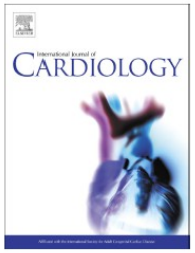
CARDIOMIOPATIA ARITMOGENE: WHAT'S NEW?

ECG e displasia aritmogena left-dominant

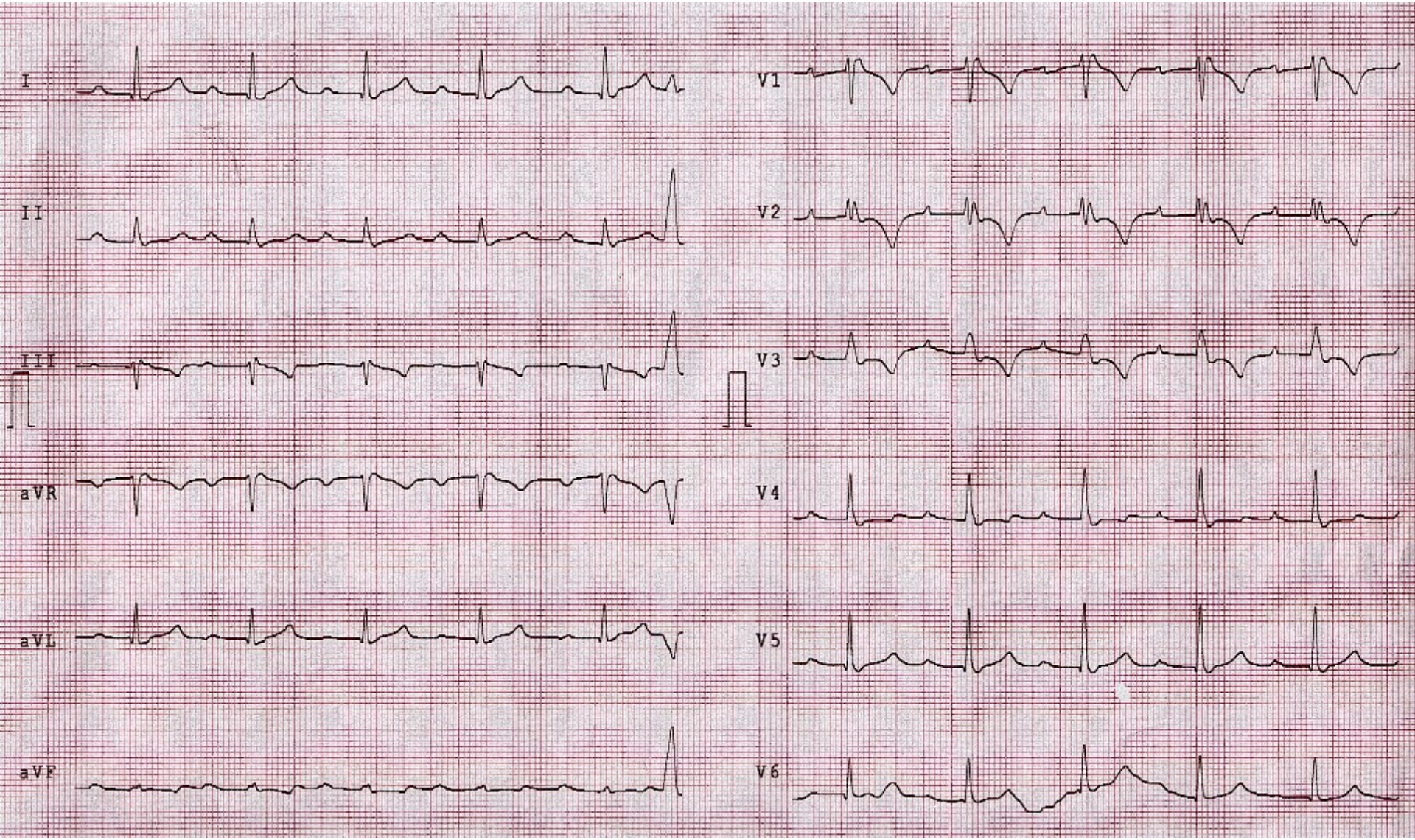
L. Calò, Roma

Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria



Domenico Corrado, Martina Perazzolo Marra, Alessandro Zorzi, Giorgia Beffagna, Alberto Cipriani, Manuel De Lazzari, Federico Migliore, Kalliopi Pilichou, Alessandra Rampazzo, Ilaria Rigato, Stefania Rizzo, Gaetano Thiene, Aris Anastasakis, Angeliki Asimaki, Chiara Bucciarelli-Ducci, Kristine H. Haugaa, Francis E. Marchlinski, Andrea Mazzanti, William J. McKenna, Antonis Pantazis, Antonio Pelliccia, Christian Schmied, Sanjay Sharma, Thomas Wichter, Barbara Bauce, Cristina Basso

Category	Right ventricle (upgraded 2010 ITF diagnostic criteria)	Left ventricle (new diagnostic criteria)
III. Repolarization abnormalities	***Major*** • Inverted T waves in right precordial leads (V_1,V_2, and V_3) or beyond in individuals with complete pubertal development (in the absence of complete RBBB)	***Minor*** • Inverted T waves in left precordial leads (V_4-V_6) (in the absence of complete LBBB)
	Minor • Inverted T waves in leads V1 and V2 in individuals with completed pubertal development (in the absence of complete RBBB) • Inverted T waves in V1,V2 ,V3 and V4 in individuals with completed pubertal development in the presence of complete RBBB.	
IV. Depolarization abnormalities	***Minor*** • Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3) • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 (in the absence of complete RBBB)	***Minor*** • Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema, or pericardial effusion)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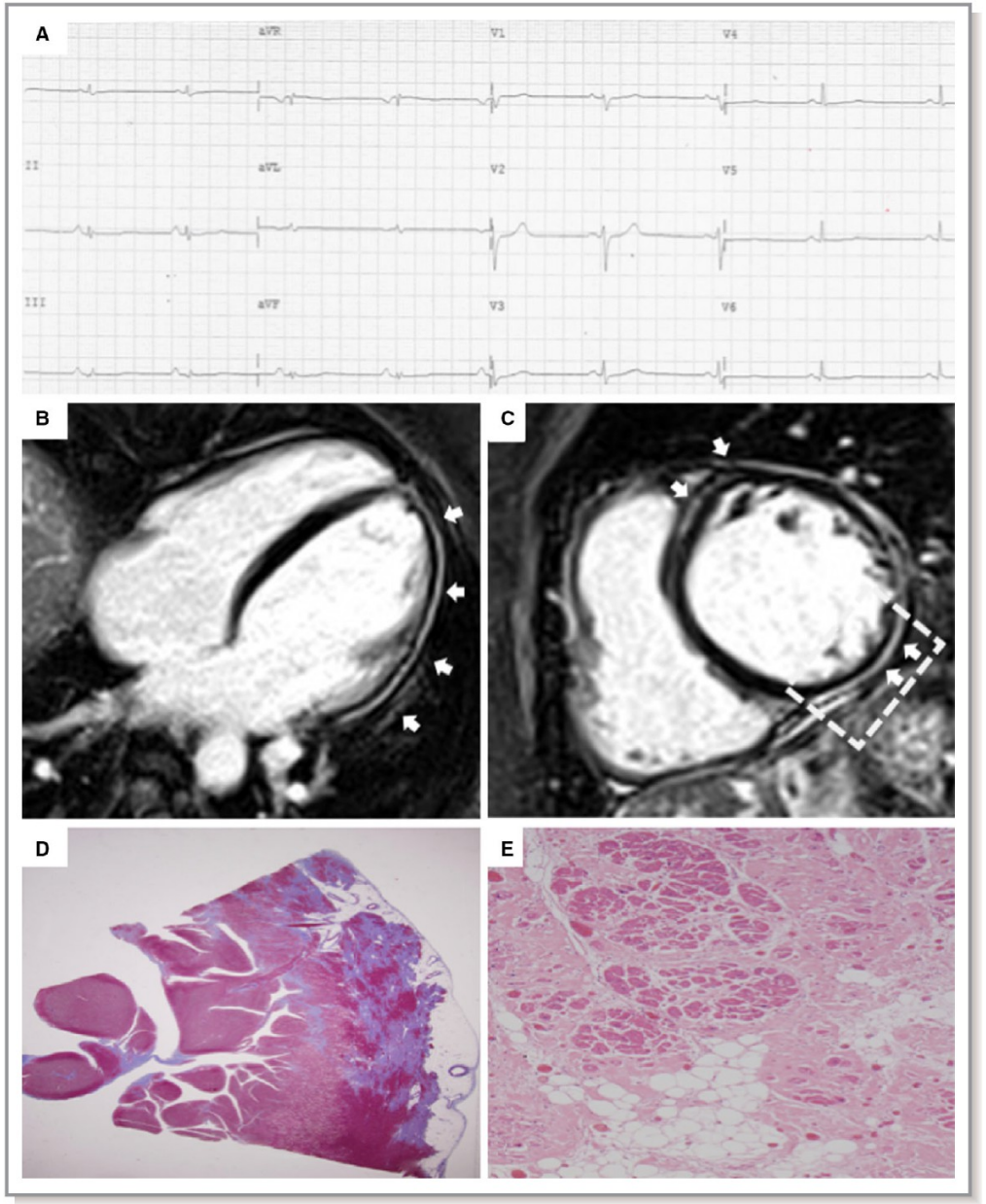
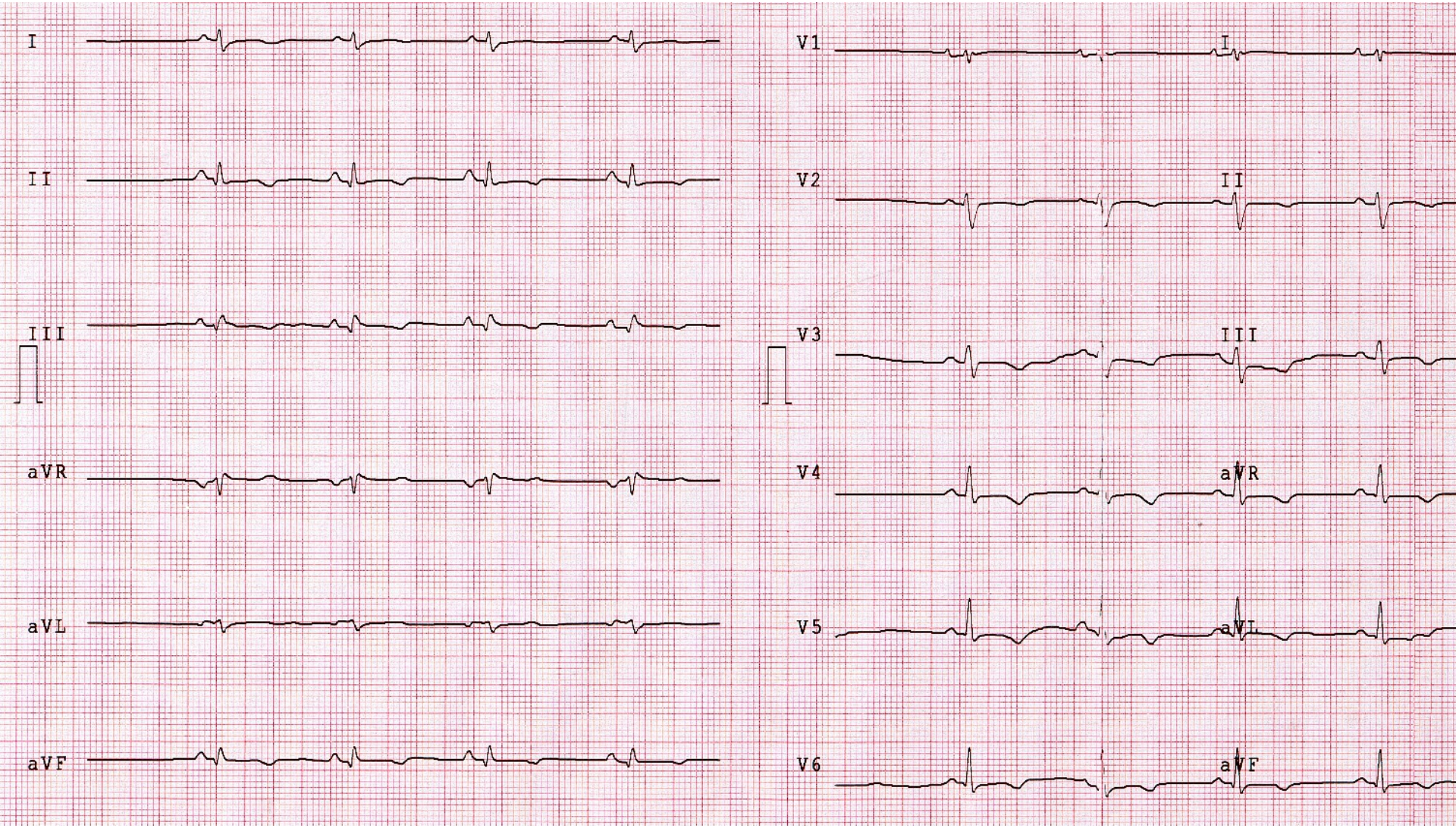


