomyopathy

Cipriani et al, JAHA 2020; 9:e014628

	ARVC-LV Phenotype n=41	DCM-LV Phenotype n=69	*P* Value
Electrocardiographic characteristics			
First degree atrioventricular block	5 (12)	11 (16)	0.590
Complete left bundle branch block	0	19 (28)	<0.001
Sokolow-Lyon Index	1 (2)	14 (20)	0.005
Left axis deviation	7 (17)	26 (38)	0.023
Left anterior fascicular block	5 (12)	14 (20)	0.277
Left atrial enlargement	6 (15)	30 (43)	0.002
Strain pattern	1 (2)	12 (17)	0.029
Low (<0.5 mV) QRS voltages in limb leads	24 (59)	3 (4)	<0.001
TWI in anterolateral leads (V1–V6)	11 (27)	10/50 (20)*	0.442
TWI in lateral leads (V5–V6±V4, I, aVL)	20 (49)	25/50 (50)*	0.908
TWI in inferolateral leads (II, III, aVF+[V5–V6±V4 or I, aVL])	13 (32)	3/50 (6)*	0.001



- 30 yo man
- Negative familiar history
- History of myocarditis
- ECG Holter monitoring: frequent PVBs, NSVT
- Echo: LV dilation, LVEF 40%



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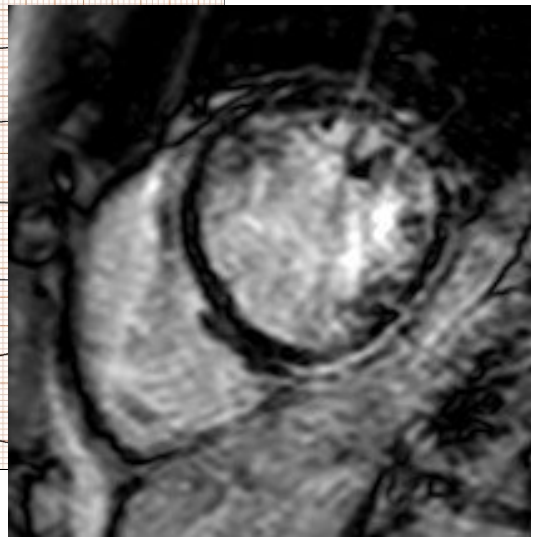

Genetic analysis: likely pathogenic variant in **Desmoplakin (DSP) gene**

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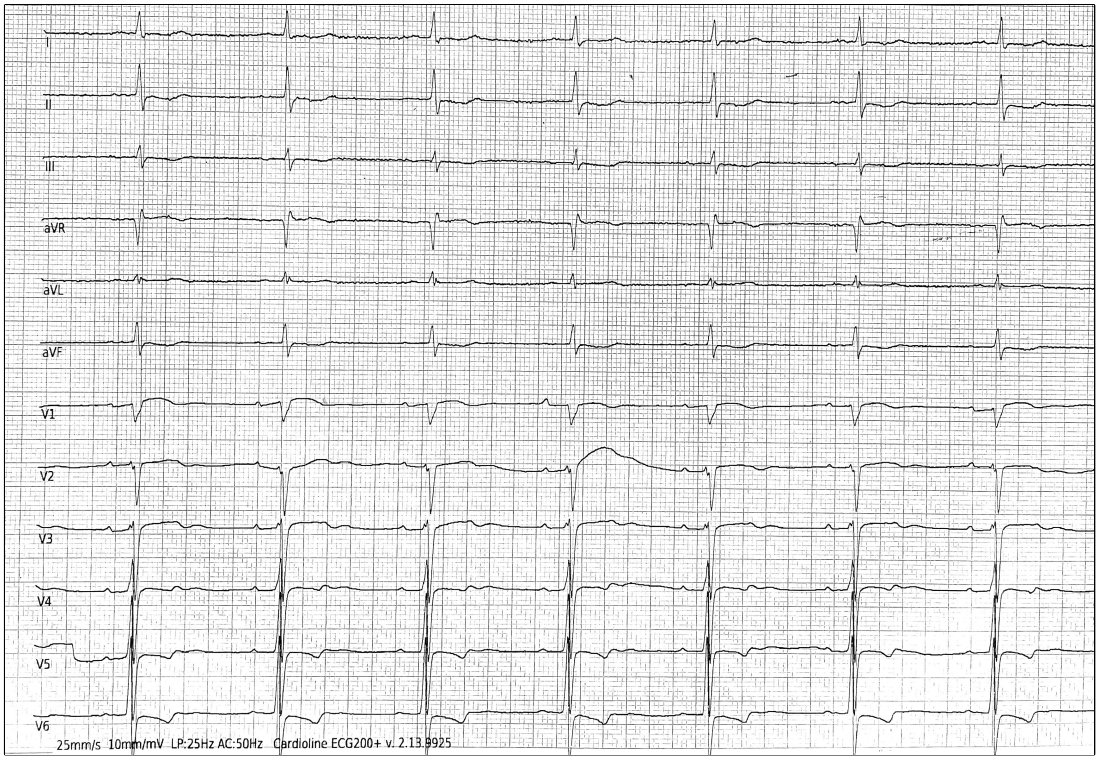
T wave inversion (TWI)



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Inferior T-wave inversion				
Merlo *et al.*, 2019[5]	414	71	32	14
Anterolateral T-wave inversion				
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- Common detected in pts with DCM
- Possible overlap with Arrhythmogenic Cardiomyopathy
- TWI could be found in ***FLNC* and *DSP* genotypes** (especially in **lateral leads**)

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Atrial Fibrillation (AF)

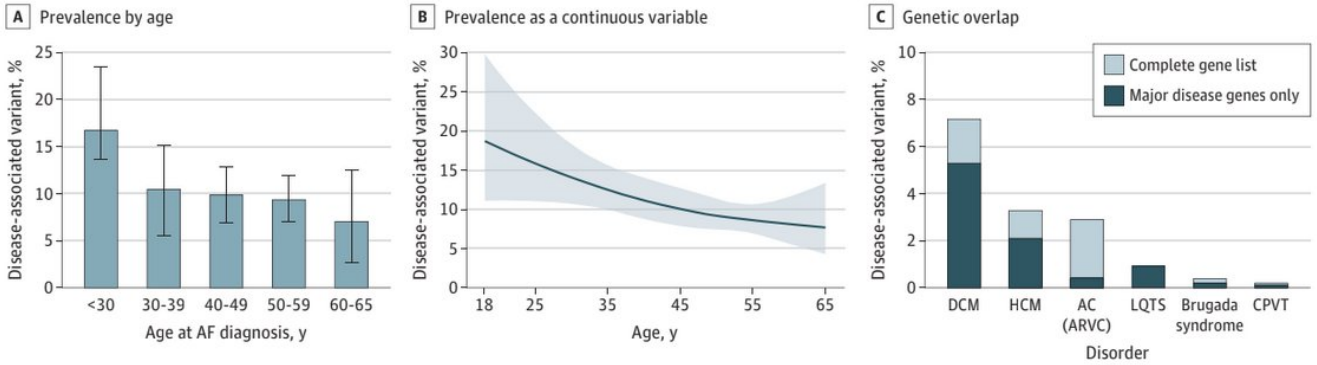
JAMA Cardiology | Original Investigation

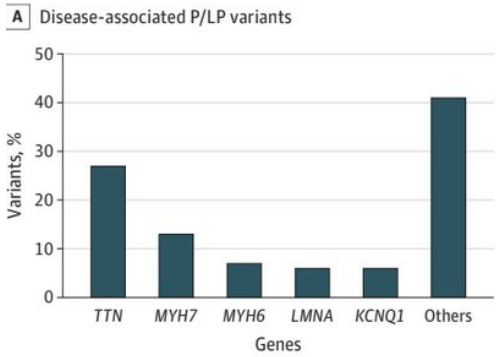
Early-Onset Atrial Fibrillation and the Prevalence of Rare Variants in Cardiomyopathy and Arrhythmia Genes

Zachary T. Yoneda, MD, MSCI; Katherine C. Anderson, MS, CSG; Joseph A. Quintana, MD; Matthew J. O'Neill, BS; Richard A. Sims, MD; Andrew M. Glazer, PhD; Christian M. Shaffer, BS; Diane M. Crawford, RN; Thomas Stricker, MD, PhD; Fei Ye, PhD; Quinn Wells, MD, MSCI; Lynne W. Stevenson, MD; Gregory F. Michaud, MD; Dawood Darbar, MBChB, MD; Steven A. Lubitz, MD, MPH; Patrick T. Ellinor, MD, PhD; Dan M. Roden, MD; M. Benjamin Shoemaker, MD, MSCI

- Prospective, observational cohort study;
- 1293 Pts with AF diagnosed **before 66 yo** that underwent whole genome sequencing;
- 934 [72.2%] male; median age at AF diagnosis, 50 [41-56] yo;
- 131 participants (**10.1%**) with a **disease-associated variant**

Figure 3. Prevalence of Disease-Associated Variants and Genetic Overlap With Inherited Cardiomyopathy and Arrhythmia Syndromes





JAMA Cardiol. 2021;6(12):1371-1379.

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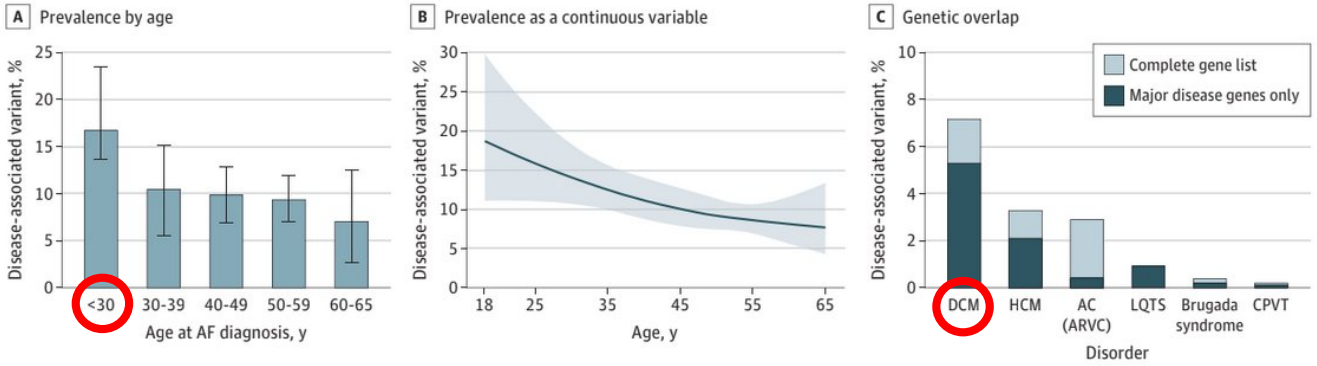

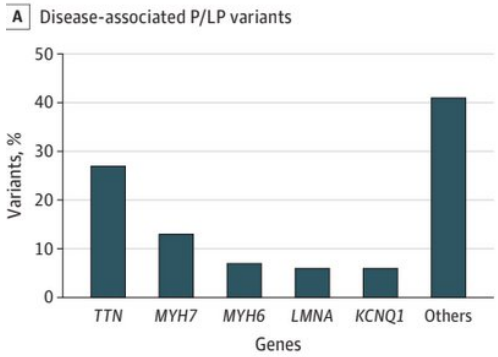

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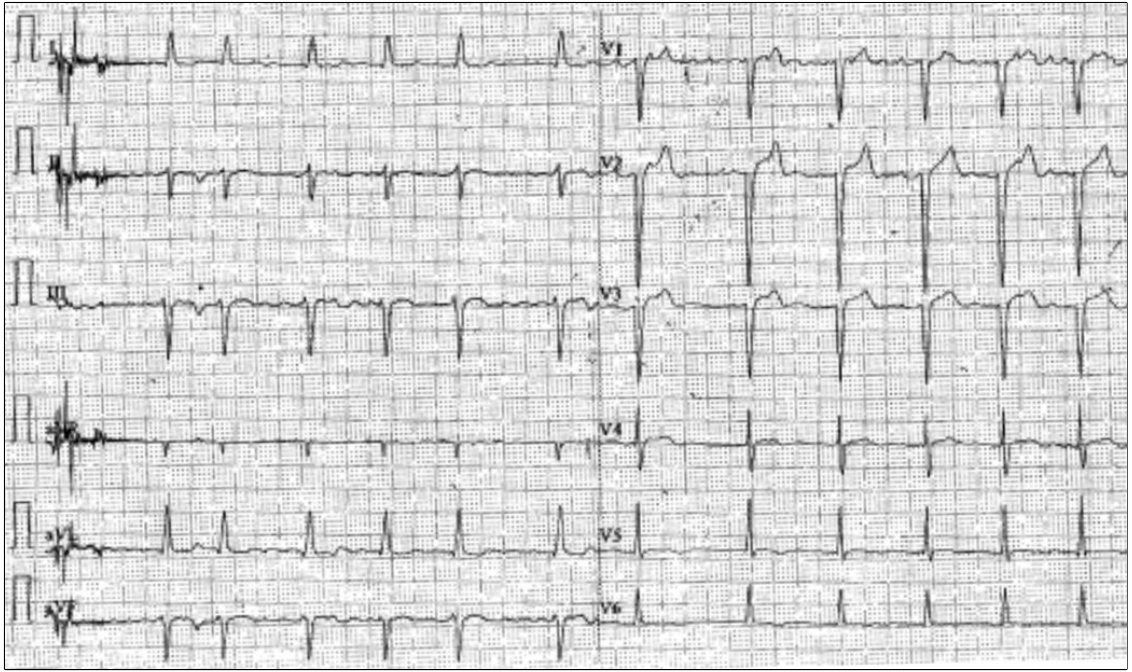
Atrial Fibrillation (AF)



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Merlo *et al.*, 2019[5]	414	71	32	3

- **Early onset** of AF in young individuals, may suggest genetic origin (LMNA, TTN, SCN5A, DES)
- Atrial fibrillation **negatively impacts** the prognosis of pts with DCM

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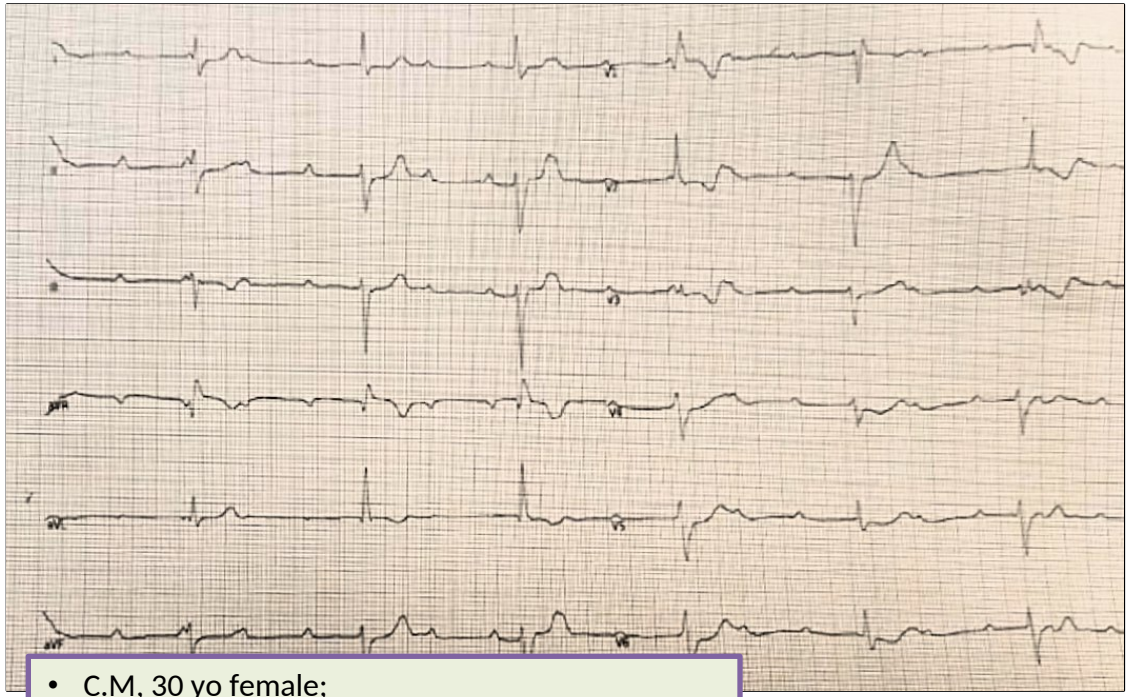
Atrio-Ventricular Block



- C.M, 30 yo female;
- Familiar history of hypertension and AF
- Negative medical history
- Symptomless
- Medical visit to obtain the certificate of eligibility to practice sports.

ECG feature	No.	Males (%)	Mean LVEF (%)	Prevalence (%)
First degree AV block				10–23
Hamby *et al.*, 1868[10]	60	–	–	18
Roberts *et al.*, 1987[3]	152	72	–	23
Merlo *et al.*, 2019[5]	414	71	32	10

- Atrioventricular conduction abnormalities in young pts could be sign of genetic disease **(neuromuscular diseases, LMNA, DES, ion channel disorders like SCN5A)**
- or non genetic disease (**cardiac sarcoidosis, myocarditis due to Lyme disease, Chagas disease**)

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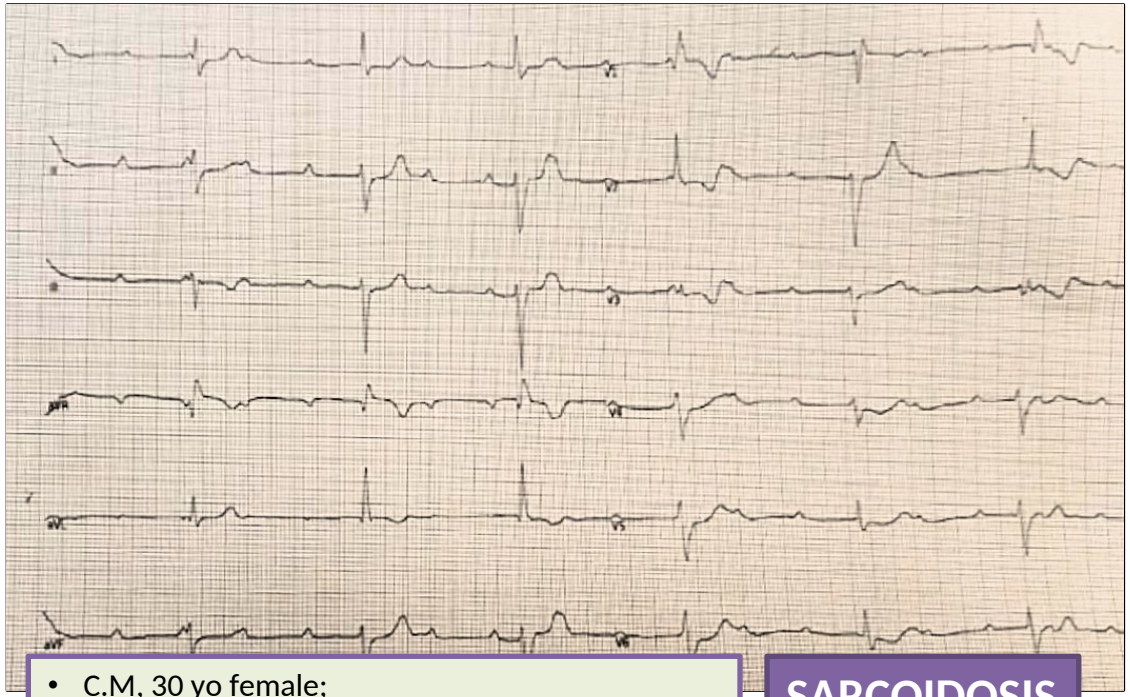

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SARCOIDOSIS

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ECG in dilated cardiomyopathy: specific findings and long-term prognostic significance

Marco Merlo[a], Denise Zaffalon[a], Davide Stolfo[a], Alessandro Altinier[a], Giulia Barbati[b], Massimo Zecchin[a], Stefano Bardari[a] and Gianfranco Sinagra[a]

I.F.C. Italian Federation of Cardiology

414 pts with DCM (mean age 45 yo, 71% male).

The study outcome measures were ***death or heart transplant (D/HT)*** and **sudden death or malignant ventricular arrhythmias (SD/MVA)**. Median follow up 125 months (IQR 77 – 216)

7% *LBBB*, 17% *LVH* according Sokolow – Lyon; ≈6% *inferior Q waves*, ≈6% *lateral Q waves*
13% *anterolateral T-waves inversion*.

Low QRS voltages in 6%, *fragmented QRS* in more than 20% of patients.

10.6% normal ECG.

J Cardiovasc Med 2019, 20:450–458

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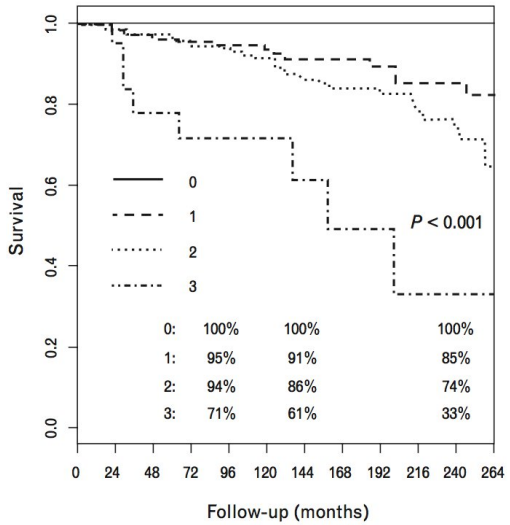

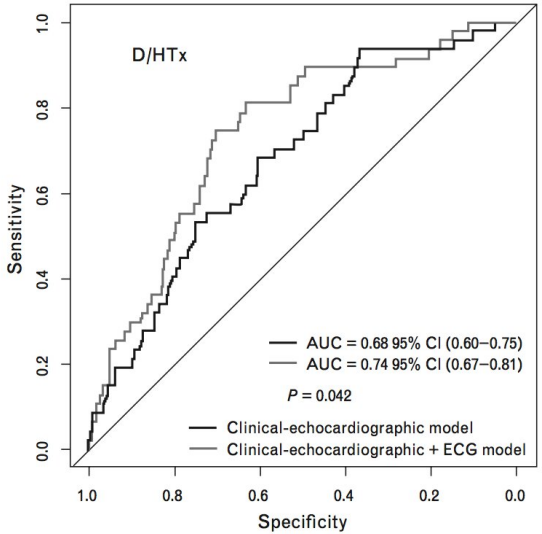

13% of pts **D/HT** at multivariate analisis:

- Heart rate [1.025; 95% CI 1.07 – 1.042; P =0.005]
- **Inverted T-waves in anterolateral leads** (HR 1.976; 95% CI 1.029 – 3.796; P = 0.041)

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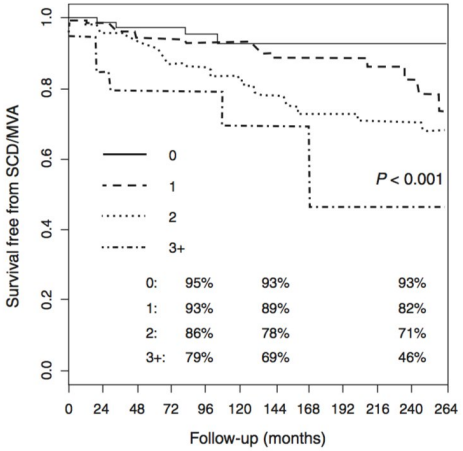
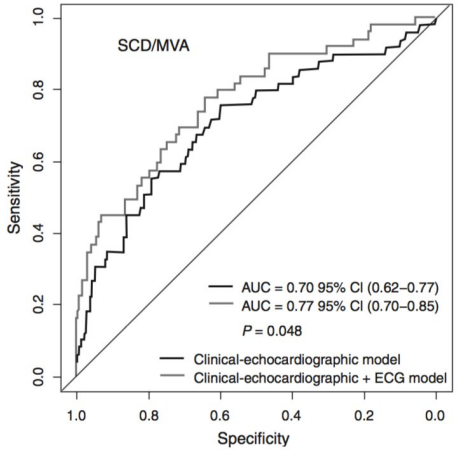
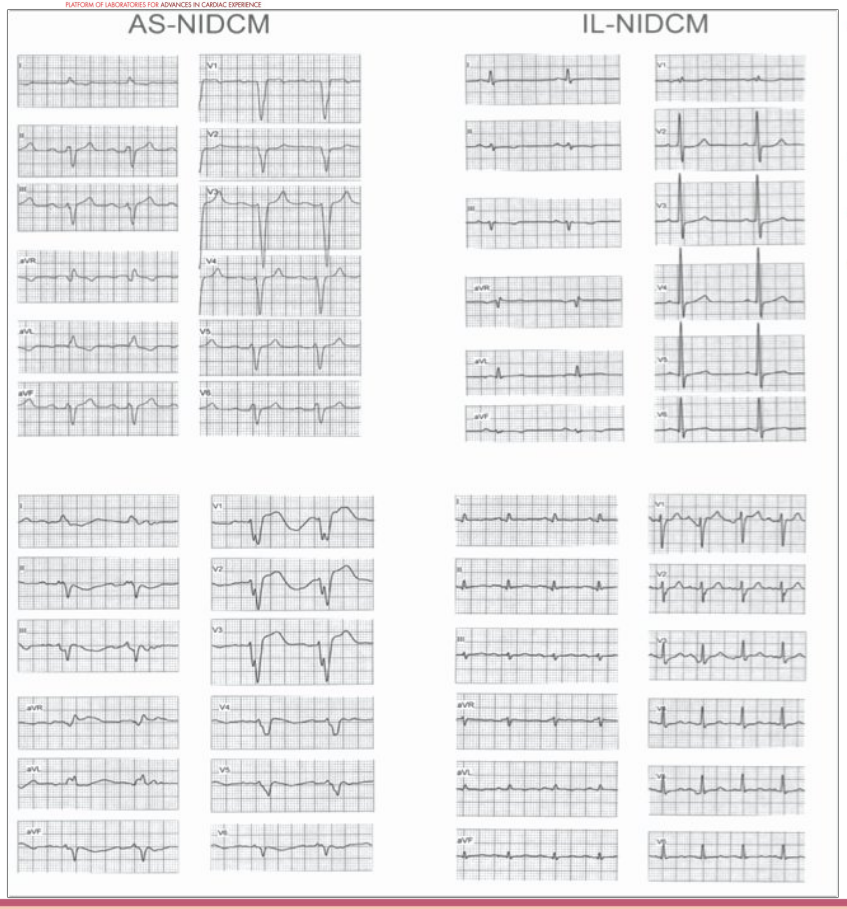




- **14%** of pts **SD/MVA**. **Predictors** at multivariate analysis:
  - **inverted T-waves in anterolateral leads** (HR 2.141; 95% CI 1.148–3.991; P = 0.017)
  - **higher amplitude of S wave in V2** (HR 0,961; 95% CI 0.933 – 0.990; P = 0.008) and **of R wave on II** (HR 0.901; 95% CI 0.834–0.972; P=0.007) **protective** factors.

J Cardiovasc Med 2019, 20:450–458



The value of the 12-lead electrocardiogram in localizing the scar in non-ischaemic cardiomyopathy

Teresa Oloriz[1], Hein J.J. Wellens[2], Giulia Santagostino[1], Nicola Trevisi[1], John Silberbauer[1], Giovanni Peretto[1], Giuseppe Maccabelli[1], and Paolo Della Bella[1]*

- 108 pts: 72 non ischemic dilated cardiomyopathy (NIDCM) and 36 minimal structural abnormalities (NICM)
- Anterospetal (AS) or inferolateral (IL) scar based on imaging and voltage mapping studies
- A small **r in V3** and the presence of substantial conduction delay with **lengthening of the PR interval**, or **QRS duration** or a **paced rhythm** with a CRT device are all criteria that suggest an **AS scar pattern**
- A **PR interval of <170 ms** and a **low voltage**, **q wave or fragmented QRS in the limb leads** is more frequently observed in cases with an **IL scar pattern**, both in NIDCM and in NICM pts.

Europace (2016) 18, 1850–1859

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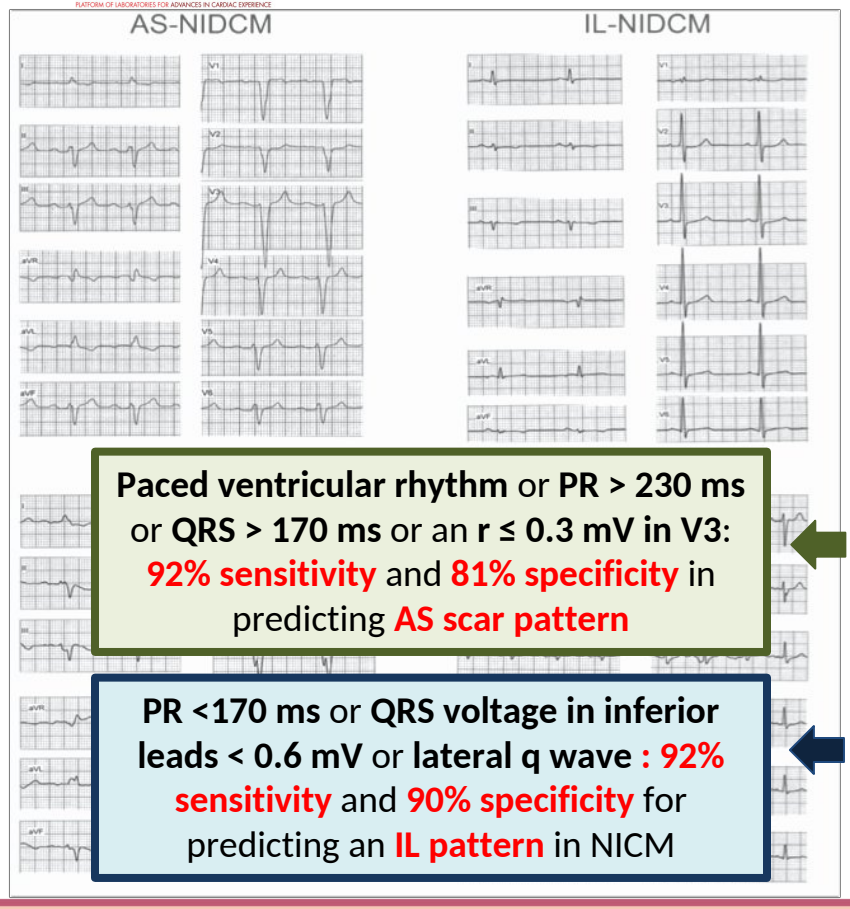

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Europace (2016) 18, 1850–1859

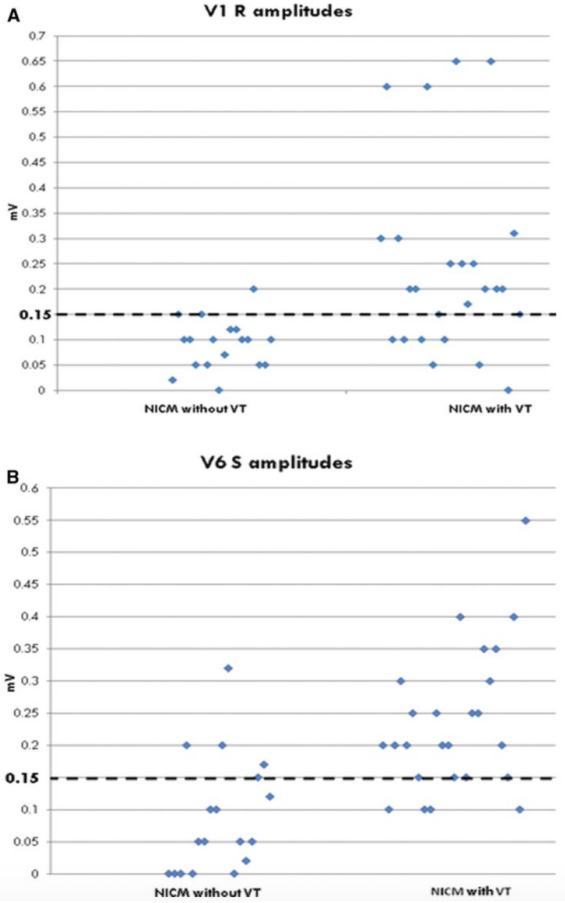
PLACE 9ª Edizione

Sinus Rhythm ECG Criteria Associated with Basal-Lateral Ventricular Tachycardia Substrate in Patients with Nonischemic Cardiomyopathy

WENDY S. TZOU, M.D., ERICA S. ZADO, P.A.-C., DAVID LIN, M.D., DAVID J. CALLANS, M.D., SANJAY DIXIT, M.D., JOSHUA M. COOPER, M.D., RUPA BALA, M.D., FERMIN GARCIA, M.D., MATHEW D. HUTCHINSON, M.D., MICHAEL P. RILEY, M.D., PH.D, RAJAT DEO, M.D., EDWARD P. GERSTENFELD, M.D., and FRANCIS E. MARCHLINSKI, M.D.