Figure 5. Electrocardiographic, CMR imaging, and histological features of a representative patient with ARVC undergoing cardiac transplantation. Basal ECG showing low voltages in limb leads and flattened T-waves in the inferolateral leads (**A**). Post-contrast CMR images in long-axis (**B**) and short-axis (**C**) views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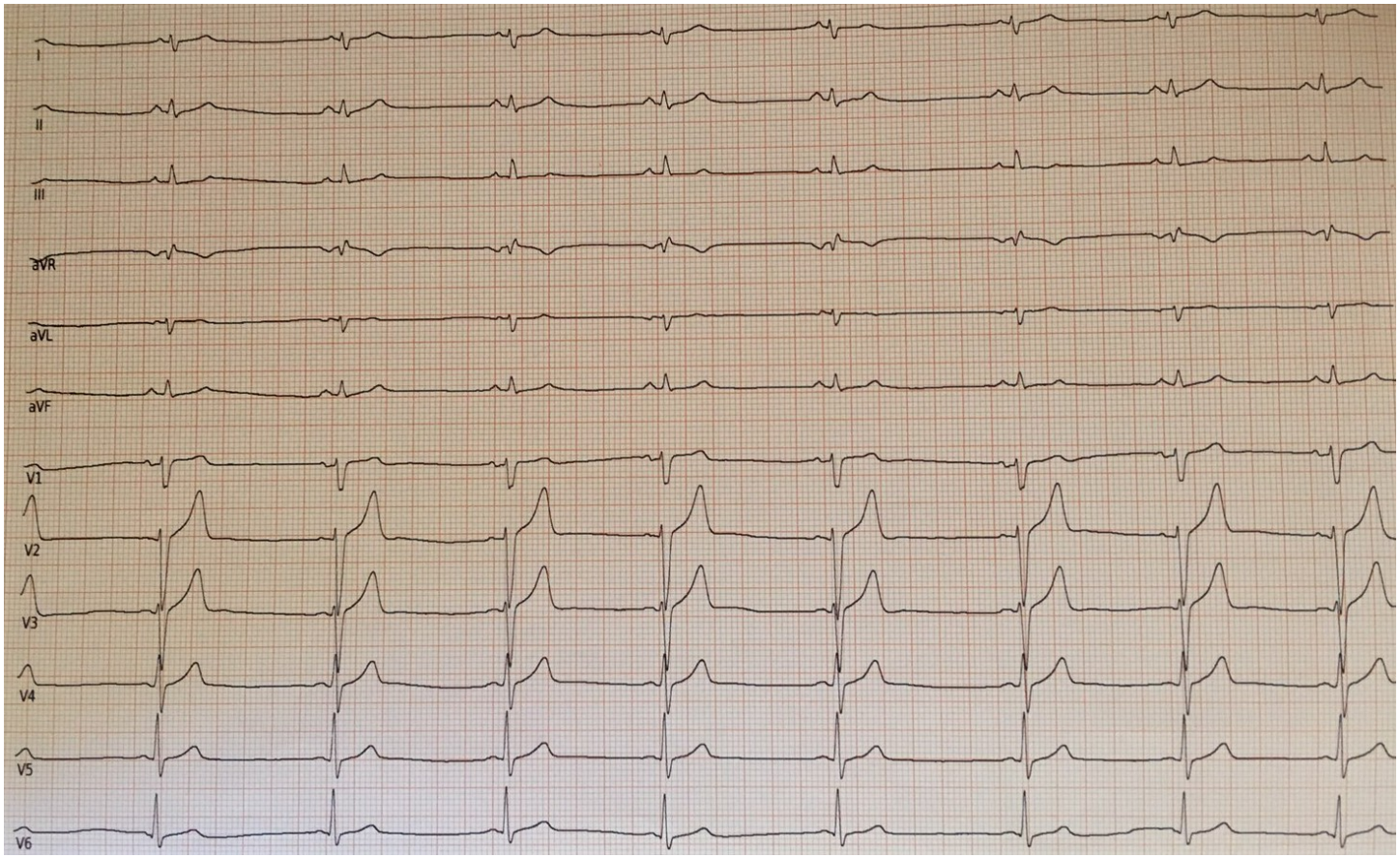
OUR EXPERIENCE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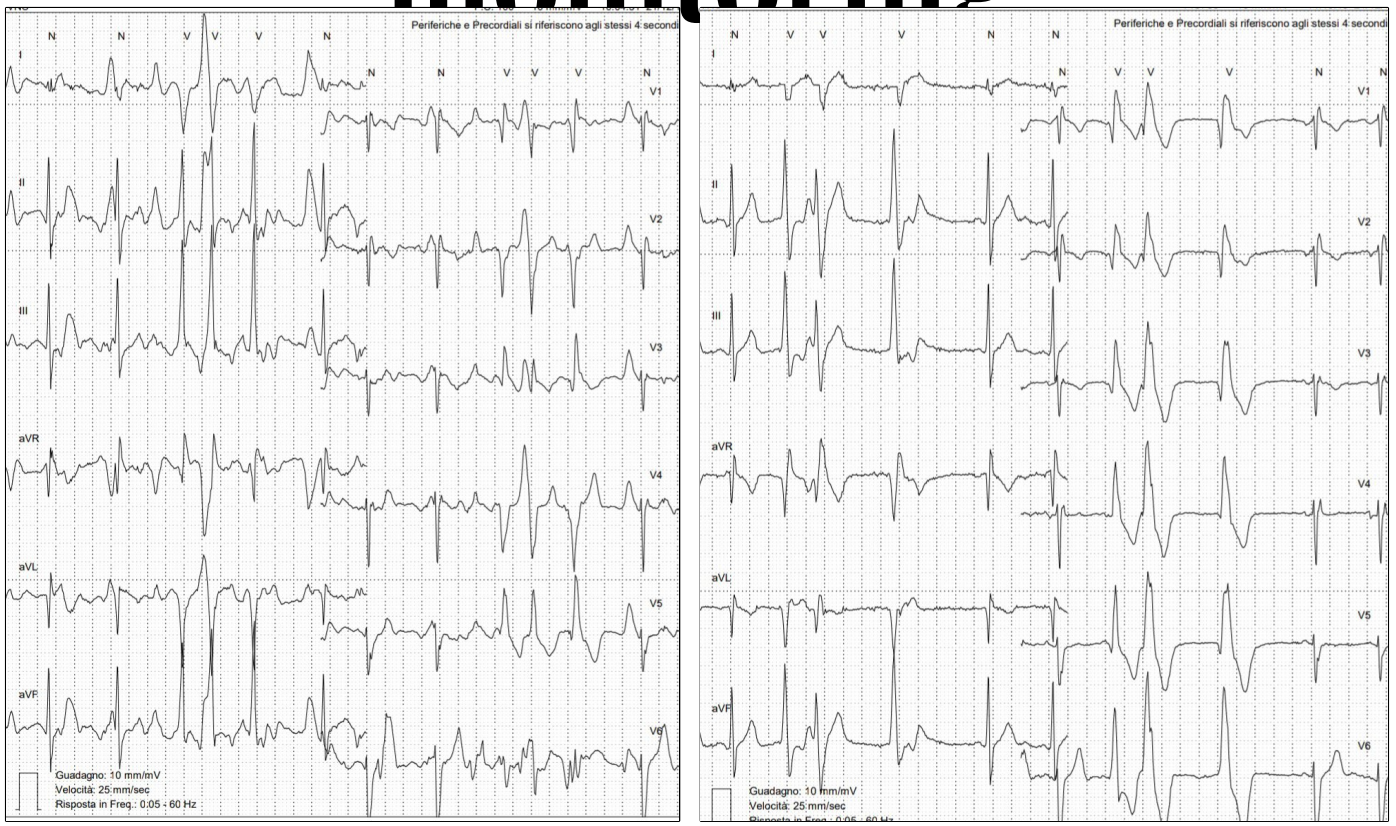
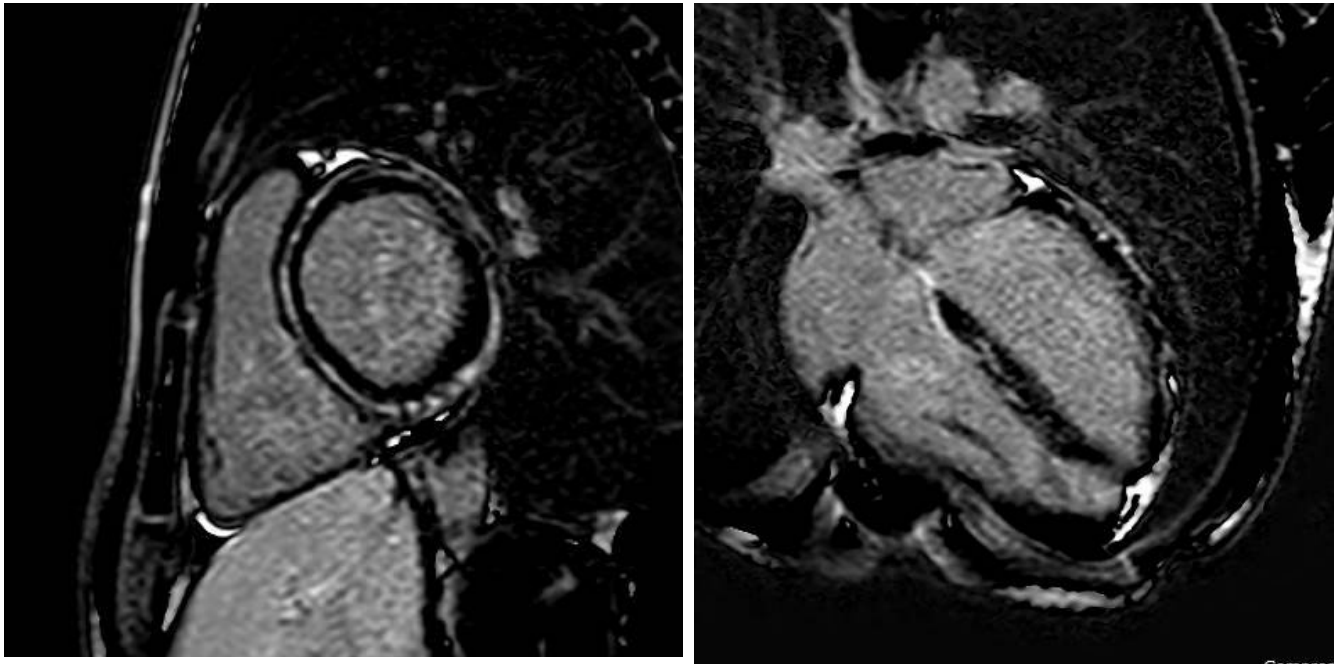
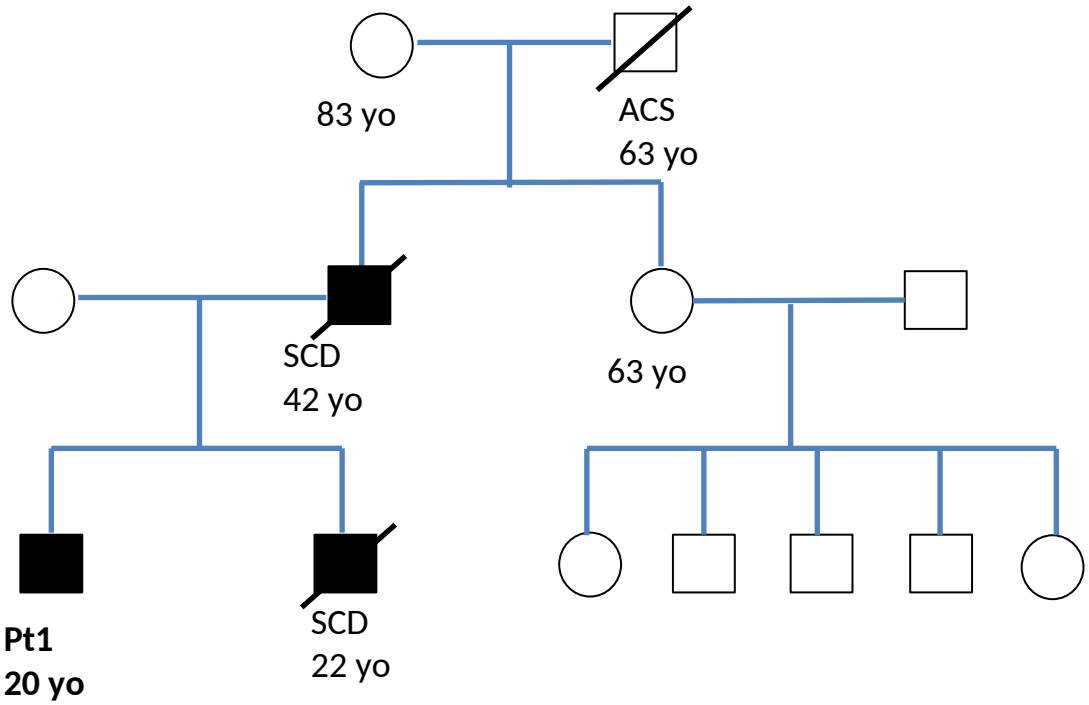
ECG Holter monitoring