Phase II: Sensitivity and Specificity of ECG Characteristics in Prospectively Identifying Basal-Lateral Scar in NICM

	Sensitivity	Specificity
V1 R ≥ 0.15 mV	1.00	0.63
V6 S ≥ 0.15 mV	0.86	0.50
V6 S:R ≥ 0.2	0.57	0.50
V1 R and V6 S ≥ 0.15 mV	0.86	0.88
V1 R ≥ 0.15 and V6 S:R ≥ 0.2	0.57	0.88



Among patients with NICM, VT, and normal QRS duration, **V1 R ≥ 0.15 mV and V6 S ≥ 0.15 mV predicted presence of basal-lateral LV areas of bipolar low voltage.** *J Cardiovasc Electrophysiol, Vol. 22, pp. 1351-1358, December 2011*

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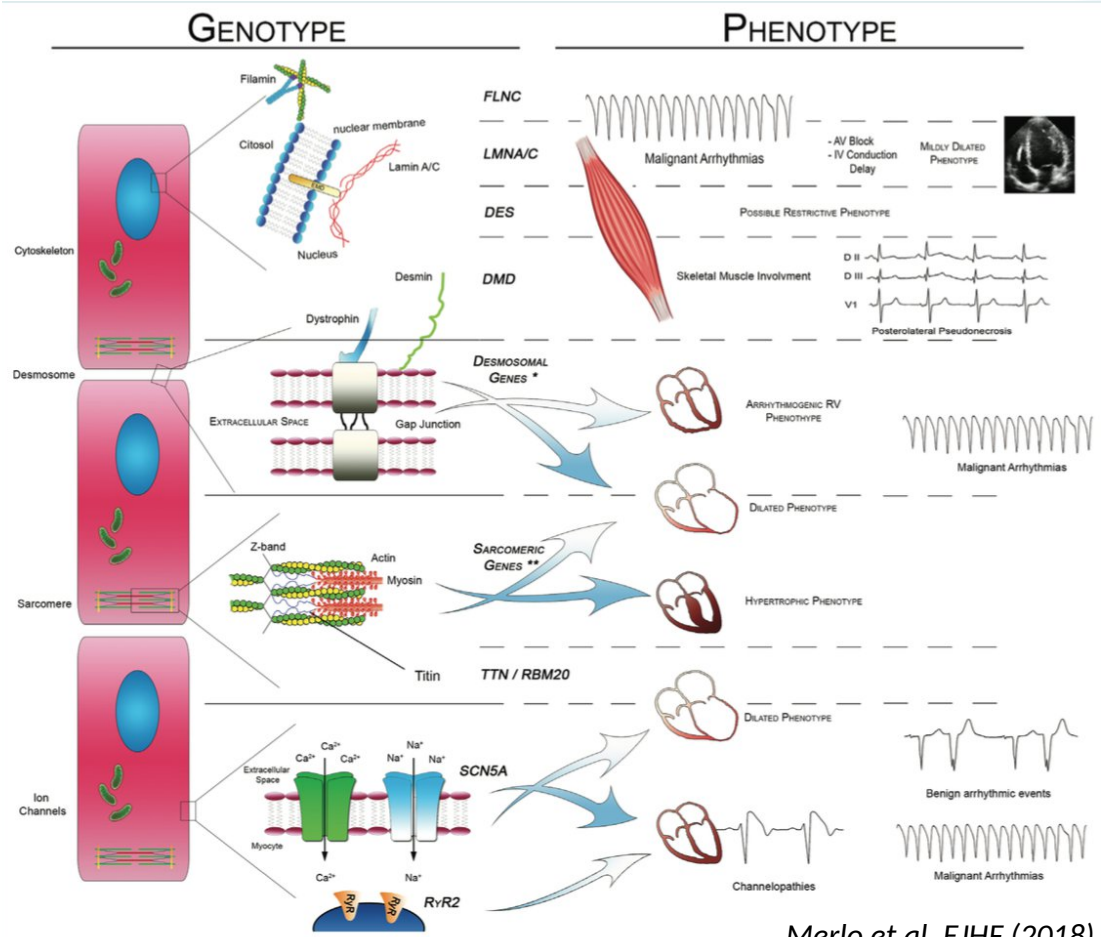
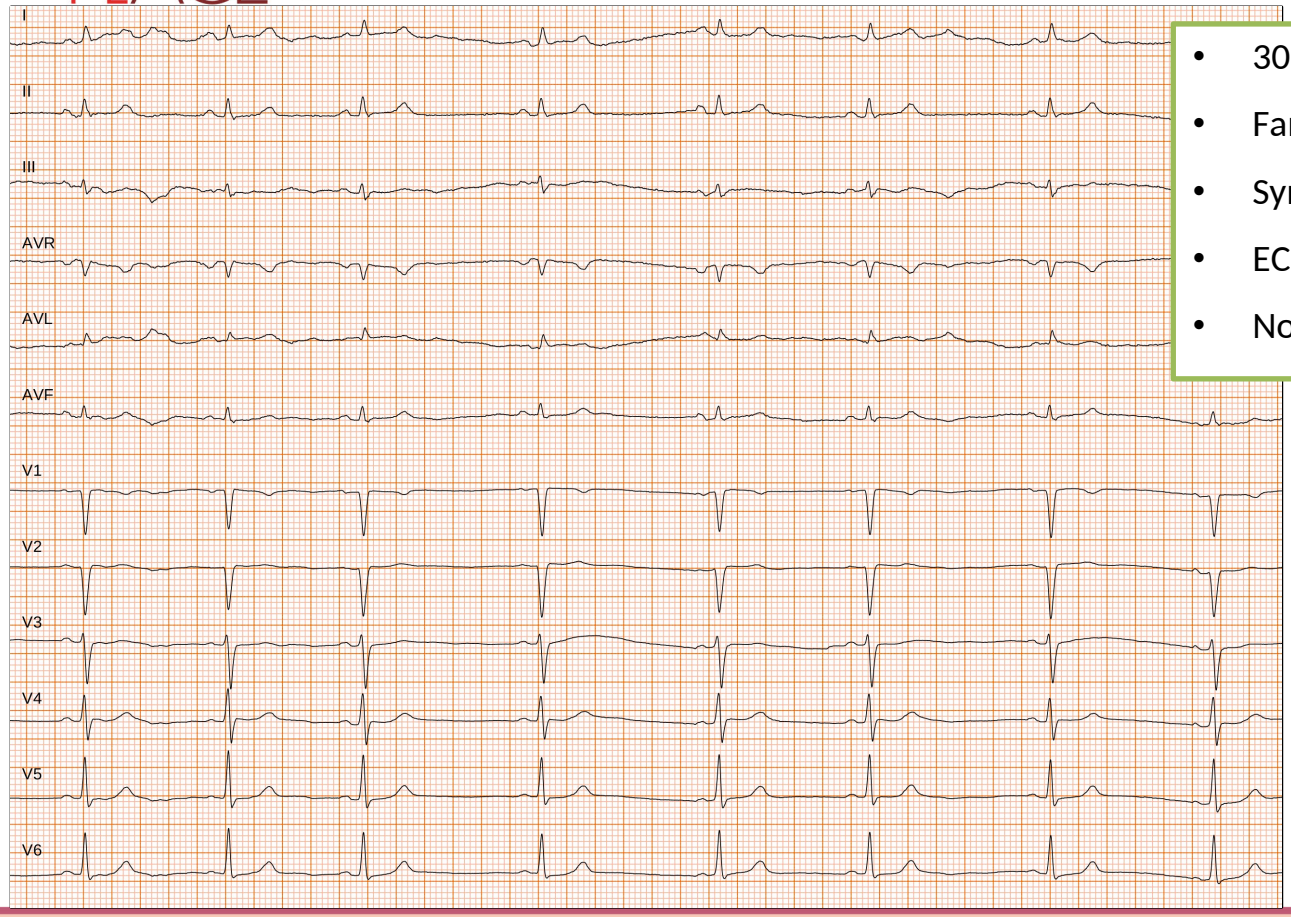
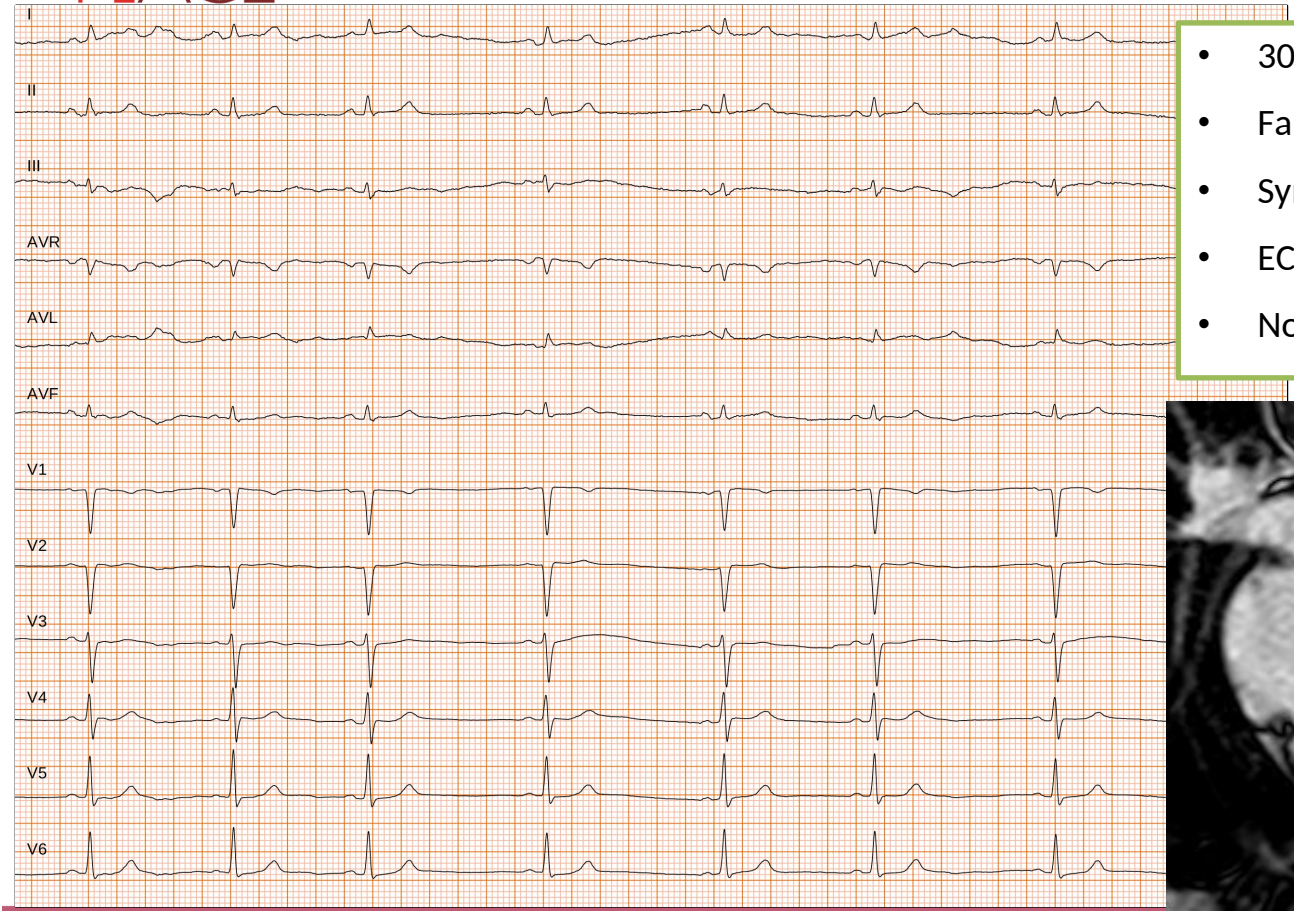
- ECG features are clues of specific genetic DCM subtypes
- The approach in ECG analysis should be focusing on specific 'red flags'



Merlo et al. EJHF (2018) ***20****, 228–239*



- 30 yo female
- Family history of DCM (Mother)
- Symptomatic for palpitation during effort
- ECG Holter monitoring: frequent PVBs
- Normal echocardiogram findings



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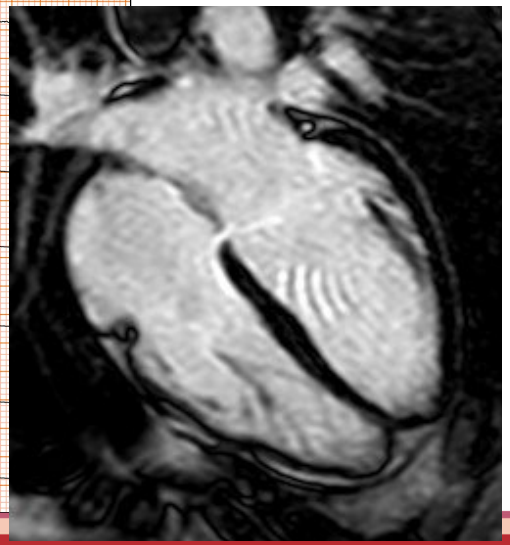

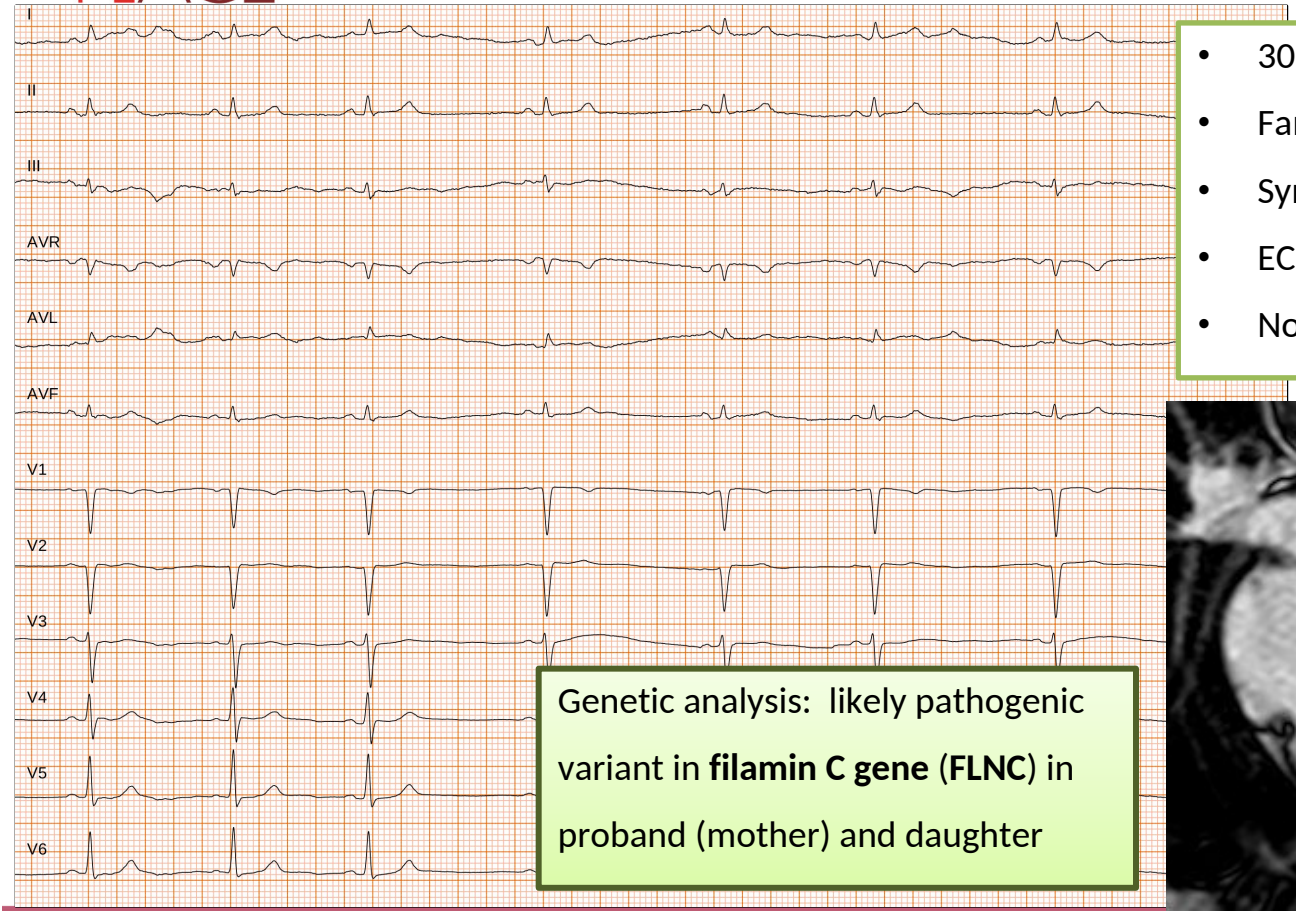

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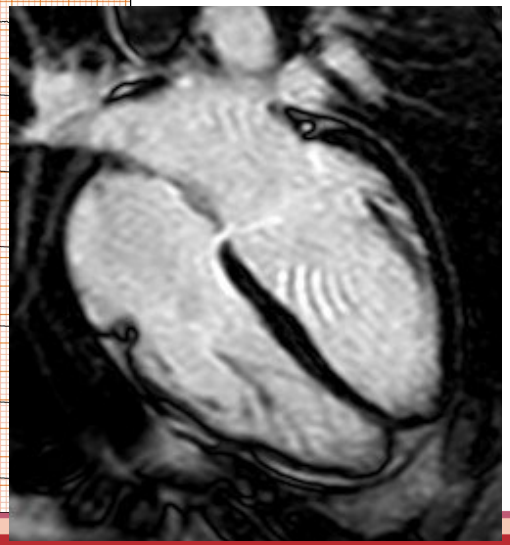
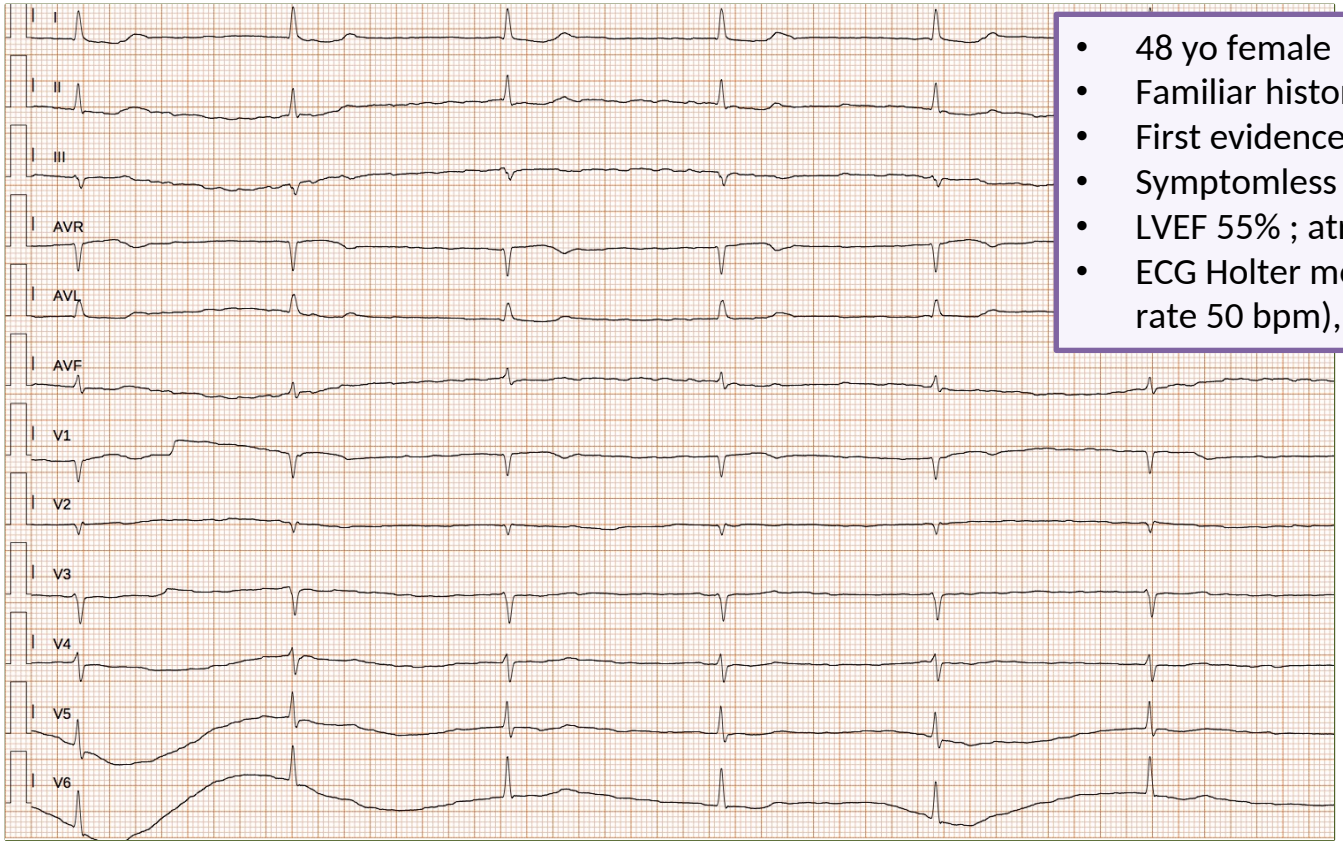
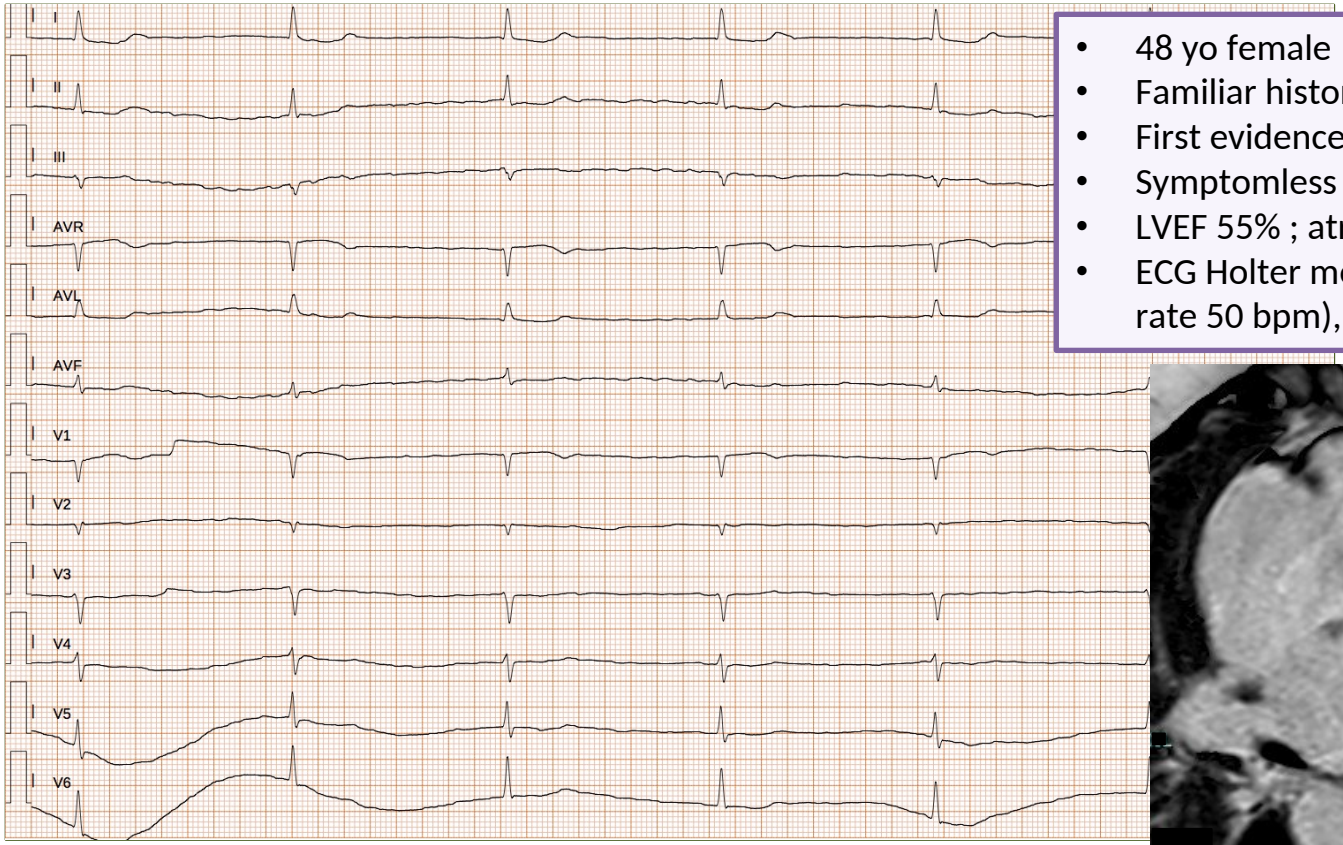


Genetic analysis: likely pathogenic variant in **filamin C gene** (**FLNC**) in proband (mother) and daughter



- 48 yo female
- Familiar history of SCD and arrhythmias (sister)
- First evidence of atrial fibrillation (AF)
- Symptomless
- LVEF 55% ; atrial enlargement
- ECG Holter monitoring: **slow AF** (average heart rate 50 bpm), frequent PVBs and couplets



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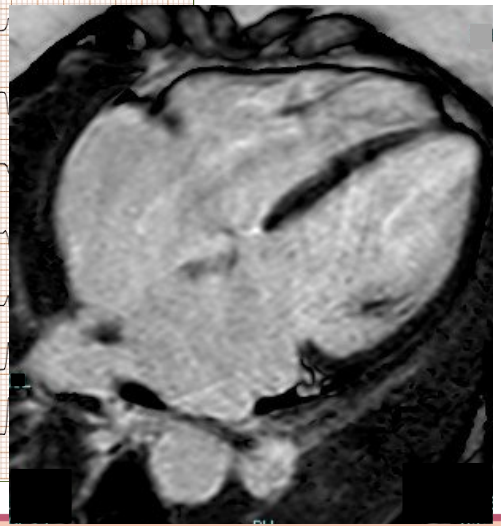

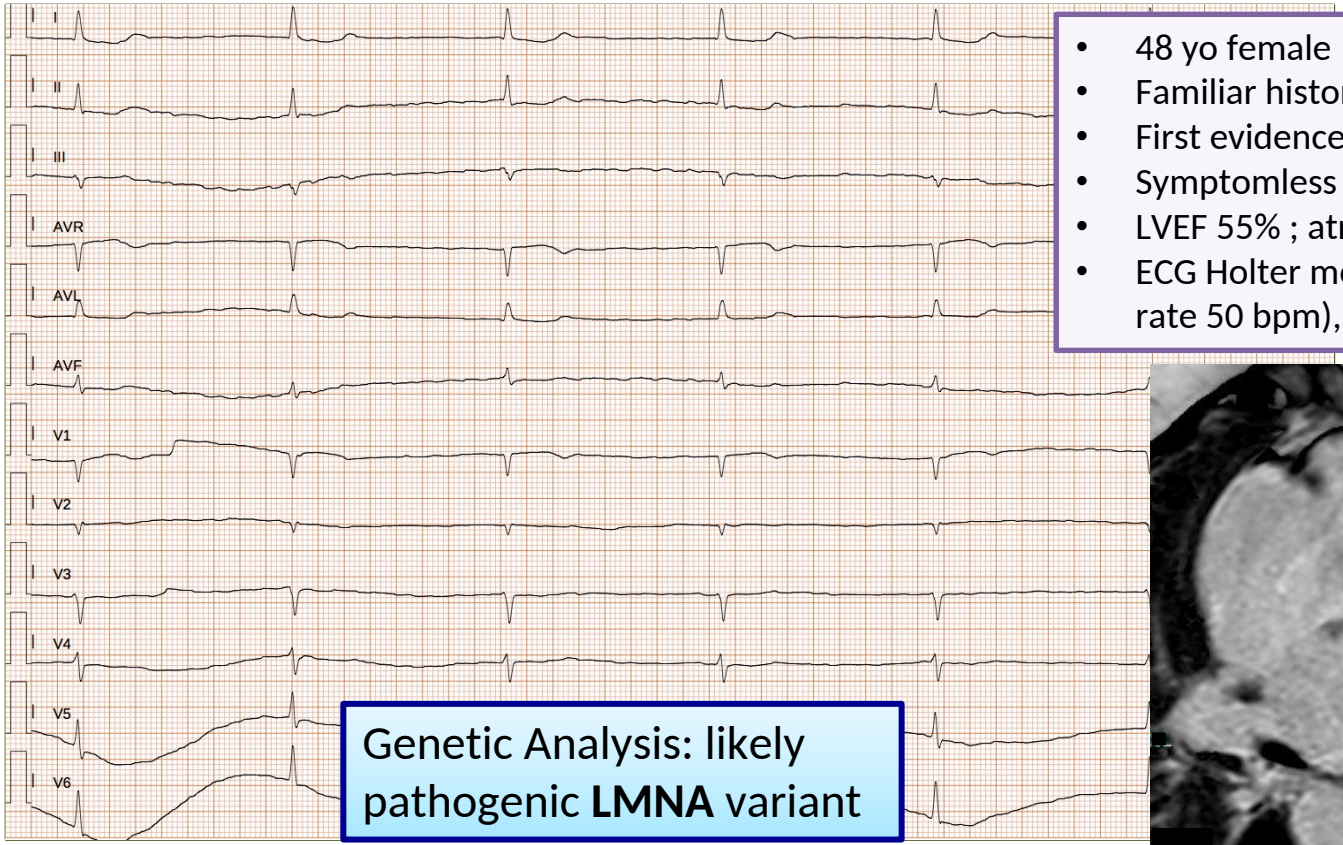

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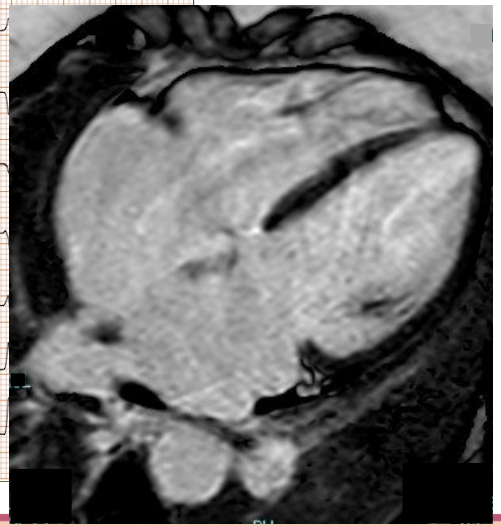


Genetic Analysis: likely pathogenic **LMNA** variant

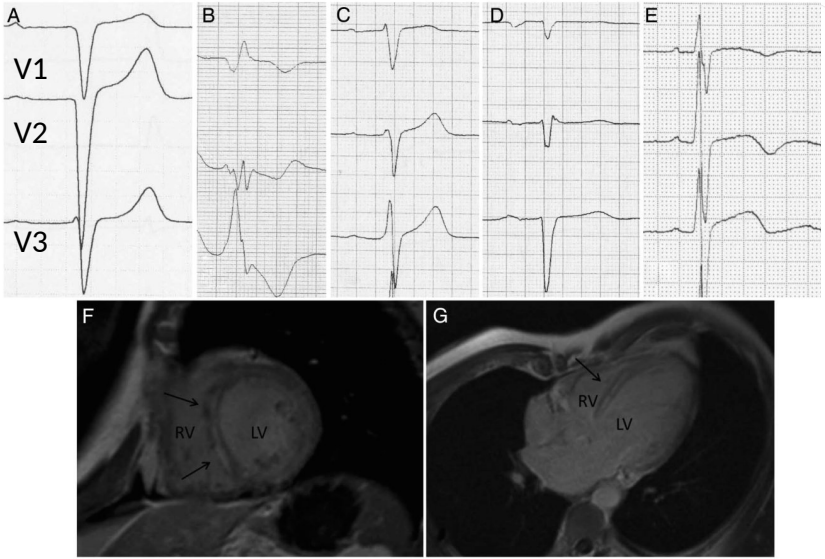
ECG in LMNA genotypes

Clinical disease presentation and ECG characteristics of *LMNA* mutation carriers

Ollila et al. Open Heart 2017;4:e000474

	LMNA mutation carriers, N=27%	DCM controls, N=78%	p Value *LMNA* vs DCM	Healthy controls, N=20%	p Value *LMNA* vs healthy control
Rhythm					
Sinus rhythm	70.4	75.6	NS	100	NS
AF	11.1	16.7		0	
Other*	18.5	7.7		0	
First AV block	37.0 (55.6)†	15.4 (20.7)	0.034	0	0.006
Current or previous AV block	59.3	24.4	0.002	0	<0.001
PTF	22.2 (30.0)	30.8 (40.0)	NS	10.0	NS
Flat P wave	33.3 (45.0)	6.4 (8.3)	0.002	0	0.012
Broad P wave	7.4 (10.0)	5.1 (6.7)	NS	0	NS
LVH	7.4 (11.8)	20.5 (34.0)	NS	0	NS
ST depression	18.5 (29.4)	32.1 (53.2)	NS	5.0	NS
T inversion	7.4 (11.8)	32.1 (53.2)	0.012	5.0	NS
QRS fragmentation	37.0	33.3	NS	5.0	0.028
Septal fragmentation	22.2	6.4	NS	0	0.062
Septal remodelling	81.5	20.5	<0.001	0	<0.001
Septal remodelling, flat P wave, or current or previous AV block	96.3	41.0	<0.001	0	<0.001
LBBB	7.4	20.5	NS	0	NS
RBBB	0	2.6	NS	0	NS
NSIVCD	3.7	7.7	NS	0	NS

*Physiological pacemaker or third AV block.
†The prevalence in brackets of only those applicable.
AF, atrial fibrillation; AV block, atrioventricular block; DCM, dilated cardiomyopathy; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; NS, not significant; NSIVCD, non-specific intraventricular conduction defect; PTF, P terminal force; RBBB, right bundle branch block.



- 27 *LMNA* mutation carriers, 78 pts with idiopathic *DCM without an LMNA mutation*; 20 healthy controls.
- ECG signs of "**septal remodelling**" in **81% LMNA mutation carriers** (**76% concordantly with septal LGE**) , 21% DCM controls and none of the healthy controls;

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PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

European Heart Journal
Open

Under Review

The Prognostic Value of the 12-lead Electrocardiogram and Cardiac Magnetic Resonance in Nonischemic Dilated Cardiomyopathy. Correlation Between Electrocardiographic and Cardiac Magnetic Resonance Findings

Leonardo Calò, MD, FESC[a]; Cinzia Crescenzi, MD[a],* Annamaria Martino, MD, PhD[a];*
Elisa Silvetti, MD[a]; Edoardo Bressi, MD[a], Alessandra Stazi,MD[a];
Fabiana Romeo, MD[a]; Maria Ludovica Danza, MD[a]; Francesco Cicogna, MD[a];
Germana Panattoni, MD, PhD[a]; Roberta Della Bona, MD, PhD[b]; Marco Rebecchi, MD[a];
Stefano Canestrelli, MD[a]; Elisa Fedele, MD[a]; Chiara Lanzillo, MD, PhD[a]; Paolo Golia, MD[a];
Ruggiero Mango, MD, PhD[c]; Armando Fusco, MD, PhD[e]; Matteo Stefanini, MD[e];
Federica Carla Sangiuolo, MD, PhD[d]; Gennaro Cice[a], MD, PhD; Ermenegildo de Ruvo, MD[a].

Our Experience ..

The **aims of the study** were:

1. To describe the **ECG characteristics** of a large cohort of patients with **DCM** and to compare them with a age and sex-matched population of healthy subjects ;

1. To **correlate ECG abnormalities with LGE-CMR findings**;

1. To explore the **prognostic value** of the comprehensive **ECG** evaluation in addition to clinical and **CMR parameters**.

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538 Patients With DCM* (Policlinico Casilino)

*LVEF <50% at baseline evaluation in the absence of possible causes of systolic impairment

Personal history; Family history; Physical Examination; ECG; Echo; ECG Holter; CMR; Genetic Test

Excluded: No interpretable ECG,paced rhythm, inadequate echo or CMR data, or follow-up

158 pts with DCM included
Median age 54±13 years; 67% men

Control Group
56 individuals
mean age 54.5±10.2 years
No familiar history, negative CMR

ECG findings ⟷ ***CMR findings***

FOLLOW UP
Composite endpoint: sudden cardiac death (SCD), aborted SCD or appropriate ICD shock forventricular tachycardia/ventricular fibrillation.