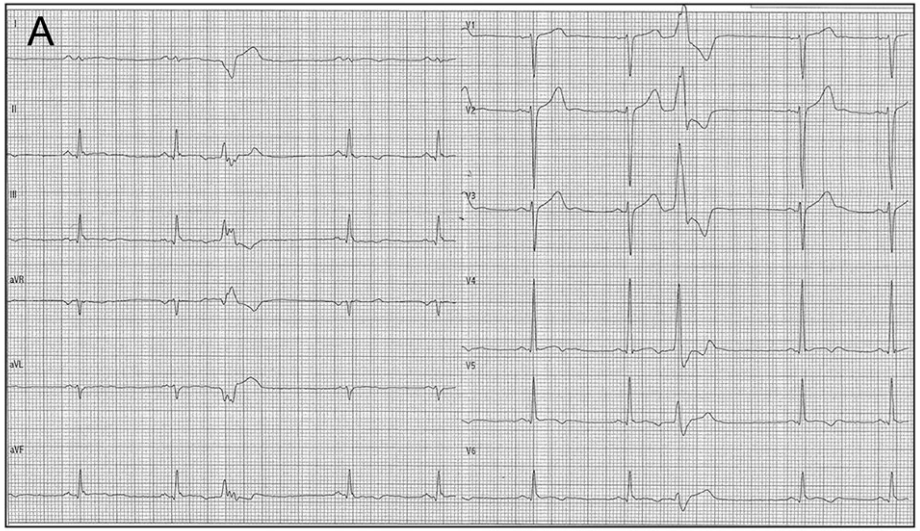
Cardiac Magnetic Resonance

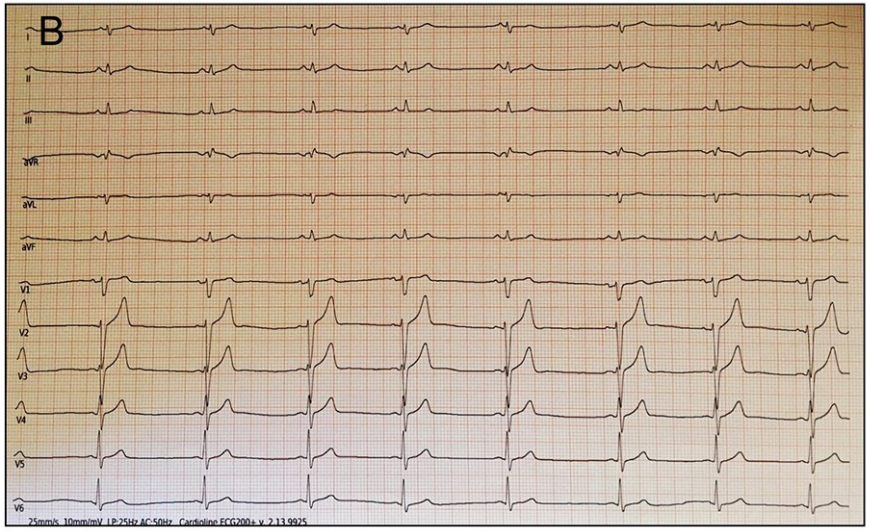


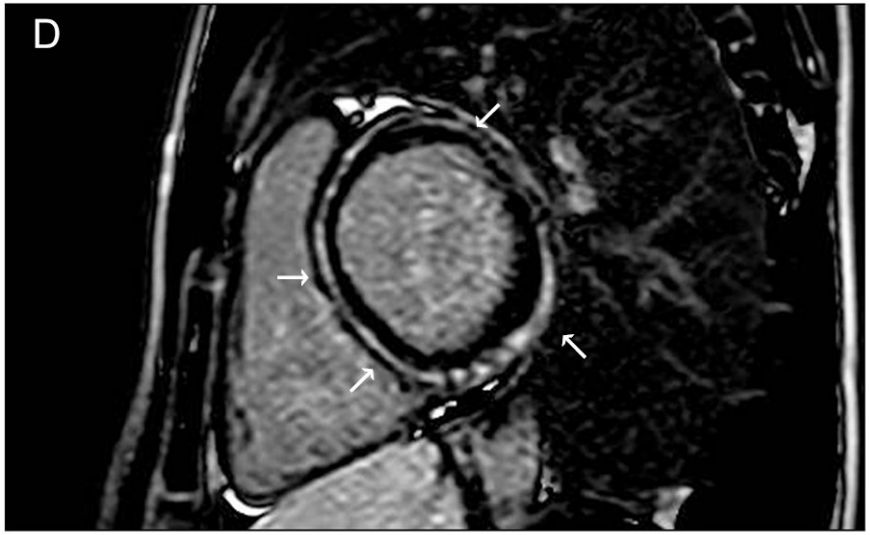
Family history



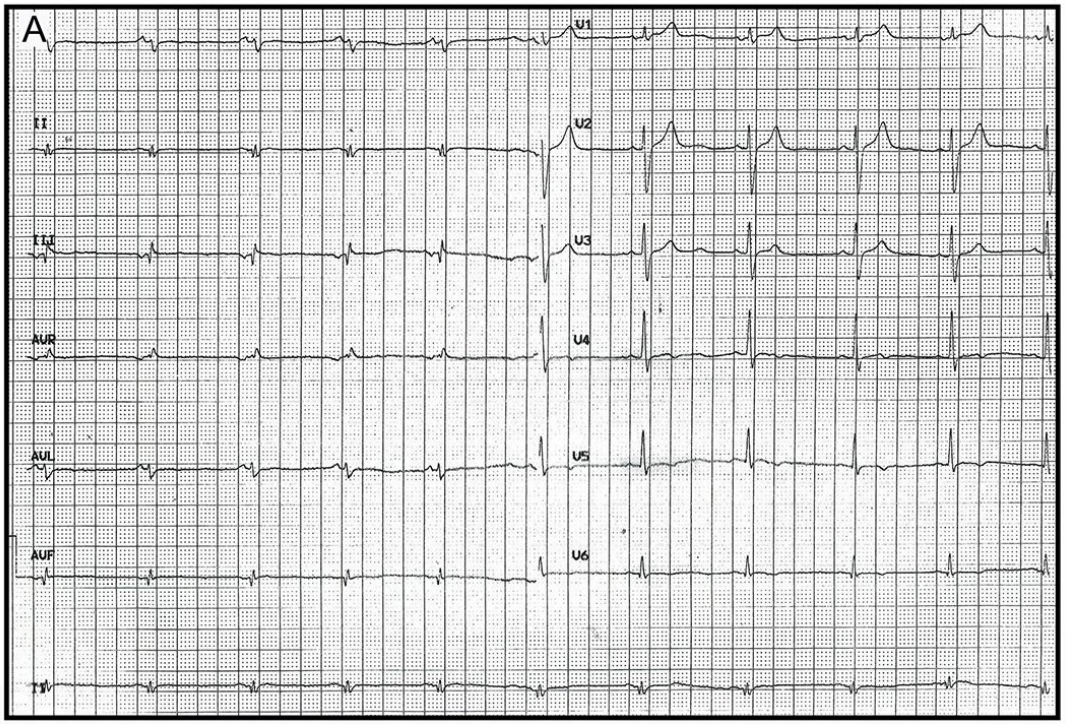
Two brothers in comparison







- Pt 9 CMR reveals ***subepicardial/intramyocardial circumferential LGE***.
- The autopsy of his brother shows the same ***LV circumferential scar***, mostly located in the subepicardium, with gross features of fibroadipose myocardial replacement.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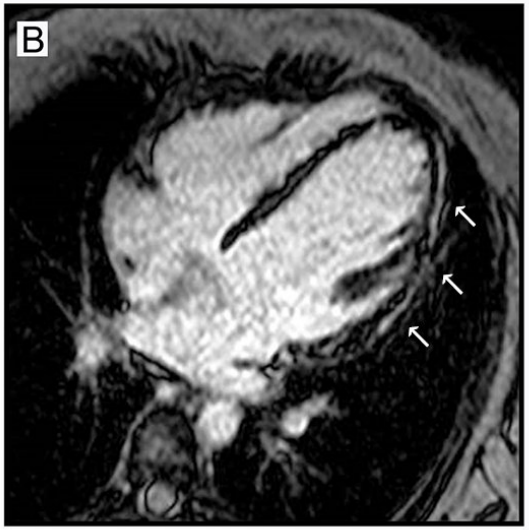
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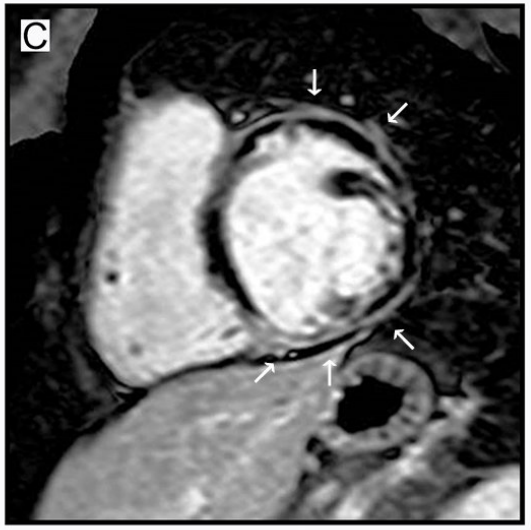