1. ECG in DCM population

	Healthy Controls (n=56)	Overall (n=159)	*P Value*[1]	LV LGE + (n=79)	LV LGE - (n=80)	*P Value*[2]
QRS (ms)	93.6±13.8	115±29	***<0.0001***	113±30	117±29	*0.45*
LVH: Sokolow-Lyon	2 (3.6)	25 (15.7)	***0.033***	8 (10.1)	17 (21.3)	*0.054*
LVH: Cornell criteria	0	27 (17.0)	***0.007***	5 (6.3)	22 (27.5)	***0.0008***
First degree AV block	10 (17.8)	29 (18.2)	*0.89*	19 (24.1)	10 (12.5)	*0.059*
NICD	5 (8.9)	4 (2.5)	*0.09*	3 (3.8)	1 (1.3)	*0.6*
RBBB	5 (8.9)	2 (1.3)	***0.019***	1 (1.3)	1 (1.3)	*1.000*
LAFB	1 (1.8)	11 (6.9)	*0.27*	10 (12.7)	1 (1.3)	***0.012***
LPFB	0	5 (3.1)	*0.4*	5 (6.3)	0 (0)	***0.028***
LBBB	1 (1.8)	45 (28.3)	***<0.0001***	17 (21.5)	28 (35.0)	*0.059*
Pathological Q waves	1 (1.8)	24 (15.1)	***0.015***	20 (25.3)	4 (5.0)	***0.0003***
Lateral distribution	0	1 (0.6)	*0.58*	1 (1.3)	0 (0)	*0.496*
Inferior distribution	0	12 (7.5)	*0.07*	8 (10.1)	4 (5.0)	*0.246*
Precordial	1 (1.8)	7 (4.4)	*0.63*	7 (8.9)	0 (0)	*0.681*
More 2 localizations	0	4 (2.5)	*0.53*	4 (5.1)	0 (0)	*0.058*
Fragmented QRS	10 (17.8)	40 (25.2)	*0.35*	17 (21.5)	23 (28.8)	*0.293*

	Healthy Controls (n=56)	Overall (n=159)	*P Value*[1]	LV LGE + (n=79)	LV LGE - (n=80)	*P Value*[2]
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Fragmented QRS	10 (17.8)	40 (25.2)	*0.35*	17 (21.5)	23 (28.8)	*0.293*

	Healthy Controls (n=56)	Overall (n=159)	P Value[1]	LV LGE + (n=79)	LV LGE - (n=80)	P Value[2]
Low-voltage QRS	14 (25)	70 (44.0)	***0.019***	43 (54.4)	27 (33.8)	***0.009***
Global	0	3 (1.9)	*0.71*	2 (2.5)	1 (1.3)	*0.620*
Limb leads	0	12 (7.5)	*0.07*	8 (10.1)	4 (5.0)	*0.35*
Precordial leads	3 (5.3)	5 (3.1)	*0.74*	3 (3.8)	2 (2.5)	*0.681*
Lateral distribution	6 (10.7)	3 (1.9)	***0.014***	2 (2.5)	1 (1.3)	*0.620*
Inferior distribution	8 (14.3)	41 (25.8)	*0.11*	22 (27.8)	19 (23.8)	*0.68*
More 2 localizations	1 (1.8)	6 (3.8)	*0.78*	6 (7.6)	0 (0)	***0.013***
QTc (msec)	408.5±20.2	437±38	***<0.0001***	428±38	445±36	***0.006***
QTc ≥440 msec	2 (3.6)	70 (44.0)	***<0.0001***	28 (35.4)	42 (52.5)	***0.045***
Tzou criteria	5 (0.89)	5 (3.1)	*0.16*	1 (1.3)	4 (5.0)	*0.367*
R >3 mm V1	4 (7.1)	5 (3.1)	*0.51*	5 (6.3)	0 (0)	***0.028***
TWI	2 (3.6)	42 (26.4)	***0.0006***	25 (31.6)	17 (21.3)	*0.137*
Inferolateral	0	9 (5.7)	*0.15*	5 (6.3)	4 (5.0)	*0.745*
Anterior	2 (3.6)	5 (3.1)	*0.77*	5 (6.3)	0 (0)	***0.028***
Inferior	0	7 (4.4)	*0.25*	5 (6.3)	2 (2.5)	*0.276*
Lateral	0	16 (10.1)	***0.03***	7 (8.9)	9 (11.3)	*0.616*
Anterolateral	0	5 (3.1)	*0.41*	3 (3.8)	2 (2.5)	*0.681*
R I + R II (mm)	14.3±4.1	12.7±5.2	*0.34*	11.1±4.9	14.3±5.0	***<0.0001***
R I + R II ≤11 mm	11 (19.6)	68 (42.8)	***0.013***	45 (57.0)	23 (28.8)	***0.0006***

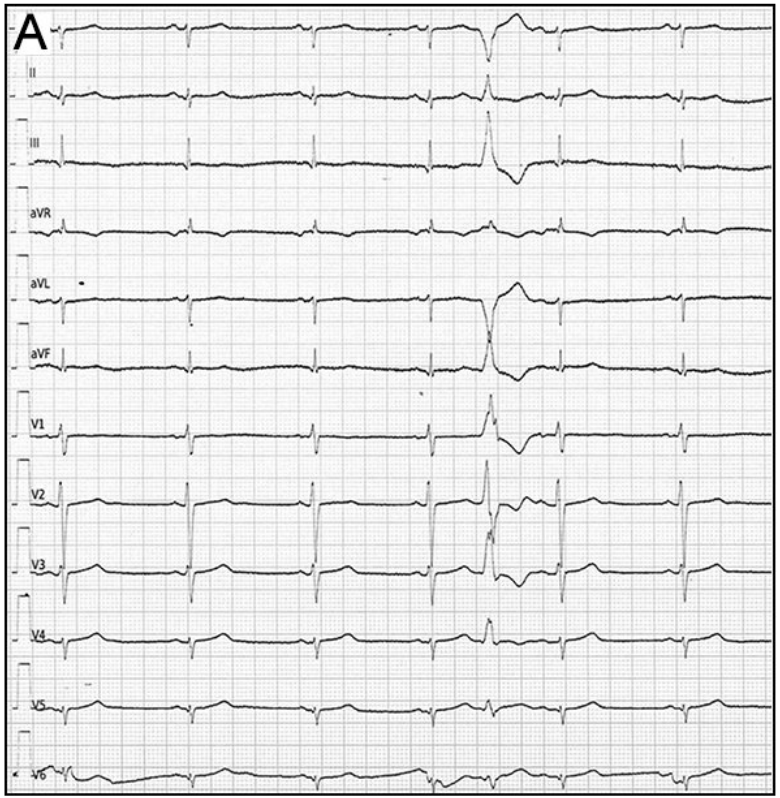
PLAC
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC

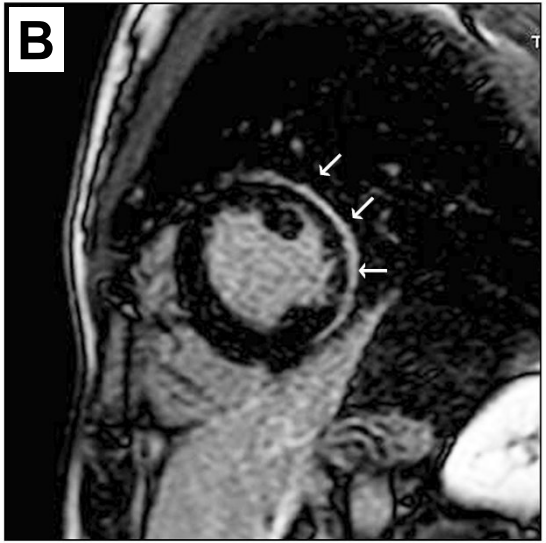
	Healthy Controls (n=56)	Overall (n=159)	P Value[1]	LV LGE + (n=79)	LV LGE - (n=80)	P Value[2]
Low-voltage QRS	14 (25)	70 (44.0)	***0.019***	43 (54.4)	27 (33.8)	***0.009***
Global	0	3 (1.9)	*0.71*	2 (2.5)	1 (1.3)	*0.620*
Limb leads	0	12 (7.5)	*0.07*	8 (10.1)	4 (5.0)	*0.35*
Precordial leads	3 (5.3)	5 (3.1)	*0.74*	3 (3.8)	2 (2.5)	*0.681*
Lateral distribution	6 (10.7)	3 (1.9)	***0.014***	2 (2.5)	1 (1.3)	*0.620*
Inferior distribution	8 (14.3)	41 (25.8)	*0.11*	22 (27.8)	19 (23.8)	*0.68*
More 2 localizations	1 (1.8)	6 (3.8)	*0.78*	6 (7.6)	0 (0)	***0.013***
QTc (msec)	408.5±20.2	437±38	***<0.0001***	428±38	445±36	***0.006***
QTc ≥440 msec	2 (3.6)	70 (44.0)	***<0.0001***	28 (35.4)	42 (52.5)	***0.045***
Tzou criteria	5 (0.89)	5 (3.1)	*0.16*	1 (1.3)	4 (5.0)	*0.367*
R >3 mm V1	4 (7.1)	5 (3.1)	*0.51*	5 (6.3)	0 (0)	***0.028***
TWI	2 (3.6)	42 (26.4)	***0.0006***	25 (31.6)	17 (21.3)	*0.137*
Inferolateral	0	9 (5.7)	*0.15*	5 (6.3)	4 (5.0)	*0.745*
Anterior	2 (3.6)	5 (3.1)	*0.77*	5 (6.3)	0 (0)	***0.028***
Inferior	0	7 (4.4)	*0.25*	5 (6.3)	2 (2.5)	*0.276*
Lateral	0	16 (10.1)	***0.03***	7 (8.9)	9 (11.3)	*0.616*
Anterolateral	0	5 (3.1)	*0.41*	3 (3.8)	2 (2.5)	*0.681*
R I + R II (mm)	14.3±4.1	12.7±5.2	*0.34*	11.1±4.9	14.3±5.0	***<0.0001***
R I + R II ≤11 mm	11 (19.6)	68 (42.8)	***0.013***	45 (57.0)	23 (28.8)	***0.0006***

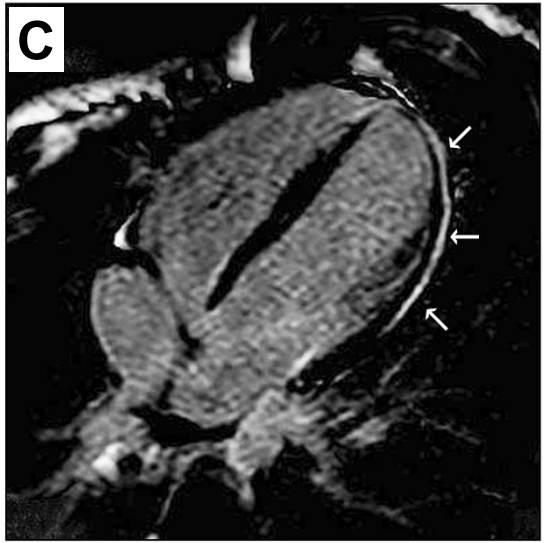
PLAC
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC

	Healthy Controls (n=56)	Overall (n=159)	P Value[1]	LV LGE + (n=79)	LV LGE - (n=80)	P Value[2]
Low-voltage QRS	14 (25)	70 (44.0)	***0.019***	43 (54.4)	27 (33.8)	***0.009***
Global	0	3 (1.9)	*0.71*	2 (2.5)	1 (1.3)	*0.620*
Limb leads	0	12 (7.5)	*0.07*	8 (10.1)	4 (5.0)	*0.35*
Precordial leads	3 (5.3)	5 (3.1)	*0.74*	3 (3.8)	2 (2.5)	*0.681*
				(2.5)	1 (1.3)	*0.620*
				(27.8)	19 (23.8)	*0.68*
				(7.6)	0 (0)	***0.013***
				8±38	445±36	***0.006***
				(35.4)	42 (52.5)	***0.045***
Tzou criteria	5 (0.89)	5 (3.1)	*0.16*	1 (1.3)	4 (5.0)	*0.367*
R >3 mm V1	4 (7.1)	5 (3.1)	*0.51*	5 (6.3)	0 (0)	***0.028***
TWI	2 (3.6)	42 (26.4)	***0.0006***	25 (31.6)	17 (21.3)	*0.137*
Inferolateral	0	9 (5.7)	*0.15*	5 (6.3)	4 (5.0)	*0.745*
Anterior	2 (3.6)	5 (3.1)	*0.77*	5 (6.3)	0 (0)	***0.028***
Inferior	0	7 (4.4)	*0.25*	5 (6.3)	2 (2.5)	*0.276*
Lateral	0	16 (10.1)	***0.03***	7 (8.9)	9 (11.3)	*0.616*
Anterolateral	0	5 (3.1)	*0.41*	3 (3.8)	2 (2.5)	*0.681*
R I + R II (mm)	14.3±4.1	12.7±5.2	*0.34*	11.1±4.9	14.3±5.0	***<0.0001***
R I + R II ≤11 mm	11 (19.6)	68 (42.8)	***0.013***	45 (57.0)	23 (28.8)	***0.0006***

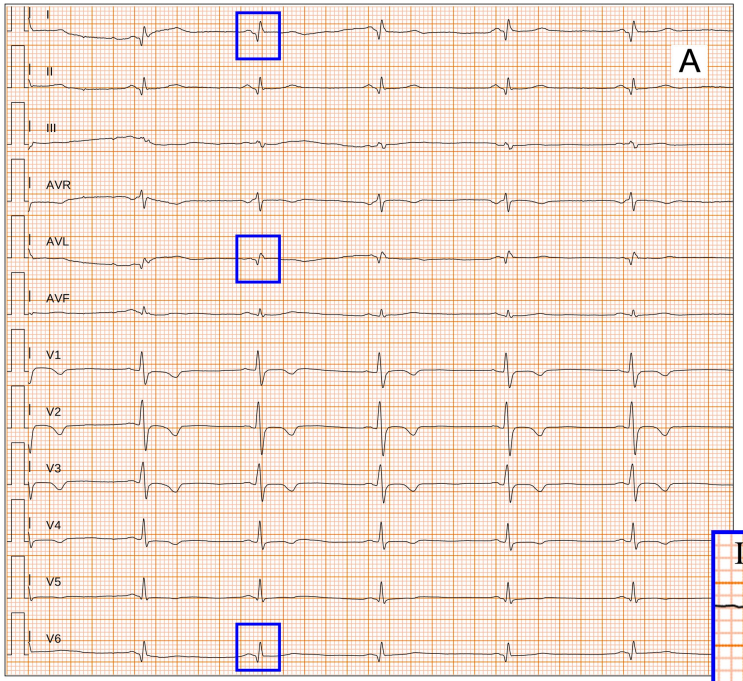
- LGE in 79 pts (**49.7%**)
- **LPFB**, **LAFB**, **pathological Q-waves**, **R in V1 >3 mm** and **sum of R-wave ≤11 mm in leads I-II** had **the greatest accuracy** for **LGE** identification (sensitivity 69.6%; specificity 66.2%; PPV 67.0% and NPV 68.8%)

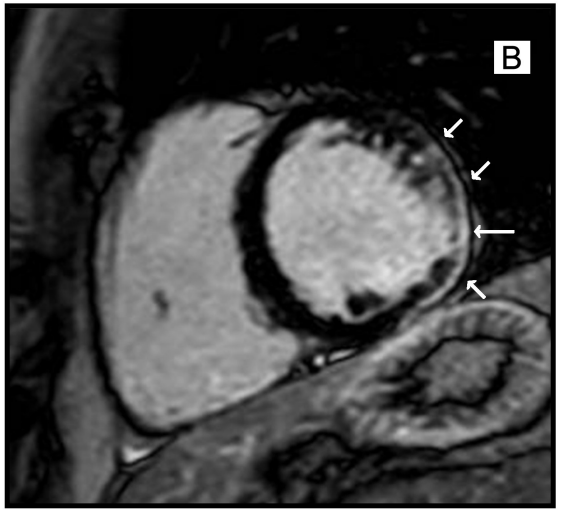


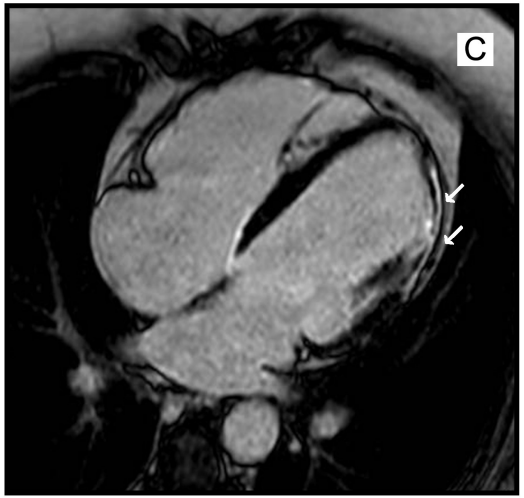


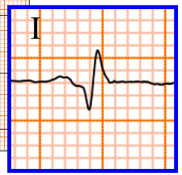


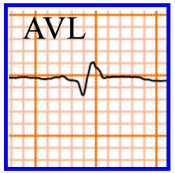
- A 21-year-old white female swimming instructor
- Mild reduction of LVEF
- Aborted Cardiac Arrest occurred just after exercise.

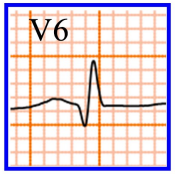

A
I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6


B


C


I


AVL


V6

2. ECG and LGE distribution

PLACE 9ª Edizione

ECG and LGE distribution

	Non Ring like (n=59)	Ringlike (n=20)	P Value
QRS (msec)	116 ± 31	106 ± 26	0.12
First degree AV block	17 (28.8)	2 (10.0)	0.16
NICD	2 (3.4)	1 (5.0)	0.73
RBBB	1 (5.0)	0	0.57
LAFB	9 (15.3)	1 (5.0)	0.42
LPFB	0	5 (25.0)	**0.0006**
LBBB	15 (25.4)	2 (10.0)	0.26
Pathological Q waves	14 (23.7)	6 (30.0)	0.79
Lateral distribution	0	1 (5.0)	0.57
Inferior distribution	7 (11.9)	1 (5.0)	0.65
Precordial distribution	5 (8.5)	2 (10.0)	0.8
More 2 localizations	2 (3.4)	2 (10.0)	0.56
Fragmented QRS	9 (15.3)	8 (40.0)	**0.044**
Lateral distribution	1 (1.7)	1 (5.0)	0.99
Inferior distribution	4 (6.8)	2 (10.0)	0.98
Precordial distribution	2 (3.4)	0	0.99
More 2 localizations	2 (3.4)	5 (25.0)	**0.013**
Low-voltage QRS	25 (42.4)	18 (90.0)	**0.005**
Global	1 (1.7)	1 (5.0)	0.99
Limb leads	3 (5.1)	5 (25.0)	**0.033**
Precordial leads	1 (1.7)	2 (10.0)	0.32
Lateral distribution	1 (1.7)	1 (5.0)	0.99
Inferior distribution	17 (28.8)	5 (25.0)	0.97
More 2 localizations	2 (3.4)	4 (20.0)	**0.053**

	Non Ring like (n=59)	Ringlike (n=20)	P Value
QTc (msec)	433±37	414±37	**<0.0001**
QTc ≥440 msec	21 (35.6)	7 (35.0)	0.83
Tzou criteria	1 (1.7)	0	0.57
R > 3 mm in V1	3 (5.1)	2 (10.0)	0.8
Bayés de Luna criteria	2 (3.4)	1 (5.0)	0.99
Poor R-wave progression	3 (5.1)	1 (5.0)	0.56
TWI	16 (27.1)	9 (45.0)	0.23
Inferolateral	3 (5.1)	2 (10.0)	0.79
Anterior	3 (5.1)	2 (10.0)	0.81
Inferior	3 (5.1)	2 (10.0)	0.81
Lateral	6 (10.2)	1 (5.0)	0.32
Anterolateral	1 (1.7)	2 (10.0)	0.33
R I (mm)	7.6±2.9	4.0±2.6	**<0.0001**
R II (mm)	4.8±2.9	3.1±2.1	**0.019**
R I + R II (mm)	12.5±4.6	7.1±3.6	**<0.0001**

Ringlike pattern was found in **49.7%** patients

PLACE 9ª Edizione

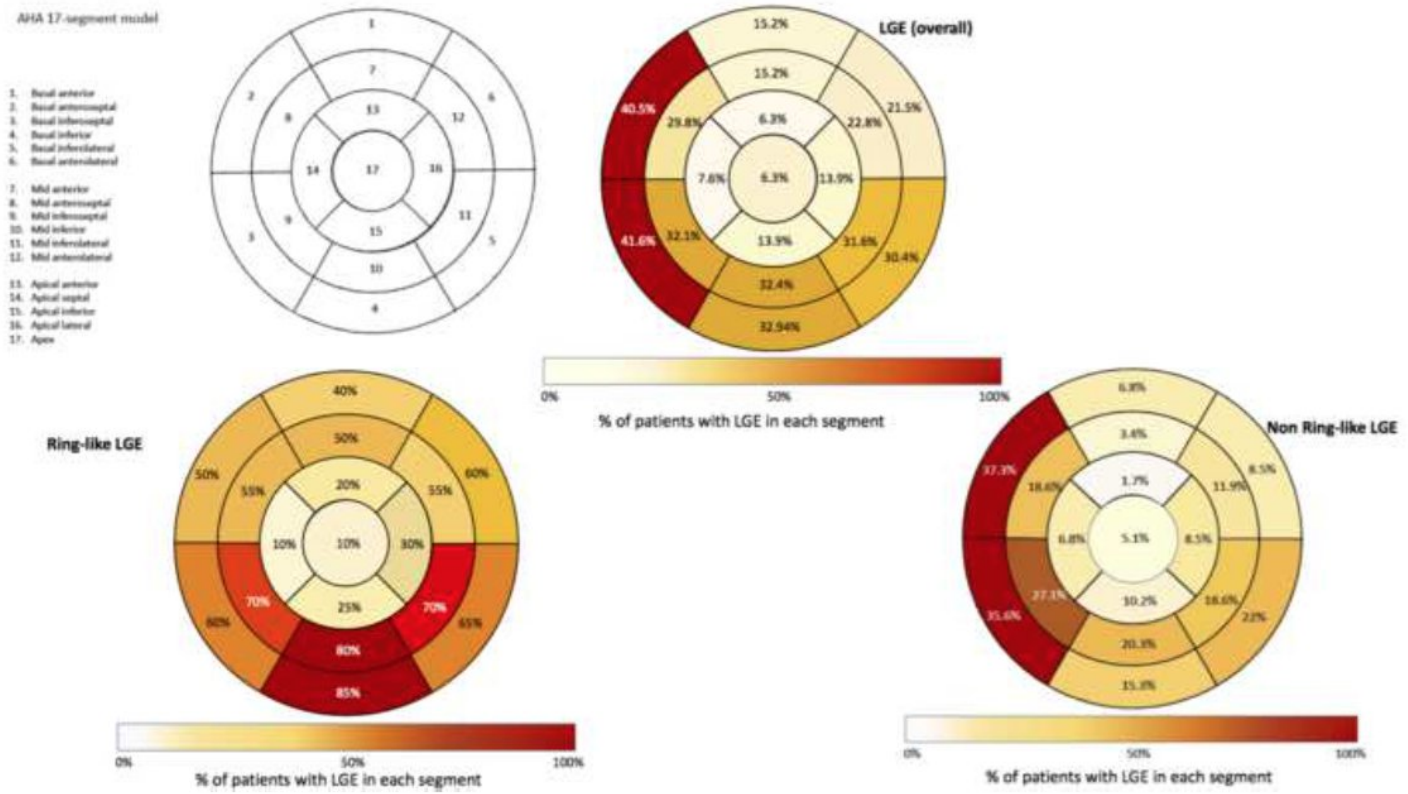
ECG and LGE distribution

	Non Ring like (n=59)	Ringlike (n=20)	P Value
QRS (msec)	116 ± 31	106 ± 26	0.12
First degree AV block	17 (28.8)	2 (10.0)	0.16
NICD	2 (3.4)	1 (5.0)	0.73
RBBB	1 (5.0)	0	0.57
LAFB	9 (15.3)	1 (5.0)	0.42
LPFB	0	5 (25.0)	**0.0006**
LBBB	15 (25.4)	2 (10.0)	0.26
Pathological Q waves	14 (23.7)	6 (30.0)	0.79
Lateral distribution	0	1 (5.0)	0.57
Inferior distribution	7 (11.9)	1 (5.0)	0.65
Precordial distribution	5 (8.5)	2 (10.0)	0.8
More 2 localizations	2 (3.4)	2 (10.0)	0.56
Fragmented QRS	9 (15.3)	8 (40.0)	**0.044**
Lateral distribution	1 (1.7)	1 (5.0)	0.99
Inferior distribution	4 (6.8)	2 (10.0)	0.98
Precordial distribution	2 (3.4)	0	0.99
More 2 localizations	2 (3.4)	5 (25.0)	**0.013**
Low-voltage QRS	25 (42.4)	18 (90.0)	**0.005**
Global	1 (1.7)	1 (5.0)	0.99
Limb leads	3 (5.1)	5 (25.0)	**0.033**
Precordial leads	1 (1.7)	2 (10.0)	0.32
Lateral distribution	1 (1.7)	1 (5.0)	0.99
Inferior distribution	17 (28.8)	5 (25.0)	0.97
More 2 localizations	2 (3.4)	4 (20.0)	**0.053**

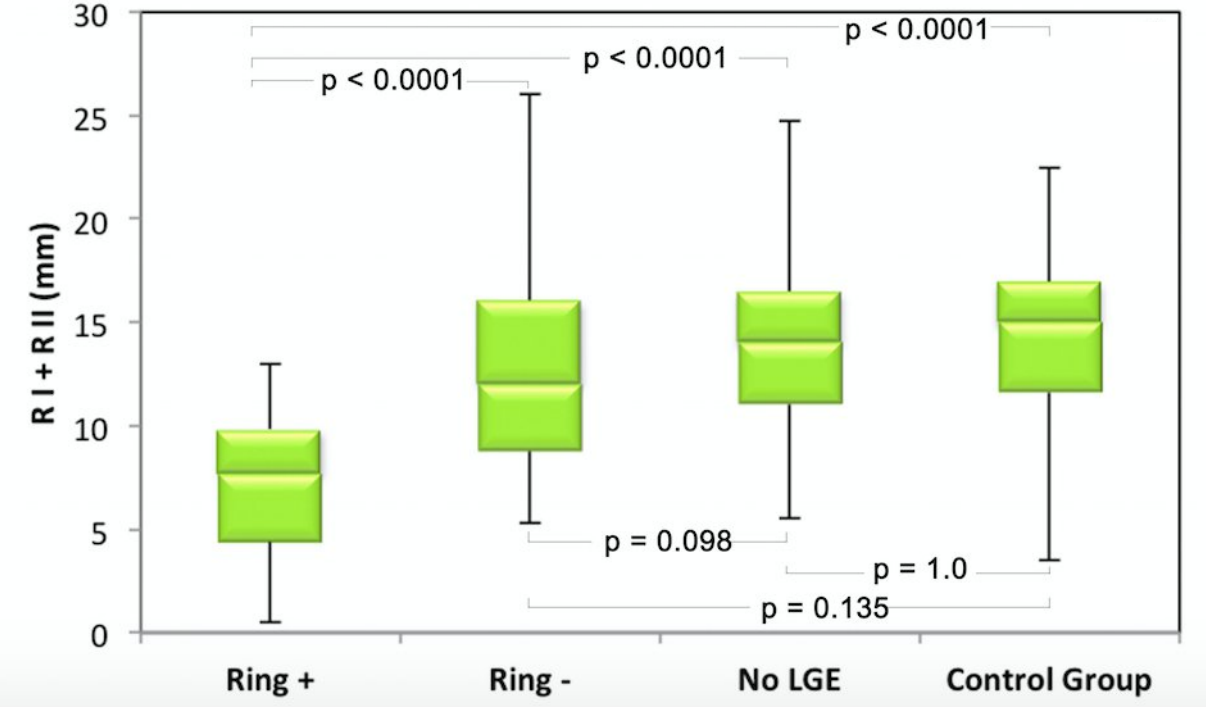
	Non Ring like (n=59)	Ringlike (n=20)	P Value
QTc (msec)	433±37	414±37	**<0.0001**
QTc ≥440 msec	21 (35.6)	7 (35.0)	0.83
Tzou criteria	1 (1.7)	0	0.57
R > 3 mm in V1	3 (5.1)	2 (10.0)	0.8
Bayés de Luna criteria	2 (3.4)	1 (5.0)	0.99
Poor R-wave progression	3 (5.1)	1 (5.0)	0.56
TWI	16 (27.1)	9 (45.0)	0.23
Inferolateral	3 (5.1)	2 (10.0)	0.79
Anterior	3 (5.1)	2 (10.0)	0.81
Inferior	3 (5.1)	2 (10.0)	0.81
Lateral	6 (10.2)	1 (5.0)	0.32
Anterolateral	1 (1.7)	2 (10.0)	0.33
R I (mm)	7.6±2.9	4.0±2.6	**<0.0001**
R II (mm)	4.8±2.9	3.1±2.1	**0.019**
R I + R II (mm)	12.5±4.6	7.1±3.6	**<0.0001**

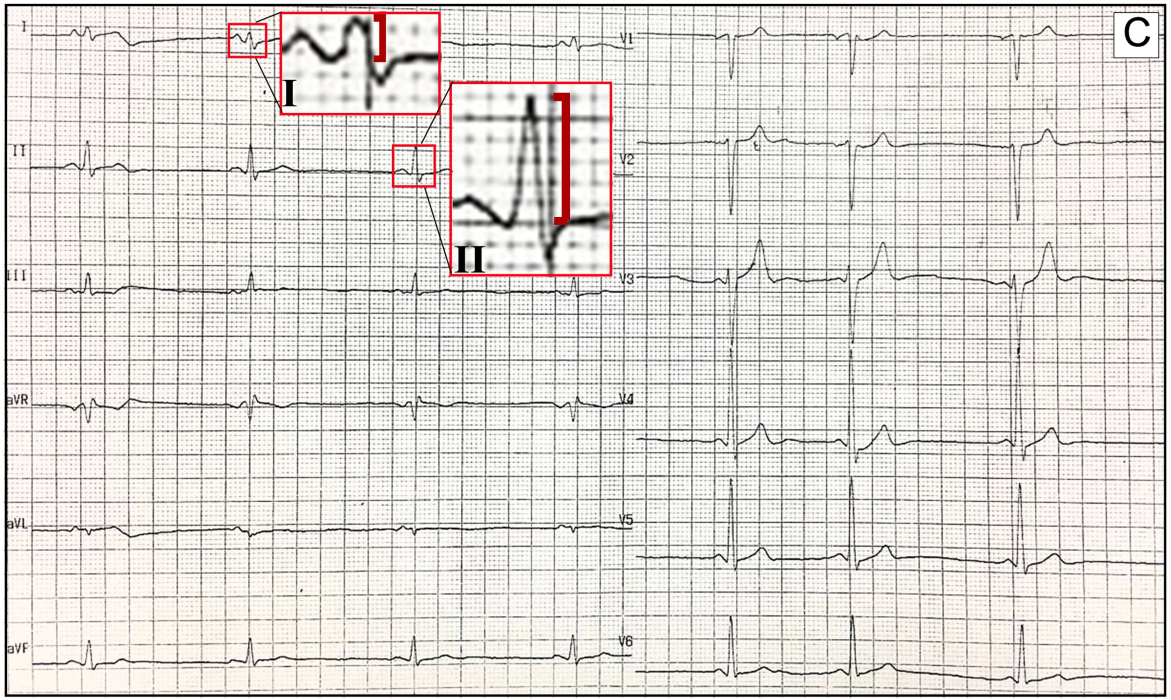
PLACE 9ª Edizione

ECG and CMR



ECG and CMR


30
25
20
15
10
5
0
R I + R II (mm)
p < 0.0001
p < 0.0001
p < 0.0001
p = 0.098
p = 1.0
p = 0.135
Ring +
Ring -
No LGE
Control Group


C
I
II
I
II
III
aVR
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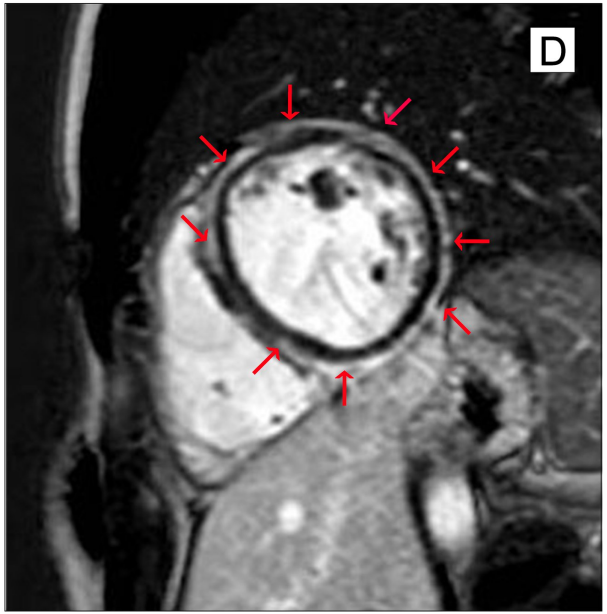
aVF
V1
V2
V3
V4
V5
V6


D

3. ECG and Major Arrhythmic Events

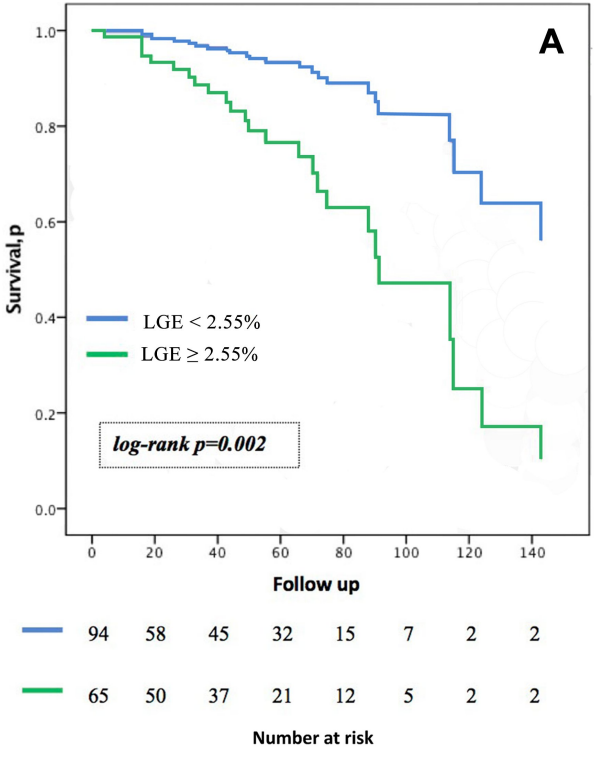
Over a median **40-months follow-up** (16.2–66),

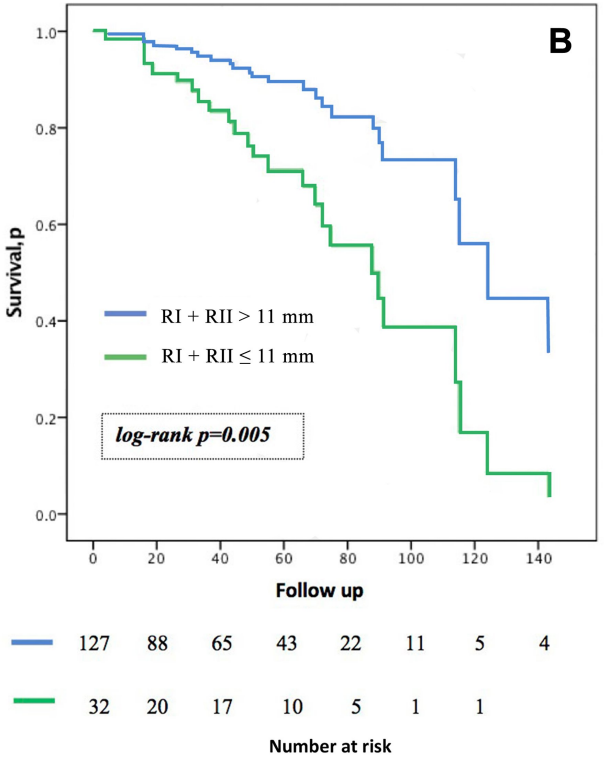
25 patients (**15.7%**) reached the composite endpoint