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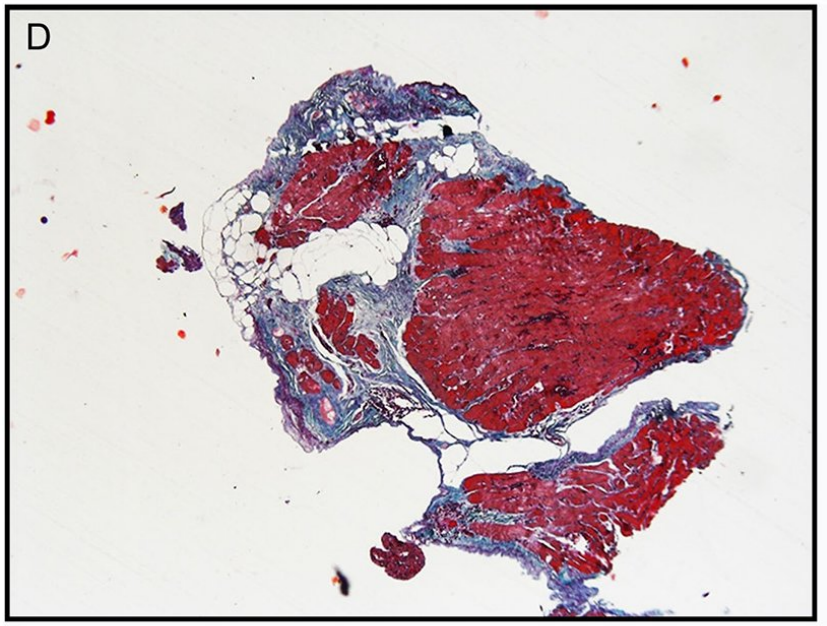
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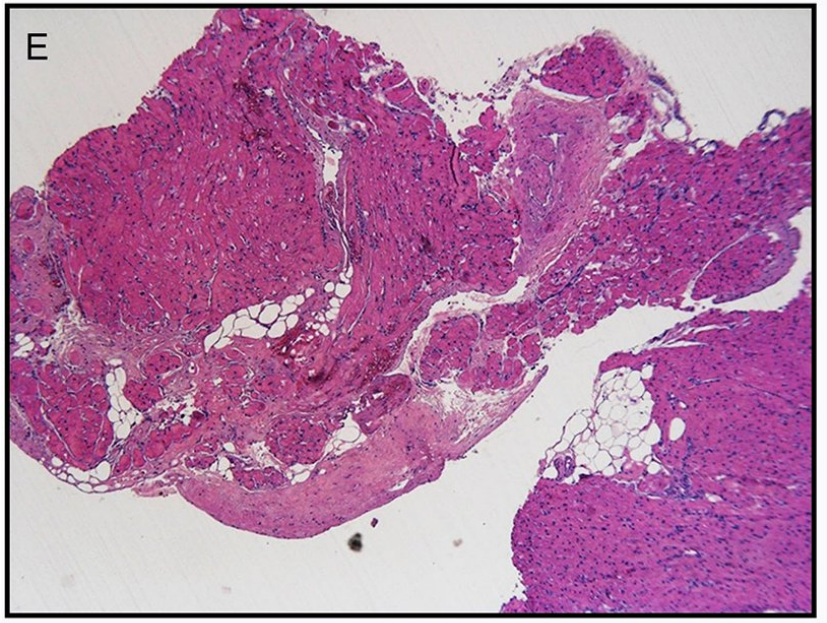
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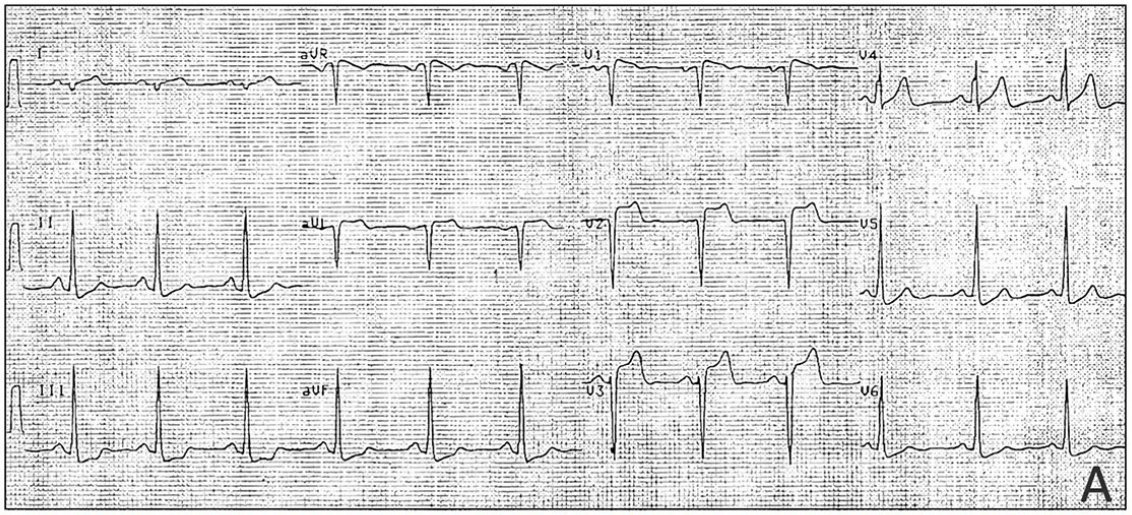
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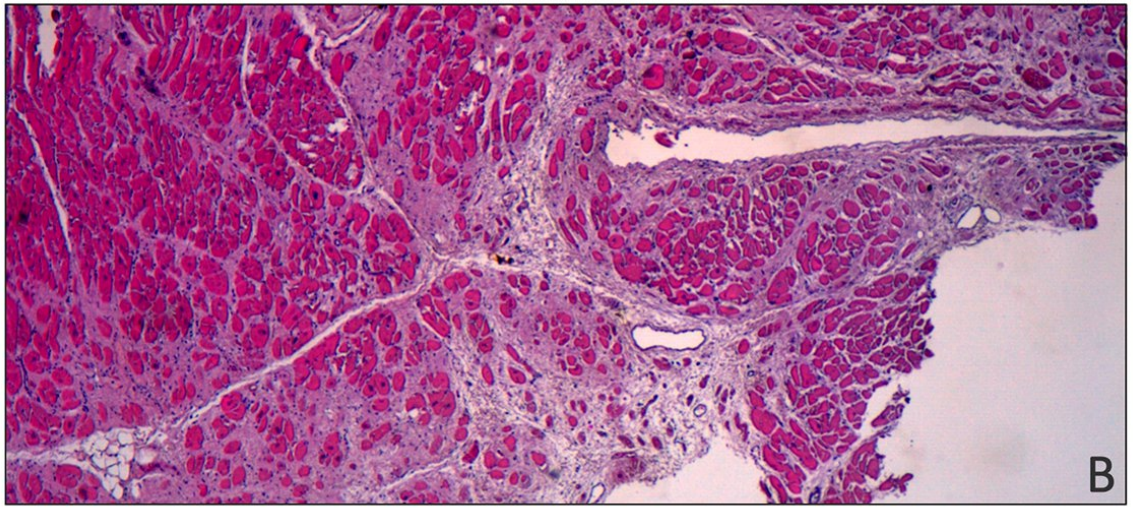
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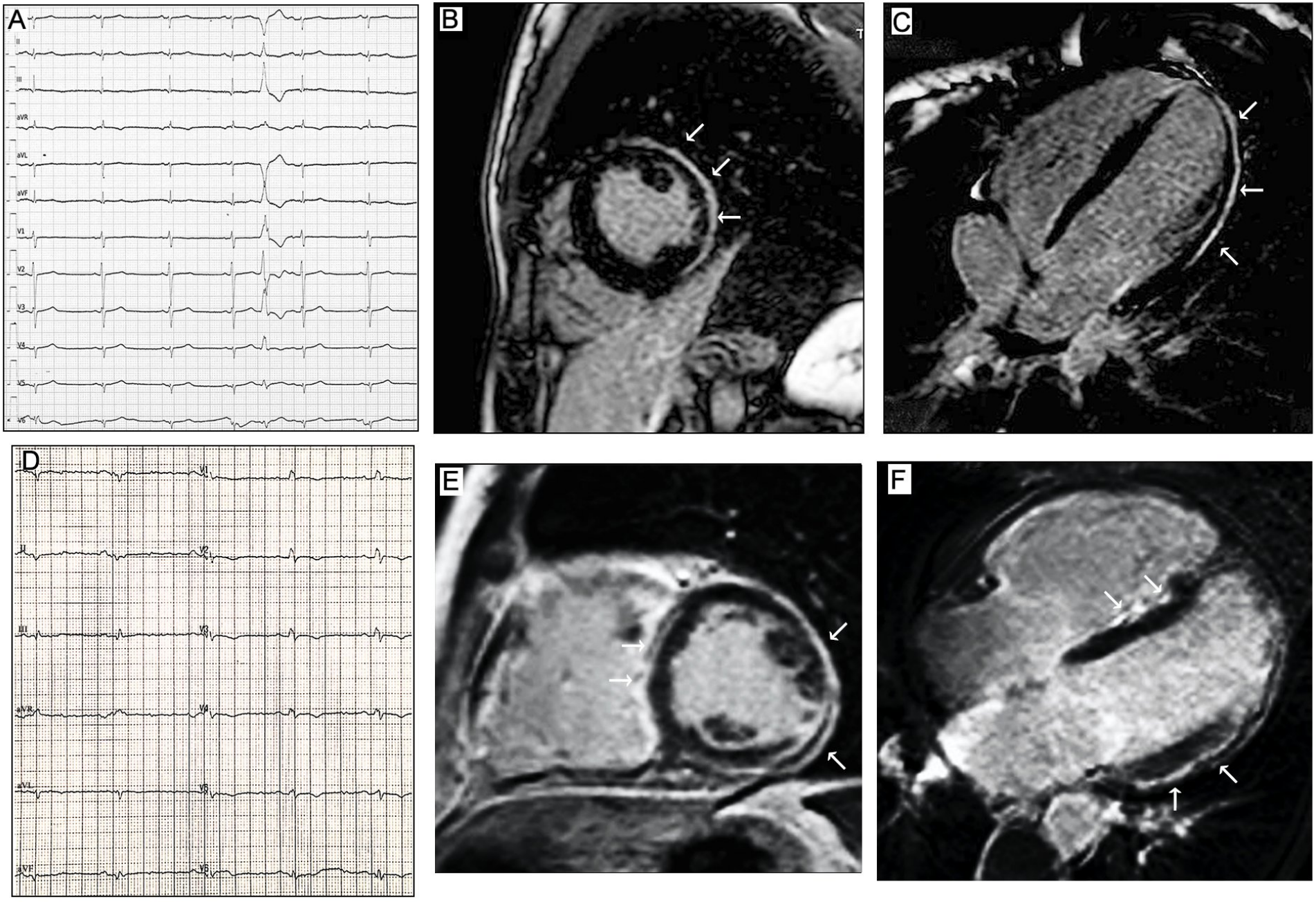
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Left Posterior Fascicular Block and Increased Risk of Sudden Cardiac Death in Young People

We retrospectively compared the clinical data for 109 consecutive individuals age ≤40 years who had ACA or SCD (86 men; 32.3 ± 5.9 years [range: 17 to 40 years]) and who had at least 1 ECG in the 3 years preceding the ACA or SCD to data for 8,892 healthy individuals age ≤40 years (6,265 men; 30.5 ± 8.6 years [range: 17 to 40 years]) consecutively referred to our institution for screening. LPFB was defined by the presence of all of the following: frontal axis 100° to 180°; rS pattern in leads I and aVL; qR pattern in III and aVF; QRS duration <110 ms; and no QS pattern in I and aVL. The association of LPFB with ACA/SCD was analyzed by nominal logistic regression and was estimated with unadjusted odds ratios (ORs) and 95% confidence intervals (CIs). The study (CARITMO) was approved by our Institutional Review Board.

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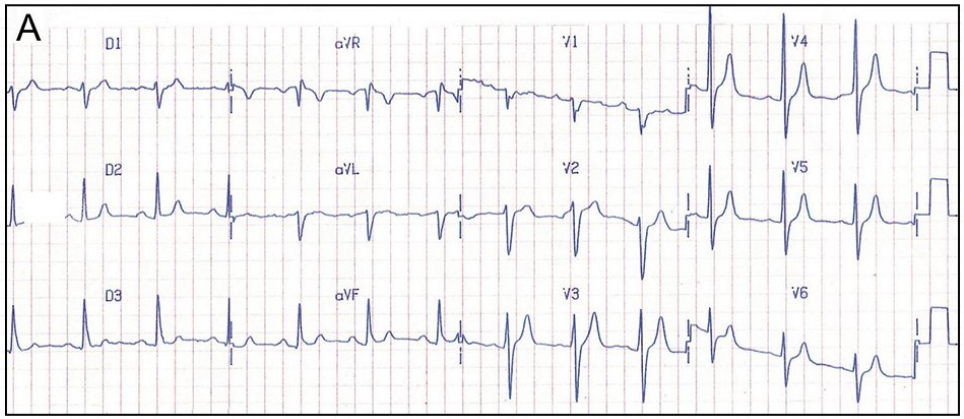
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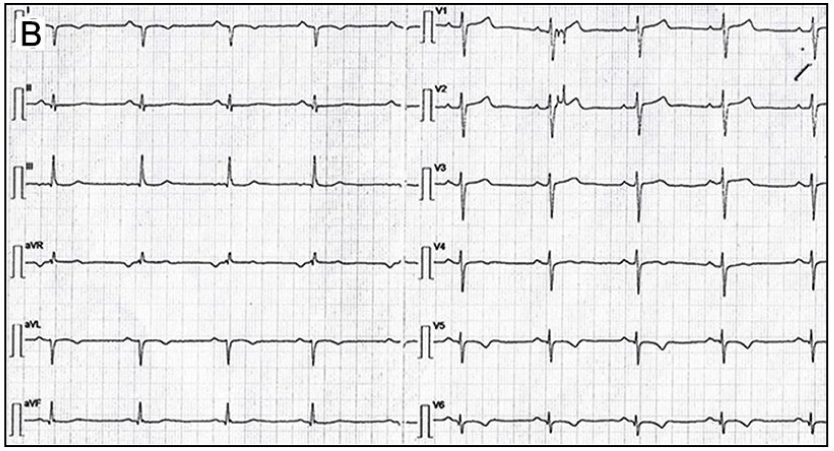
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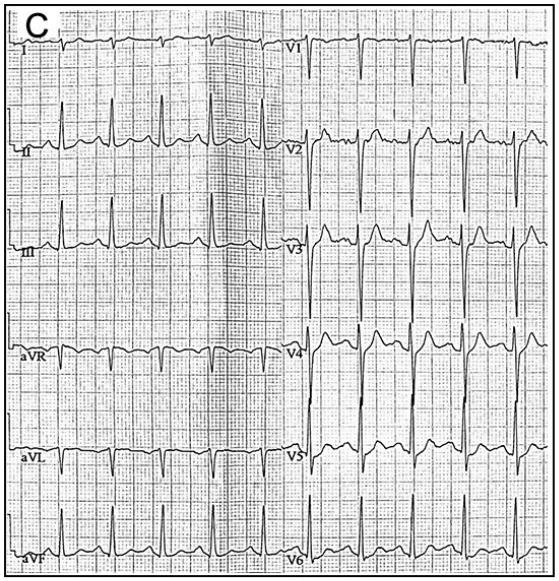
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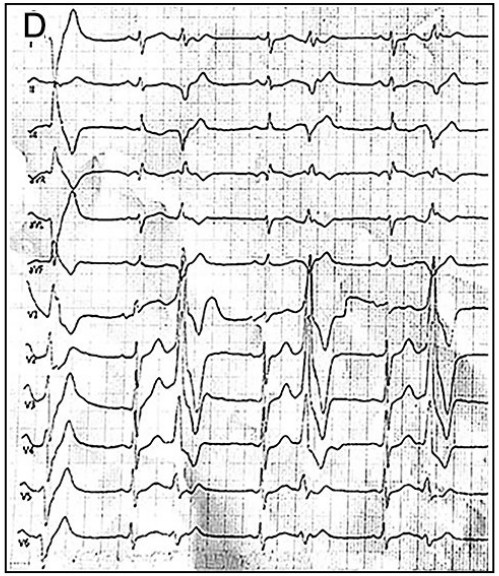
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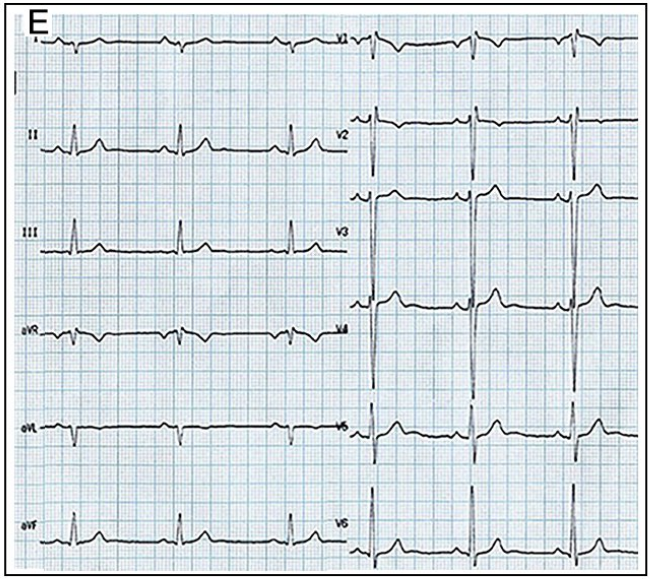
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LPFB as a Sign for Cardiomyopathy and Increased Risk of SCD in Young People