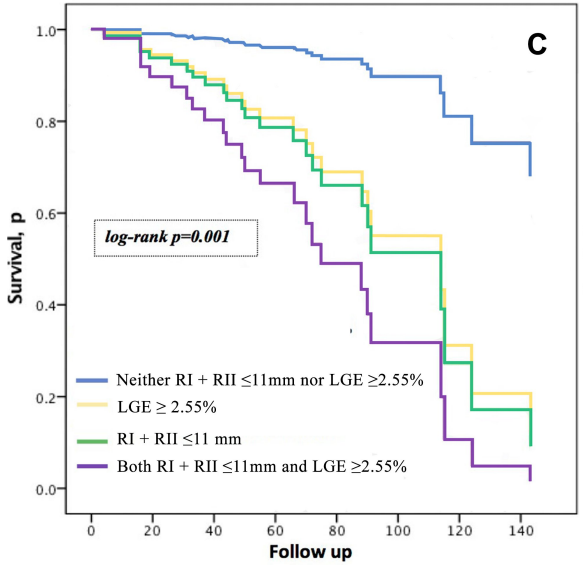
	Overall (n=159)	Major Arrhythmic Events (n=25)	No Major Arrhythmic Events (n=134)	P Value
ECG				
QRS (msec)	115 ± 29	110 ± 25	116 ± 29	**<0.0001**
LVH: Sokolow-Lyon criteria	25(15.7)	1 (4.0)	24 (17.9)	0.71
LVH: Cornell criteria	27 (17.0)	3 (12.0)	24 (17.9)	0.75
LAFB	11 (6.9)	2 (8.0)	9 (6.7)	0.84
LPFB	5 (3.1)	5 (20.0)	0 (0)	**<0.0001**
LBBB	45 (28.3)	6 (24.0)	39 (29.1)	0.603
Pathological Q waves	24 (15.1)	8 (32.0)	16 (11.9)	**0.010**
Fragmented QRS	40 (25.2)	8 (32.0)	32 (23.9)	0.390
Low-voltage QRS	70 (44.0)	16 (64.0)	54 (40.3)	**0.028**
Global	3 (1.9)	1 (4.0)	2 (1.5)	0.403
Limb leads	12 (7.5)	3 (12.0)	9 (6.7)	0.61
Precordial leads	5 (3.1)	2 (8.0)	3 (2.2)	0.176
Lateral distribution	3 (1.9)	0 (0)	3 (2.2)	1.000
Inferior distribution	41 (25.8)	9 (36.0)	32 (23.9)	0.31
More 2 localization	6 (3.8)	1 (4.0)	5 (3.7)	1.000
QTc ≥440 msec	70 (44.0)	12 (48.0)	59 (44.0)	0.83
Tzou criteria	5 (3.1)	0 (0)	5 (3.7)	1.000
R > 3 mm V1	6 (3.8)	2 (8.0)	4 (3.0)	0.239
TWI	42 (26.4)	9 (36.0)	33 (24.6)	0.236
Anterior	5 (3.1)	3 (12.0)	2 (1.5)	**0.028**

Table 5. Probability of major arrhythmic events in relation to clinical, electrocardiographic and structural parameters: univariate and multivariate analysis.

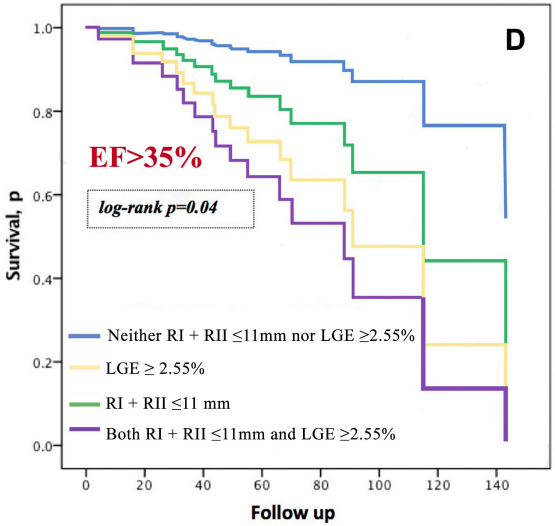
	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P value*	HR	95% CI	*P value*
Clinical parameters						
Age	0.99	0.96-1.1	*0.390*			
Sex	1.96	0.7-5.2	*0.181*			
Unexplained syncope	2.2	0.9-5.3	*0.084*			
NSVT	5.2	1.6-17.4	***0.008***			
Structural parameters						
LGE	3.4	1.4-8.6	***0.010***			
LGE ≥ 2.55%	3.9	1.6-9.9	***0.004***	2.8	1.1-7.4	***0.04***
LGE ≥ 5.1%	0.8	0.3-2.2	*0.664*			
Ring-like pattern	3.6	1.6-8.2	***0.003***			
ECG parameters						
LPFB	5.2	1.8-14.9	***0.003***	3.3	1.1-10.4	***0.04***
Pathological Q waves	3.6	1.5-8.4	***0.004***			
R I + R II ≤11 mm	3.1	1.3-6.9	***0.008***	2.7	1.2-6.5	***0.02***


A
Survival,p
1.0
0.8
0.6
0.4
0.2
0.0
LGE < 2.55%
LGE ≥ 2.55%
log-rank p=0.002
0 20 40 60 80 100 120 140
Follow up
94 58 45 32 15 7 2 2
65 50 37 21 12 5 2 2
Number at risk

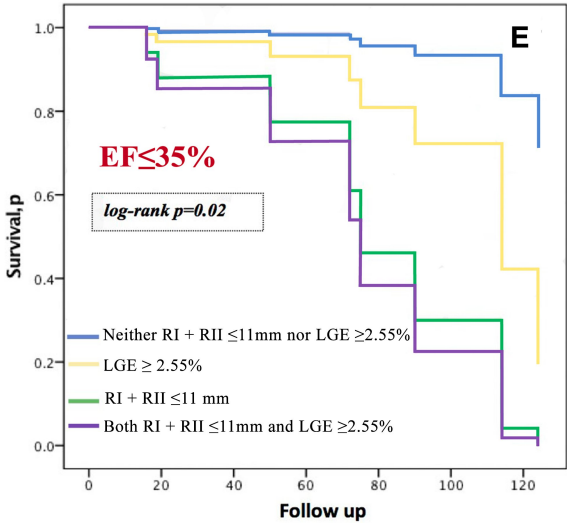

B
Survival,p
1.0
0.8
0.6
0.4
0.2
0.0
RI + RII > 11 mm
RI + RII ≤ 11 mm
log-rank p=0.005
0 20 40 60 80 100 120 140
Follow up
127 88 65 43 22 11 5 4
32 20 17 10 5 1 1
Number at risk



Number at risk								
	83	51	39	28	13	6	3	2
	44	37	26	15	9	5	2	2
	11	7	6	4	2	1		
	21	13	11	6	3			



Number at risk								
	44	28	21	14	6	2	1	1
	27	22	16	9	7	3	1	1
	4	3	2	2	1	1		
	13	9	8	5	2			



Number at risk								
	39	23	18	14	7	4	2	
	17	15	10	6	2	2	1	
	7	4	4	2	1			
	8	4	3	1	1			

Conclusions (1)

- DCM phenotype includes several acquired and genetic causes, which could determine the different outcome in DCM patients. **SCD may be the first manifestation** in asymptomatic patients and a correct and timely diagnosis is challenging.

- ECG is a simple, cost-effective, widespread available tool and yieldsan instant result.

Conclusions (2)

- ECG in patients with DCM is **rarely normal** and ECG abnormalities should trigger initiation of diagnostic work up. ECG abnormalities could precede overt structural changes

- The approach in ECG analysis should be focusing on specific '**red flags**'

- Specific ECG signs deserve proper clinical attention and **provide an incremental prognostic value in addition to clinical, structural and genetic data** in the identification of patients with **"DCM arrhythmogenic phenotype"**

Extra (Genetic findings)

	Healthy Controls (n=56)	Overall (n=159)	*P Value*[1]	LV LGE + (n=79)	LV LGE – (n=80)	*P Value*[2]
Genetics						
Positive test*	-	23/67 (34.3)	-	18/48 (37.5)	5/19 (26.3)	*0.55*
Functional gene groups	-		-			
LMNA	-	7/23 (30.4)	-	7/18 (38.9)	0/5 (0)	*0.26*
DSP, DSG, FLNC	-	8/23 (34.8)	-	7/18 (38.9)	1/5 (20.0)	*0.79*
Titin, MYH7, MYBPC3, RYR2, RBM20, TSEN2	-	8/23 (34.8)	-	4/18 (22.2)	4/5 (80.0)	*0.06*

- LGE was detected in 92.8% patients with DSP/FLNC and LMNA 24 genotypes.
- **Septal LGE** distribution was observed in 5 out of 7 pts with **LMNA** mutations; **inferolateral LGE** distribution was present in **subjects with DSP/FLNC mutations**.

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Extra (Genetic findings)

	LMNA (n=7)	FLNC/DSP (n=7)	P Value
QRS (msec)	114±27	93±11	0.08
LVH: Sokolow-Lyon criteria	0	0	0.99
LVH: Cornell criteria	0	1 (14.3)	0.99
First degree AV block	3 (42.9)	0	0.19
NICD	0	0	-
RBBB	1 (14.3)	0	0.99
LAFB	1 (14.3)	1 (14.3)	0.32
LFPB	0	0	-
LBBB	1 (14.3)	0	0.99
Pathological Q waves	2 (28.6)	0	0.45
Lateral distribution	0	0	-
Inferior distribution	0	0	-
Precordial distribution	1 (14.3)	0	0.99
More 2 localizations	1 (14.3)	0	0.99
Fragmented QRS	0	0	-
Lateral distribution	0	0	-
Inferior distribution	0	0	-
Precordial distribution	0	0	-
More 2 localizations	0	0	-

	LMNA (n=7)	FLNC/DSP (n=7)	P Value
Low-voltage QRS	5 (71.4)	6 (85.7)	0.76
Global	0	0	-
Limb leads	0	2 (28.6)	0.44
Precordial leads	1 (14.3)	1 (14.3)	0.32
Lateral distribution	0 (0.0)	1 (14.3)	0.99
Inferior distribution	3 (42.9)	2 (28.6)	0.99
More 2 localizations	1 (14.3)	0	0.99
QTc (msec)	452 ± 28	411 ± 39	**0.045**
QTc 440 msec	5 (71.4)	2 (28.6)	0.29
Tzou criteria	0	0	-
R >3 mm V1	0	1 (14.3)	0.99
Bayés de Luna criteria	0	0	-
Poor R-wave progression in precordial leads	1 (14.3)	0	0.99
TWI	2 (28.6)	3 (42.9)	0.99
Inferolateral	0	1 (14.3)	0.99
Anterior	0	0	-
Inferior	2 (28.6)	0	0.45
Lateral	0	2 (28.6)	0.44

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PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

Extra (CMR findings)

	Healthy Controls (n=56)	Overall (n=159)	*P Value*[1]	LV LGE + (n=79)	LV LGE – (n=80)	*P Value*[2]
Cardiac magnetic resonance						
LVEDVi (ml/m2)	74.8±18.1	113.3±36.8	***<0.0001***	111.3±36.8	115.1±36.9	*0.11*
LVEF, %	63.8±5.5	35.2±10.0	***<0.0001***	36.4±9.8	34±10	*0.11*
RVEDVi (ml/m2)	73.4±18.9	74.3±24.1	*0.58*	75.1±24.7	73.4±23.6	*0.72*
RVEF, %	64±8.6	51.5±13.5	*0.17*	53.0±12.9	50.0±14.0	*0.29*
LV Mass index (g/m2)	58.6±11.5	69.1±20.9	***0.005***	65.8±20.5	74±20.1	*0.09*
Intramyocardial fat signal	0	3 (1.9)	***0.03***	2 (2.5)	1 (1.3)	*0.9*
Segments with LGE	-	2±3; 0(0-3)	-	4±3; 3 (2-5)	-	-
LGE extent						
- LGE <2.55%	-	14 (8.8)	-	14 (17.7)	-	-
- LGE ≥2.55% and <5.1%	-	37 (23.3)	-	37 (46.8)	-	-
- LGE ≥ 5.1%	-	28 (17.6)	-	28 (35.4)	-	-
LGE location						
- Ringlike pattern	-	20 (12.6)	-	20 (25.3)	-	-
- Non-ringlike pattern	-	59 (37.1)	-	59 (74.7)	-	-
Septal	-	31 (19.5)	-	31 (39.2)	-	-
free wall	-	25 (15.7)	-	25 (31.6)	-	-
septal + free wall	-	3 (1.9)	-	3 (3.8)	-	-
LGE pattern						
- Subepicardial	-	17 (10.7)	-	17 (21.5)	-	-
- Midwall	-	50 (31.4)	-	50 (63.3)	-	-
- Subendocardial/transmural	-	7 (4.4)	-	7 (8.9)	-	-
- Mixed	-	5 (3.1)	-	5 (6.3)	-	-

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PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

Extra (CMR findings)

	0<%LGE<2.55 (n=14)	%LGE ≥ 2.55 (n=65)	P Value
QRS (msec)	123 ± 37	111 ± 28	0.37
First degree AV block	5 (35.7)	14 (21.5)	0.43
NICD	0	3 (4.6)	0.96
LAFB	1 (7.1)	9 (13.8)	0.81
LPFB	0	5 (7.7)	0.64
LBBB	6 (42.9)	11 (16.9)	0.074
Pathological Q waves	5 (35.7)	15 (23.1)	0.52
Lateral distribution	0	1 (1.5)	0.78
Inferior distribution	5 (35.7)	3 (4.6)	**0.0027**
Precordial distribution	0	7 (10.8)	0.342
More 2 localizations	0	4 (6.2)	0.78
Fragmented QRS	3 (21.4)	14 (21.5)	0.73
Lateral distribution	0	2 (3.1)	0.78
Inferior distribution	2 (14.3)	4 (6.2)	0.63
Precordial distribution	0	2 (3.1)	0.78
More 2 localizations	1 (7.1)	6 (9.2)	0.79
Low-voltage QRS	5 (35.7)	38 (58.5)	0.12
Global	0	2 (3.1)	0.78
Limb leads	0	8 (12.3)	0.34
Precordial leads	0	3 (4.6)	0.96
Lateral distribution	1 (1.7)	1 (1.5)	0.78
Inferior distribution	4 (28.6)	18 (27.7)	0.79
More 2 localizations	0	6 (9.2)	0.53

	0<%LGE<2.55 (n=14)	%LGE ≥ 2.55 (n=65)	P Value
QTc (msec)	437±35	426±38	0.323
QTc ≥440 msec	5 (35.7)	23 (35.4)	0.78
Tzou criteria	0	1 (1.5)	0.39
R >3 mm V1	2 (14.3)	3 (4.6)	0.46
Bayés de Luna criteria	1 (7.1)	2 (3.1)	0.78
Poor R-wave progression	0	4 (6.2)	0.78
TWI	3 (21.4)	22 (33.8)	0.55
Inferolateral	1 (7.1)	4 (6.2)	0.64
Anterior	1 (7.1)	4 (6.2)	0.64
Inferior	0	5 (7.7)	0.63
Lateral	0	7 (10.8)	0.44
Anterolateral	1 (7.1)	2 (3.1)	0.96
QRS I (mm)	8.9±4.3	7.3±2.9	0.19
R I (mm)	8.0±3.8	6.4±3.1	0.097
QRS II (mm)	7.6±3.0	6.2±2.8	0.08
R II (mm)	5.4±2.9	4.2±2.8	0.13
R I + R II (mm)	13.4±5.6	10.6±4.7	**0.054**
R I + R II ≤ 11 mm	6 (42.9)	39 (60.0)	0.24

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Extra (Clinical data)

	Healthy Controls (n=56)	Overall (n=159)	*P Value*[1]	LV LGE + (n=79)	LV LGE – (n=80)	*P Value*[2]
Age at diagnosis, years	54.5±10.2	54.5±13.0	*0.89*	54.3±14.4	54.7±11.5	*0.97*
Male gender	38 (67.9)	107 (67.3)	*0.99*	58 (73.4)	49 (61.3)	*0.14*
Proband	-	154 (96.9)	-	75 (94.9)	79 (98.8)	*0.36*
Family history of DCM	0	32 (20.1)	***0.00001***	19 (24.1)	13 (16.3)	*0.3*
Family history of SCD	0	19 (11.9)	***0.014***	11 (13.9)	8 (10.0)	*0.6*
NYHA class I-II	56 (100)	142 (89.3)	***0.0013***	72 (91.1)	70 (87.5)	*0.18*
NYHA class III	0	17 (10.7)	***0.024***	7 (8.9)	10 (12.5)	*0.18*
Atrial fibrillation	0	27 (17.0)	***0.002***	17 (21.5)	10 (12.5)	*0.2*
ICD recipients	-	91 (57.2)	***<0.0001***	53 (67.1)	38 (47.5)	***0.02***
primary prevention	-	79 (49.7)	-	43 (54.4)	36 (45)	***0.008***
secondary prevention	-	12 (7.6)	-	10 (12.7)	2 (2.5)	***0.008***
Unexplained syncope	0	16 (10.1)	***0.029***	10 (12.7)	6 (7.5)	*0.43*
NSVT	0	82 (51.6)	***<0.0001***	56 (70.9)	26 (32.5)	***<0.0000***

Extra (ECG data)

Table S1. QRS and R wave voltage in limb leads according to presence or absence of LGE.