109 young consecutive patients with **ACA/SCD**

Pre-ACA/SCD **ECG analysis**

LPFB in **10 (9%)** patients

CMR in 6 patients

Abnormal CMR in **6 (100%)**

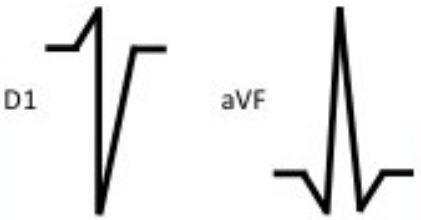
- **LV LGE** in **6 (100%)**
  - Inferolateral LGE in 3
  - Inferior LGE in 1
  - Inferoseptal in 1
  - Diffuse in 1
- **LV systolic dysfunction** in **4 (80%)**

Autopsy in **3** patients; **EMB** in **1** patients

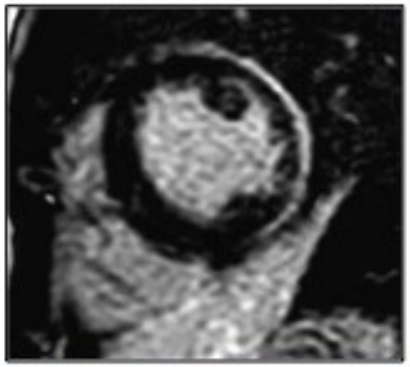
- **Abnormal histopathological findings** in **4 (100%)**
- **LV fibrosis** in **4 (100%)**

Genetic analysis in **5** patients

- **Pathogenic variants** in **2 (40%):** DSG2, TTN
- **VUS** in **1 (20%):** TTN



LFPB Odds Ratio for SCD/ACA
112.2 (95% CI 43.3-290.2)



8892 young **healthy** individuals

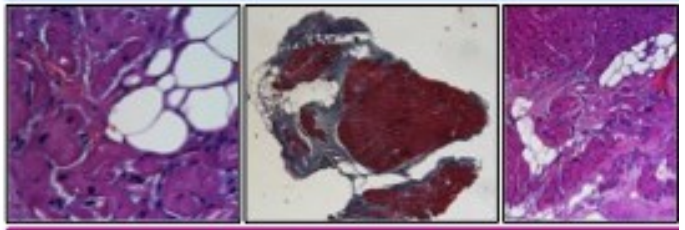
ECG analysis

LPFB in **8 (0.09%)** patients

CMR in 6 healthy subjects

Abnormal CMR in **4 (67%)**

- **LV LGE** in **2 (33%)**
- **LV systolic dysfunction** in **1 (17%)**
- **LV hypertrophy** in **1 (17%)**



Genetic analysis in **3** subjects

- **Pathogenic variant** in **1 (33%):** DSP

54 subjects with typical LV subepicardial LGE distribution

5 with fibro-fatty infiltration at histological analysis (biopsy) and 1 autopsy with negative or presence or VUS

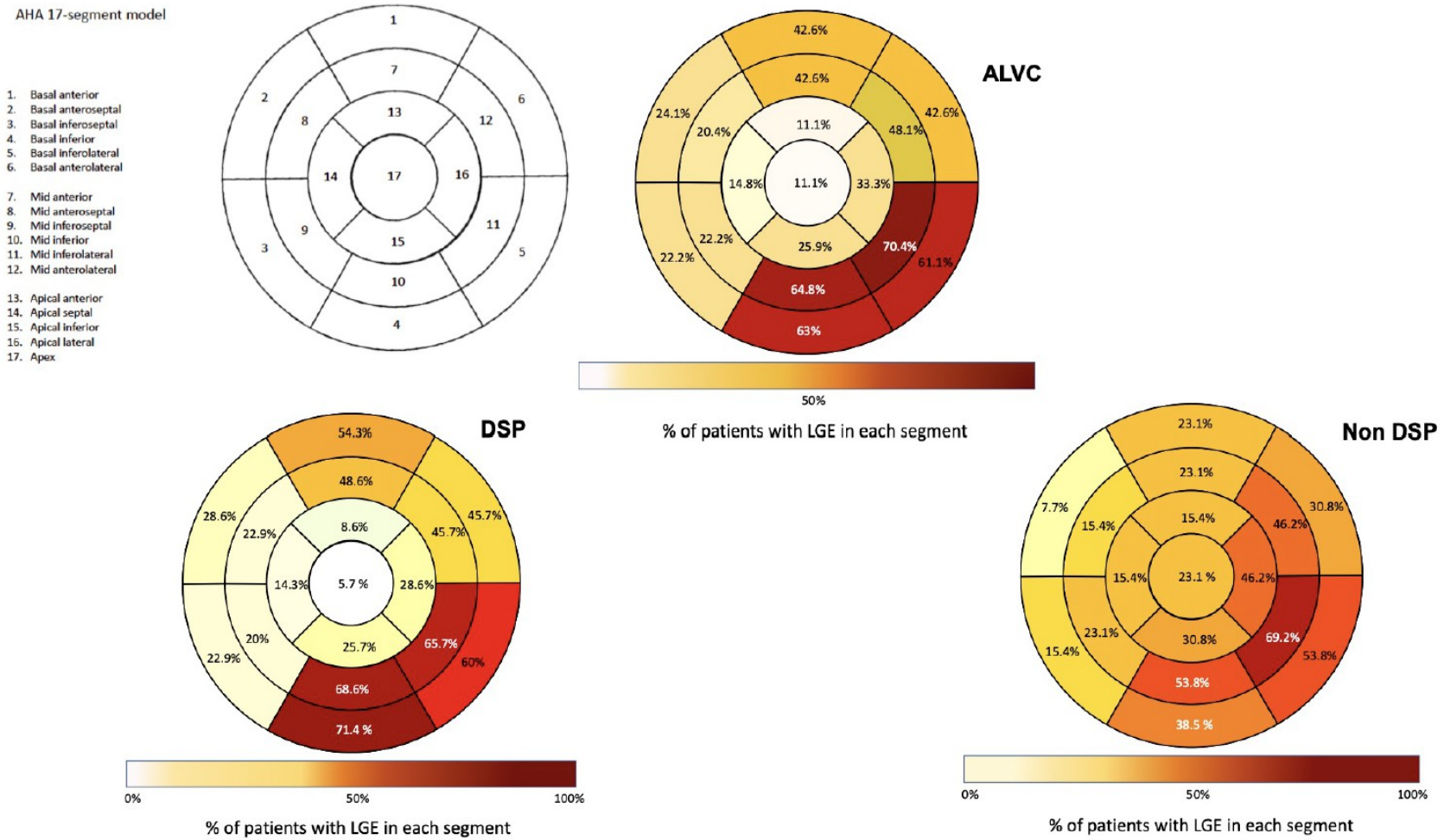
48 with positive genetic testing for pathogenic/likely pathogenic variants associated with ARVC with LV involvement affected by left dominant AC

- **35 (72.9%) gene DSP; 7 (14.6 %) gene DSG; 3 gene PKP, 3 JUP**

	ALVC (n=54)
Age at diagnosis, years	39±15
Male, n (%)	32 (59.3)
Probands, n (%)	40 (74.1)
Family history of ACM/DCM, n (%)	23 (42.6)
Family history of SCD, n (%)	18 (33.3)
NYHA class I-II, n (%)	52 (96.3)
NYHA class III, n (%)	2 (3.7)
Atrial fibrillation, n (%)	4 (7.4)
Unexplained syncope, n (%)	8 (14.8)
NSVT, n (%)	26 (48.1)
Cardiac magnetic resonance	
LVEDVi (ml/m2)	97.6±24.5
LVEF, %	49.5±10.0
LV WMA, %	35 (64.8)
RVEDVi (ml/m2)	85.8±18.8
RVEF, %	54.3±9.3
RV WMA, %	13 (24.1)
Intramyocardial fat signal, n (%)	22 (40.7)
Segments with LGE	6±3; 6 (4-8)
LGE pattern	
- Ringlike, n (%)	28 (51.9)
LGE distribution	
- Subepicardial, n (%)	35 (64.8)
- Midmural, n (%)	10 (18.5)
- Transmural, n (%)	9 (16.7)
Genetic testing	
Pathogenic/likely pathogenic variant, n (%)	48/54 (88.9)
DSP, n (%)	35/48 (72.9)
Non-DSP, n (%) *	13/48 (27.1)

	Pedigree	Gene	ACMG Variant Criteria	Deoxyribonucleic acid change	Amino acid change
1	Proband	PKP2	LP	c.1216delG	p.Val406fs
2	Proband	DSP	P	c.1707-1708insAC	p.Met571Glnfs*8
3	Proband	DSP	LP	c.7180delA	p.Arg2394fs*ter
4	Proband	DSG2	LP	c.1912G>A	p.Gly638Arg
5	Proband	DSG2	LP	c.445G>T	p.Val149Phe
6	Proband	DSC2	LP	c.977A>C	p.Gln326Pro
7	Proband	DSP	LP	c.3932_3936del	p.Gln1311Profs*13
8	Family member	DSP	P	c.5851 C>T	p.Arg1951Ter
9	Family member	DSP	P	c.5851 C>T	p.Arg1951Ter
10	Proband	DSG2	LP	c.1003A>G	p.Thr335Ala
11	Family member	DSP	LP	c.2848delA	p.ile950Leu
12	Proband	DSP	P	c.2497 C>T	p.Gln833ter
13	Family member	DSP	LP	c.1351C>T	p.Arg451Cys
14	Proband	DSP	LP	c2584C>T	p.Gln862Ter
15	Family member	DSP	LP	c.1351C>T	p.Arg451Cys
16	Family member	PKP2	P	c.2447_2448del	p.Thr816Argfs*10
17	Proband	DSP	LP	c.1352G>C	p.Arg451Pro
18	Proband	DSP	P	c.3203_3204delAG	p.Glu1068Valfster19
19	Proband	DSP	P	c.5210delG	p.Gly1737AspfsTer16
20	Proband	DSP	P	c.5210delG	p.Gly1737AspfsTer16
21	Family member	DSP	P	c.3465G>A	p.Trp1155Ter
22	Proband	JUP	P	c.2069A>G	p.Arg690Ser
23	Proband	JUP	P	c.2069A>G	p.Arg690Ser
24	Proband	DSP	LP	c.6478C>T	p.R2160X
25	Proband	DSP	LP	c.G3793T	p.Glu1265X
26	Proband	DSP	LP	c.356dupA	p.I120Nfs*16
27	Proband	DSP	LP	c.1891C>T	p.(Gln631*)
28	Family member	DSP	LP	c.3793G>T	p.E1265X
29	Proband	DSP	LP	c.7248dupT	p.D2417X
30	Family member	DSP	LP	c.3337C>T	p.R1113X
31	Proband	DSP	LP	c.3465G>A	p.Trp1155*
32	Proband	DSP	P		6p25.1-p24.3
33	Proband	DSC2	LP	c.2078G>T	p.Gly693Val
34	Proband	DSP	LP	c.537_554del	p.Arg2334*
35	Proband	DSG2	P	c.1912G>A	p.Gly638Arg
36	Family member	DSG2	P	c.1912G>A	p.Gly638Arg
37	Proband	DSP	LP	c.448C><T	p.Arg150*
38	Proband	DSP	P	c.6852C>T	p.Arg2284*
39	Proband	DSP	LP	c.860A>G	p.Asn287Ser
40	Proband	DSP	VUS	c.212T>G	p.Ile71Ser
41	Proband	DSC2	VUS	c.907G>A	p.Val303Met
42	Proband	DSP/DSG2	LP	DSP: c.212T>G ; DSG2: c.561T>G	DSP: p.Ile71Ser; DSG2 p.Asp187Glu
43	Proband	JUP	LP	c.1359G>T	p.Glu453Asp
44	Proband	DSP	LP	c.2000delG	p.Trp667fs*0
45	Family member	DSP	LP	c.860A>G	p.Asn287Ser
46	Family member	DSP	LP	c.860A>G	p.Asn287Ser
47	Family member	DSP	P	c.1267-2A>G	
48	Proband	DSP	LP	c.448C>T	p.Arg150
49	Family member	DSG2	P	c.271G>T	p.Gly91Ter
50	Proband	DSP	P	c.4198C>T	p.Arg1400*

Distribution of late gadolinium enhancement



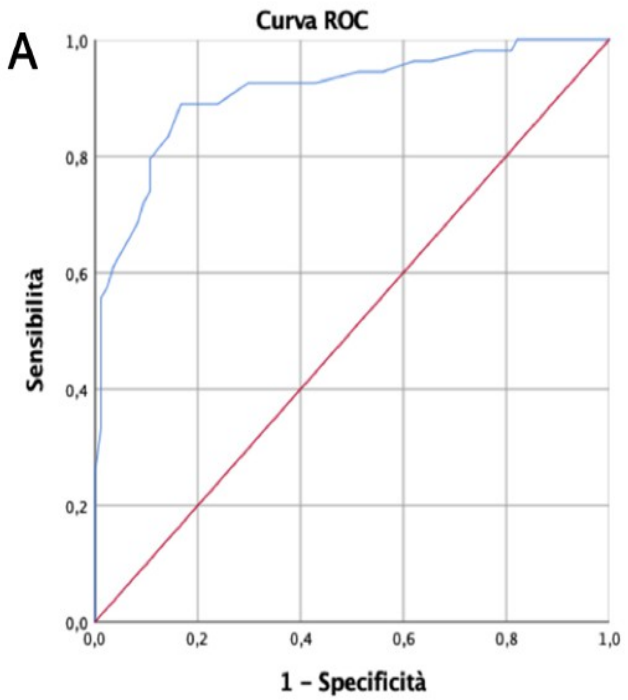
VOLTAGES IN LIMB LEADS

	Controls (n=84)	ALVC (n=54)	P Value
Lead I QRS	7 (5-8.5)	4.5 (3-6)	**<0.0001**
Lead I r wave	6 (4-7)	3 (1.9-4.1)	**<0.0001**
Lead I s wave	0.1 (0-1.5)	1 (0-2)	0.07
Lead II QRS	10.4 (8-12.5)	6.5 (4.2-9.1)	**<0.0001**
Lead II r wave	9.5 (6.6-12)	4 (2-6.5)	**<0.0001**
Lead II s wave	1 (0-2)	1 (0-2)	0.11
Lead aVF QRS	8 (5.1-10.5)	5 (4-7.6)	**0.0004**
Lead aVF r wave	7 (3.3-9)	3.5 (2-6.1)	**<0.0001**
Lead aVF s wave	1 (0-2)	1 (0-2)	0.70
Lead III QRS	7 (5-8.5)	6 (3.5-8)	**0.028**
Lead III r wave	5 (2-7.4)	3 (1-5.5)	**0.0055**
Lead III s wave	1 (0-2.4)	0.5 (0-2.3)	0.83
Lead aVR QRS	8 (7-9.5)	5 (4-6.1)	**<0.0001**
Lead aVR r wave	1 (0.3-1.5)	1 (0.5-1.3)	0.35
Lead aVR s wave	0 (0-7)	0 (0-1.3)	**0.0001**
Lead aVL QRS	4.1 (3-6.2)	4 (2.5-5)	0.28
Lead aVL r wave	2 (1-4)	2 (0.5-3.5)	0.38
Lead aVL s wave	1 (0-2.5)	0.8 (0-2.6)	0.39

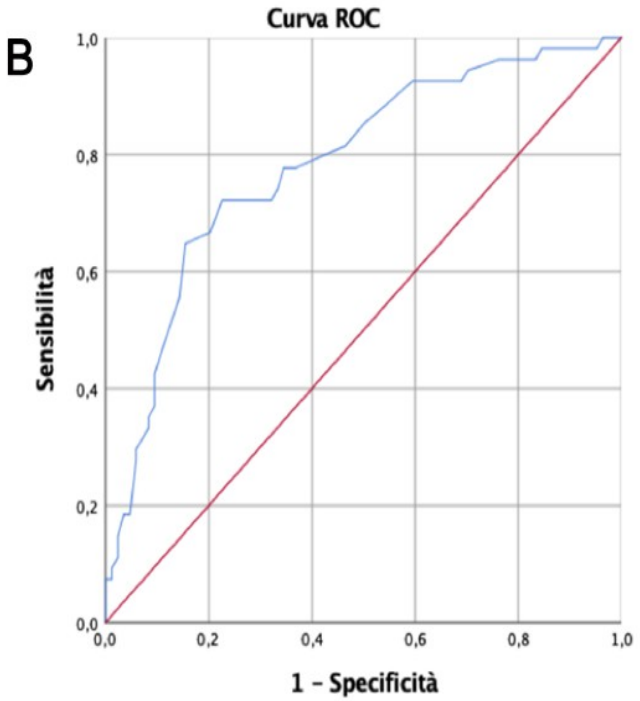
VOLTAGES IN PRECORDIAL LEADS

	Controls (n=84)	ALVC (n=54)	P Value
Lead V1 QRS	9.3 (7-12.9)	6.8 (4.5-9)	**0.0007**
Lead V1 r wave	1.5 (1-2)	1 (1-2.6)	0.40
Lead V1 s wave	8 (6-10)	5 (3-7.1)	**<0.0001**
Lead V2 QRS	13 (9-17.5)	11 (7.5-16.6)	0.24
Lead V2 r wave	2.8 (1.8-4.4)	3 (1.9-5)	0.68
Lead V2 s wave	9 (6.1-14)	8.3 (5-11.8)	0.07
Lead V3 QRS	15.3 (12-19)	11.8 (7.4-16)	**0.0003**
Lead V3 r wave	6 (4-10)	4 (2.4-6.3)	**0.003**
Lead V3 s wave	7.3 (4-11.4)	7 (4-9)	0.17
Lead V4 QRS	16 (10.6-19.8)	11.3 (9-16.6)	**0.0026**
Lead V4 r wave	11 (8-16)	8 (5.9-11.1)	**0.0002**
Lead V4 s wave	4 (1.5-5.9)	4 (2-6.3)	0.39
Lead V5 QRS	14.5 (10.6-18)	11 (8-14.3)	**0.0011**
Lead V5 r wave	12.5 (8.6-16)	8.5 (6.5-11)	**<0.0001**
Lead V5 s wave	2 (0.1-3)	2 (0.9-4)	0.18
Lead V6 QRS	11.1 (9-15.5)	8.9 (6.9-11.1)	**0.0001**
Lead V6 r wave	10 (7.5-14)	7 (5-9)	**<0.0001**
Lead V6 s wave	1 (0-1.9)	1 (0-2)	0.27
RI + RII	15 (13-17.5)	7 (5-10.6)	**<0.0001**
SV1 + RV6	18.8 (15.5-23)	12 (9-17)	**<0.0001**