	Overall (n=159)	LV LGE + (n=79)	LV LGE - (n=80)	P Value
QRS I	8.3±3.4	7.5±3.2	9.0±3.5	**0.006**
R I	7.7±3.5	6.7±3.3	8.7±3.5	**0.0005**
QRS II	6.9±2.8	6.4±2.8	7.3±2.8	0.06
R II	5.0±2.8	4.4±2.8	5.6±2.7	**0.007**
QRS III	7.4±3.9	7.0±3.6	7.8±4.2	0.24
R III	1.6±1.6	1.6±1.7	1.6±1.4	0.99
QRS aVL	7.0±3.3	6.5±3.1	7.5±3.4	0.062
R aVL	6.2±3.5	5.5±3.4	6.9±3.5	**0.014**
QRS aVF	5.8±2.8	5.6±2.7	6.1±2.9	0.23
R aVF	2.5±1.9	2.4±1.9	2.7±1.9	0.22
QRS aVR	6.6±2.8	6.1±2.6	7.2±2.8	**0.013**
R aVR	0.7±1.0	1.0±1.0	0.5±0.8	**<0.0001**
R I + R II	12.7±5.2	11.1±4.9	14.3±5.0	**<0.0001**

	Overall (n=159)	Major Arrhythmic Events (n=25)	No Major Arrhythmic Events (n=134)	P Value
Age at diagnosis, years	54.5±13.0	52.0±14.4	55.0±12.7	0.290
Male gender	107 (67.3)	20 (80.0)	87 (64.9)	0.21
Family history of DCM	32 (20.1)	3 (12.0)	29 (21.6)	0.4
Family history of SCD	19 (11.9)	0	19 (14.2)	0.045
NYHA class I-II	142 (89.3)	21 (84.0)	121 (90.3)	0.49
NYHA class III	17 (10.7)	4 (16.0)	13 (9.7)	0.49
Atrial fibrillation	27 (17.0)	5 (20.0)	22 (16.4)	0.89
ICD recipients	91 (57.2)	23 (92.0)	68 (50.7)	**0.0003**
Unexplained syncope	16 (10.1)	7 (28.0)	9 (6.7)	**0.004**
NSVT	82 (51.6)	22 (88.0)	60 (44.8)	**<0.0002**
Genetics				
Positive test*	23/67 (34.3)	6/14 (42.9)	17/53 (32.0)	0.83
LMNA	7/23 (30.4)	2/6 (33.3)	5/17 (29.4)	0.74
DSP, DSG, FLNC	8/23 (34.8)	2/6 (33.3)	6/17 (35.3)	0.68
Titin, MYH7, MYBPC3, RYR2, RBM20, TSEN2	8/23 (34.8)	2/6 (33.3)	6/17 (35.3)	0.68

	Overall (n=159)	Major Arrhythmic Events (n=25)	No Major Arrhythmic Events (n=134)	P Value
Cardiac magnetic resonance				
LVEDVi (ml/m2)	113.3±36.8	102.1±37.3	115.2±36.5	**0.046**
LVEF, %	35.2±10.0	37.6±9.9	34.8±10	0.14
RVEDVi (ml/m2)	74.3±24.1	72.3±21.5	74.6±24.5	0.81
RVEF, %	51.5±13.5	54.5±13.0	51.0±13.5	0.26
LV Mass index (g/m2)	69.1±20.9	67.9±21.4	69.3±21.0	0.7
Intramyocardial fat signal	3 (1.9)	1 (4.0)	2 (1.5)	0.403
LGE	79 (49.7)	19 (76.0)	60 (44.8)	**0.008**
Segments with LGE	2±3; 0 (0-3)	3.5±3.2; 3 (0.5-5)	1.7±2.8; 0 (0-2)	**0.0013**
LGE location				
- Ringlike pattern	20 (12.6)	9 (36.0)	11 (8.2)	**0.0004**
- Non-ringlike pattern	59 (37.1)	10 (40.0)	49 (36.6)	**0.025**
Septal	31 (19.5)	8 (32.0)	23 (17.2)	0.58
free wall	25 (15.7)	2 (8.0)	23 (17.2)	**0.051**
septal + free wall	3 (1.9)	0	3 (2.2)	1.0
LGE extent				
- LGE <2.55%	14 (8.8)	0	14 (10.4)	0.129
- LGE ≥2.55% and <5.1%	37 (23.3)	14 (56.0)	23 (17.2)	**<0.0001**
- LGE ≥ 5.1%	28 (17.6)	5 (20.0)	23 (17.2)	0.733

Over a median **40-months follow-up** (16.2–66),

25 patients (**15.7%**) reached the composite endpoint

ECG in LMNA genotypes

ORIGINAL RESEARCH ARTICLE

Circulation

Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

Table 2. Associations Between Predictors and Survival in the Derivation Sample

Characteristics	Model			
	Full Multiple Variable	*P* Value	Final	*P* Value
Age at baseline, y	0.99 (0.97–1.01)	0.200		
Men	1.80 (1.1–2.95)	0.029	1.67 (1.1–2.55)	0.017
Nonmissense *LMNA* mutation	1.78 (1.12–2.85)	0.043	1.76 (1.16–2.65)	0.007
AV block				
First degree*	2.74 (1.34–5.61)	0.002	2.35 (1.34–4.12)	0.003
>First degree†	3.51 (1.5–8.19)	0.001	2.86 (1.54–5.31)	<0.001
Atrial arrhythmia	1.19 (0.71–1.99)	0.524		
Nonsustained VT	2.25 (1.34–3.79)	0.002	2.15 (1.36–3.41)	0.001
Left ventricular ejection fraction, %	0.98 (0.96–1.00)	<0.001	0.98 (0.97–1)	0.017

839 adult pts with *LMNA* mutations: 444 pts in the derivation sample and 145 pts in the validation sample

A **5-year** estimated risk threshold **≥7%** predicted **96.2%** of LTVTA and net reclassified 28.8% of patients with LTVTA in comparison with the guidelines-based approach

Karim Wahbi, MD, PhD et al; Circulation 2021

JACC Journals

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

OBJECTIVES The aim of this study was to demonstrate the association between truncating mutations in *FLNC* and the development of high-risk dilated and arrhythmogenic cardiomyopathies.

METHODS *FLNC* was studied using next-generation sequencing in 2,877 patients with inherited cardiovascular diseases. A characteristic phenotype was identified in probands with truncating mutations in *FLNC*. Clinical and genetic evaluation of 28 affected families was performed. Localization of filamin C in cardiac tissue was analyzed in patients with truncating *FLNC* mutations using immunohistochemistry.

RESULTS Twenty-three truncating mutations were identified in 28 probands previously diagnosed with dilated, arrhythmogenic, or restrictive cardiomyopathies. Truncating *FLNC* mutations were absent in patients with other phenotypes, including 1,078 patients with hypertrophic cardiomyopathy. Fifty-four mutation carriers were identified among 121 screened relatives. The phenotype consisted of left ventricular dilation (68%), systolic dysfunction (46%), and myocardial fibrosis (67%) inferolateral negative T waves and low QRS voltages on electrocardiography (33%); ventricular arrhythmias (82%); and frequent sudden cardiac death (40 cases in 21 of 28 families). Clinical skeletal myopathy was not observed. Penetrance was >97% in carriers older than 40 years. Truncating mutations in *FLNC* cosegregated with this phenotype with a dominant inheritance pattern (combined logarithm of the odds score: 9.5). Immunohistochemical staining of myocardial tissue showed no abnormal filamin C aggregates in patients with truncating *FLNC* mutations.

CONCLUSIONS Truncating mutations in *FLNC* caused an overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies complicated by frequent premature sudden death. Prompt implantation of a cardiac defibrillator should be considered in affected patients harboring truncating mutations in *FLNC*.

- Filamin C gene (*FLNC*) variants account for about 4% of DCM cases
- Filamin C protein is essential in providing mechanical link and signal transmission between sarcomere and plasmatic membrane
- Overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies complicated by frequent premature SCD
- VAs often before overt LV dysfunction

Ortiz-Genga et al. J Am Coll Cardiol 2016;68:2440–51)

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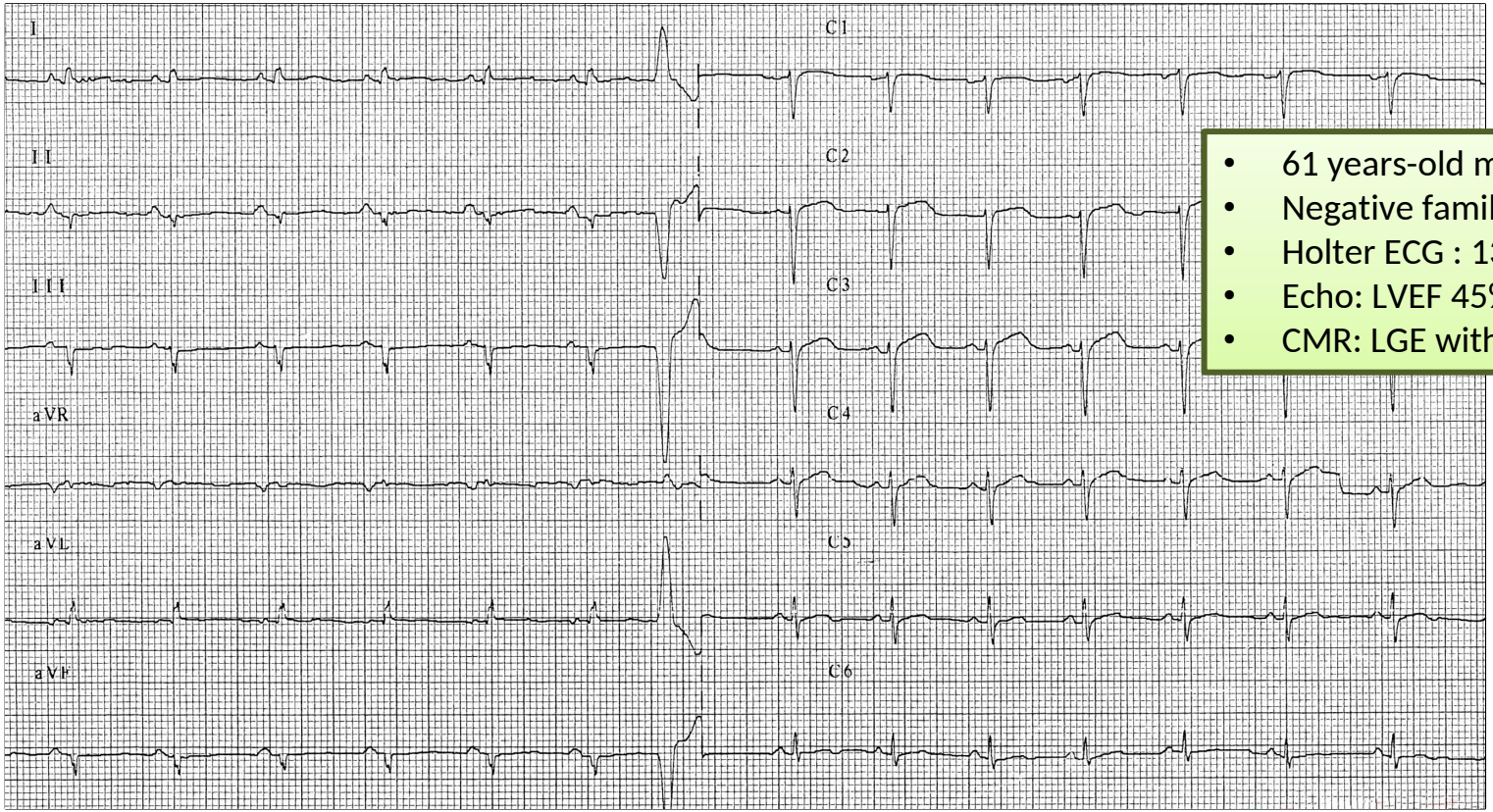
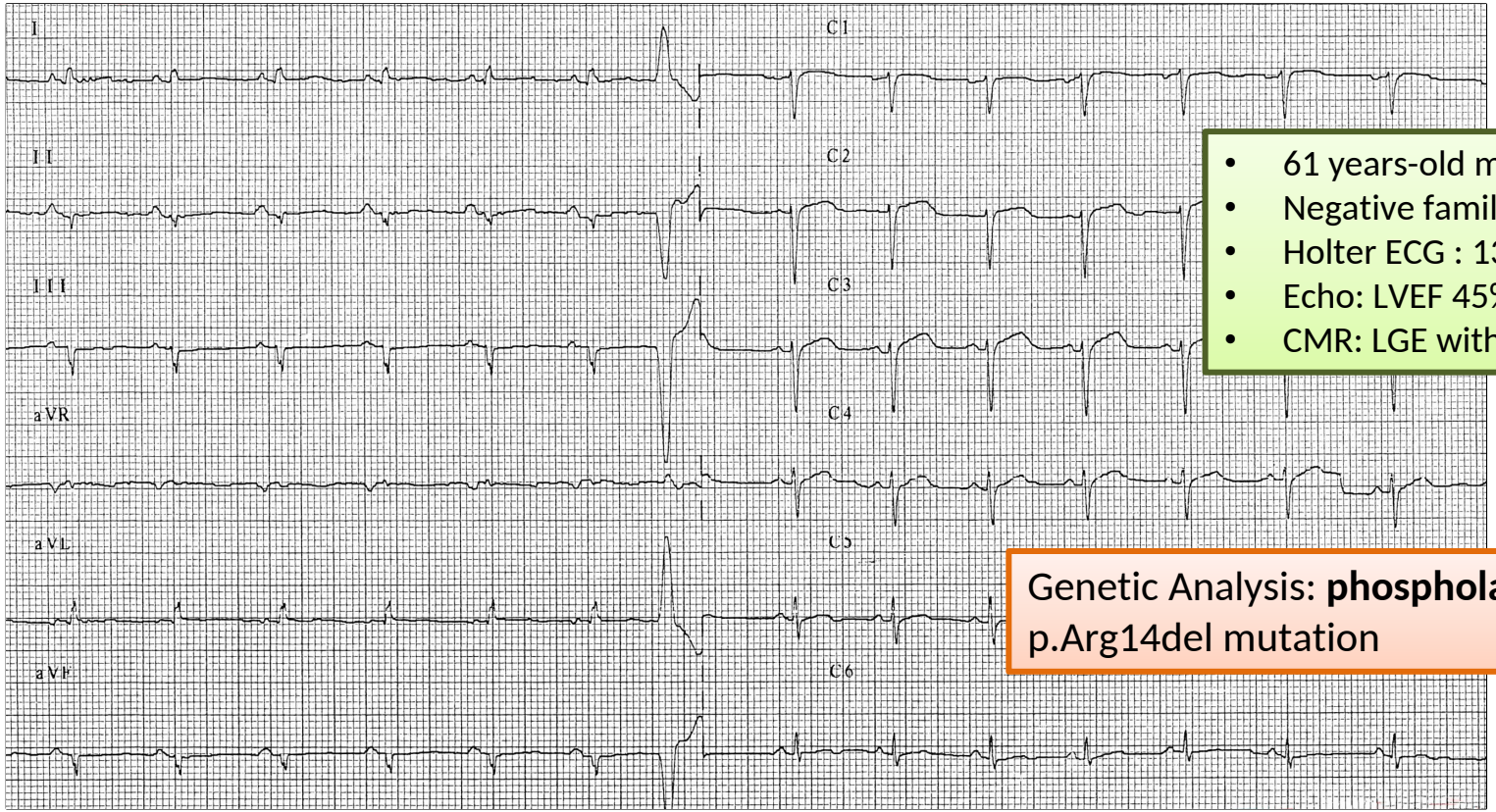
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE



- 61 years-old man
- Negative familiar history of DCM/SCD
- Holter ECG : 1377 PVC
- Echo: LVEF 45%
- CMR: LGE with ringlike pattern



- 61 years-old man
- Negative familiar history of DCM/SCD
- Holter ECG : 1377 PVC
- Echo: LVEF 45%
- CMR: LGE with ringlike pattern

Genetic Analysis: **phospholamban (PLN)** p.Arg14del mutation

PLACE 9ª Edizione

ESC European Society of Cardiology
European Heart Journal (2021) 42, 2842–2850
doi:10.1093/eurheartj/ehab294

CLINICAL RESEARCH
Arrhythmias

Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers–reaching the frontiers of individual risk prediction

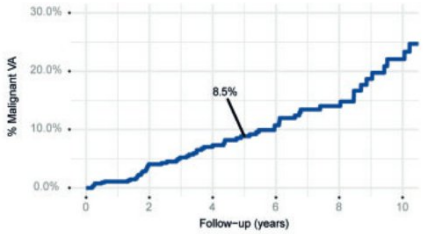
Tom E. Verstraelen [1]*, Freyja H.M. van Lint [2,3], Laurens P. Bosman [4], Remco de Brouwer [5], Virginnio M. Proost [1], Bob G.S. Abeln [1], Karim Taha [4], Aeilko H. Zwinderman[6], Cathelijne Dickhoff[7], Toon Oomen[8], Bas A. Schoonderwoerd[9], Gerardus P. Kimman[10], Arjan C. Houweling [2], Juan R. Gimeno-Blanes[11,12], Folkert W. Asselbergs[4,13], Paul A. van der Zwaag [14], Rudolf A. de Boer [5], Maarten P. van den Berg [5], J. Peter van Tintelen [2,3], and Arthur A.M. Wilde [1,12]

- 679 PLN p.Arg14del mutation carriers with no history of malignant VA at baseline; median age 42 years. **10.6% composite endpoint of malignant VA**
- **Significant predictors** were LVEF, PVC count/24 h, amount of negative T waves, and presence of low-voltage.
- The multivariable model had an excellent discriminative ability

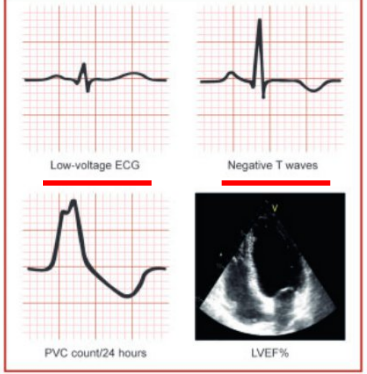
Mutation specific risk prediction of malignant ventricular arrhythmia (VA)

In phospholamban (*PLN*) mutation carriers

Time from first cardiac evaluation to first malignant VA (N=679)



Mutation specific risk factors



Time from first cardiac evaluation to first malignant VA stratified by risk quintile