	CONTROLS	ALVC	
RI + RII	15 (13-17.5)	7 (5-10.6)	**<0.0001**
SV1 + RV6	18.8 (15.5-23)	12 (9-17)	**<0.0001**



Sum of R-wave in I-II



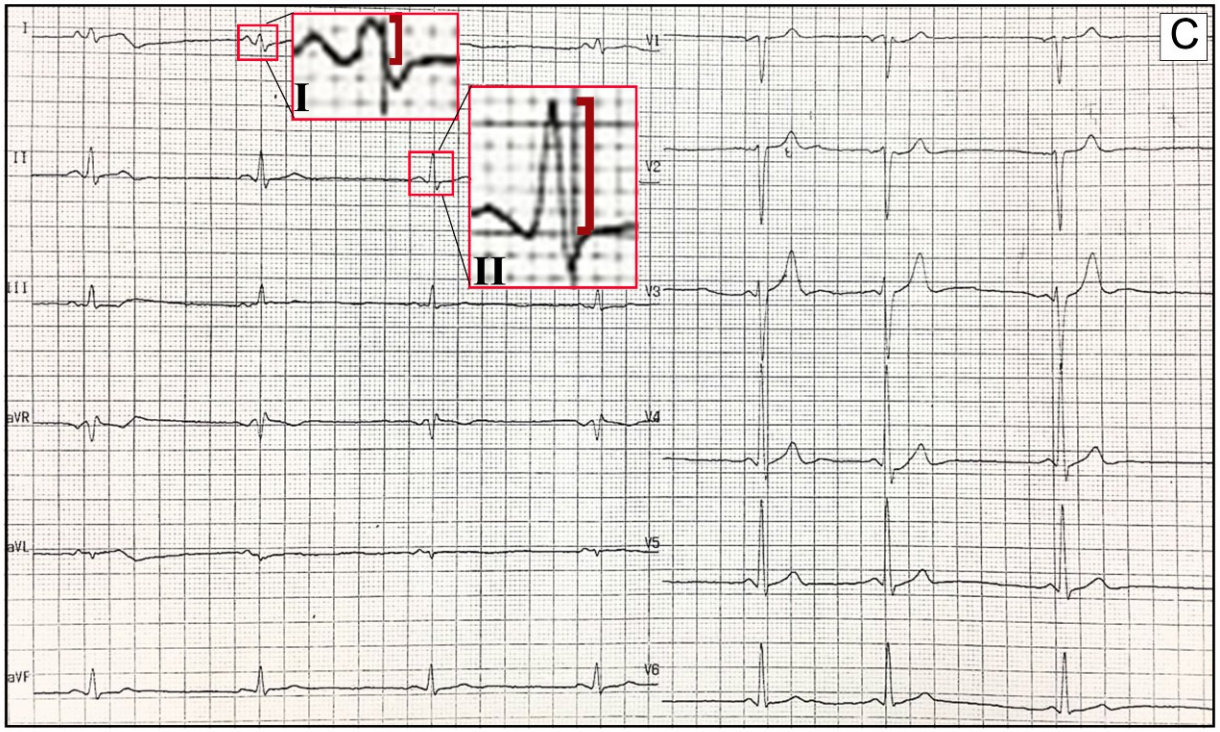
Sum of S wave in V1 and R in V6

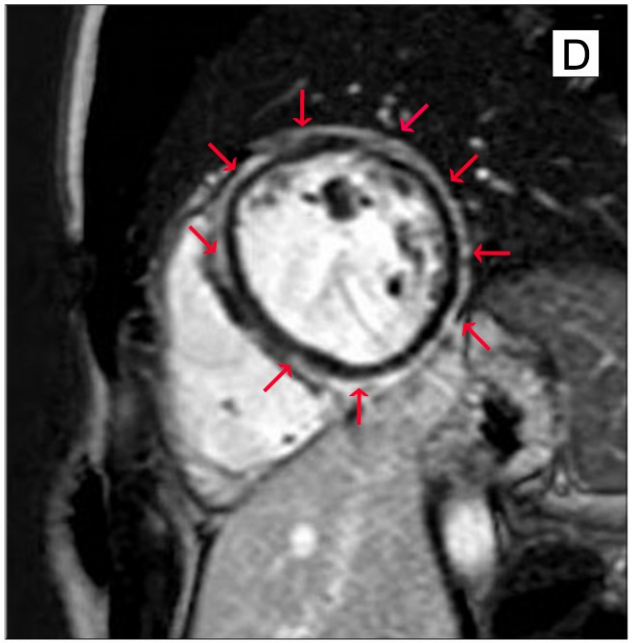
Area under curve = 0.909
(0.856-0.962), p <0.0001.

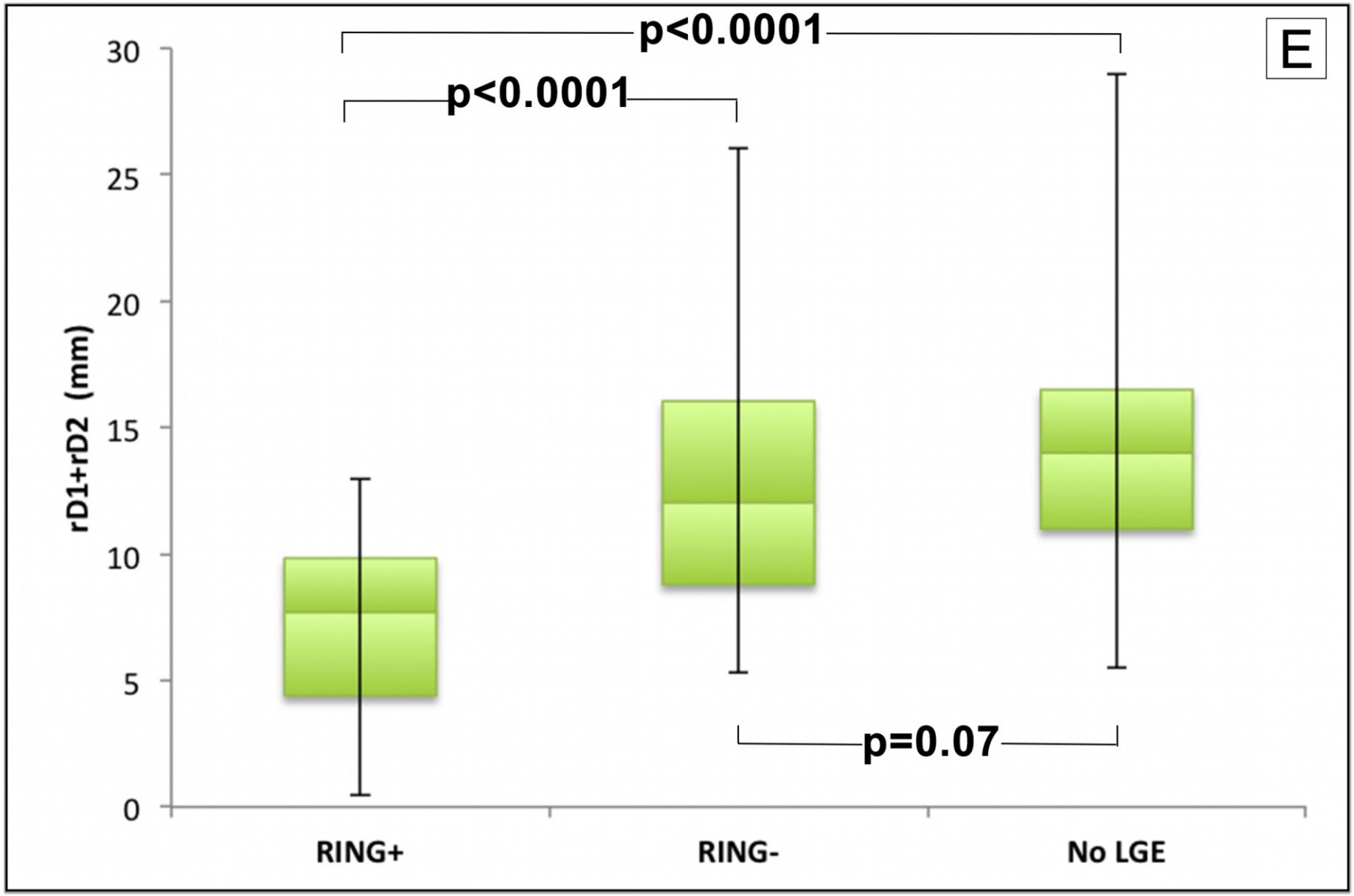
Best cut-off value 8 mm
(sensitivity 57.4%, specificity 97.6%)

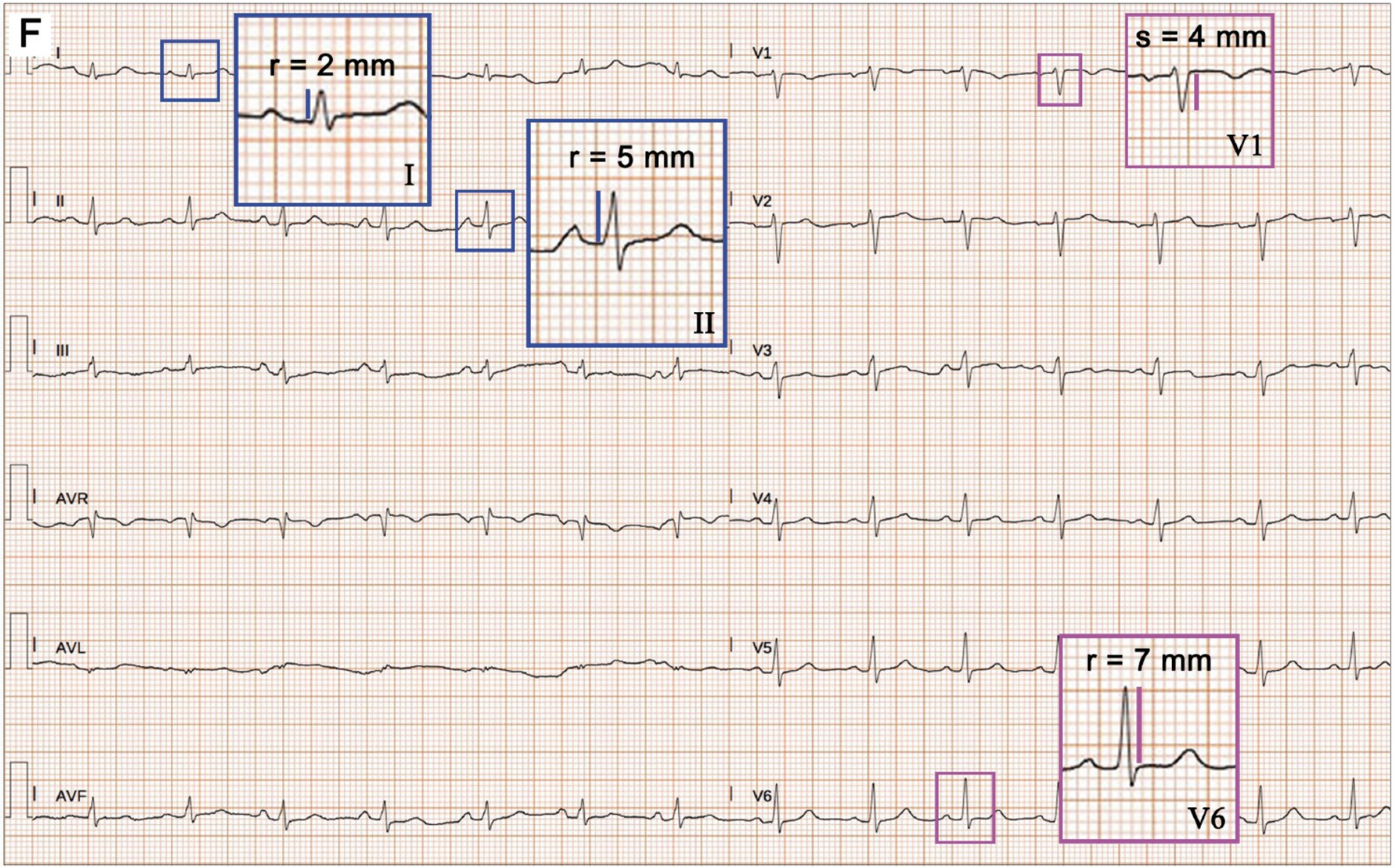
Area under curve = 0.784
(0.704-0.863), p<0.0001.

Best cut-off value 12 mm
(sensitivity 55.5%, specificity 85.7)


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


D


E
p<0.0001
p<0.0001
p=0.07
rD1+rD2 (mm)
30
25
20
15
10
5
0
RING+
RING-
No LGE



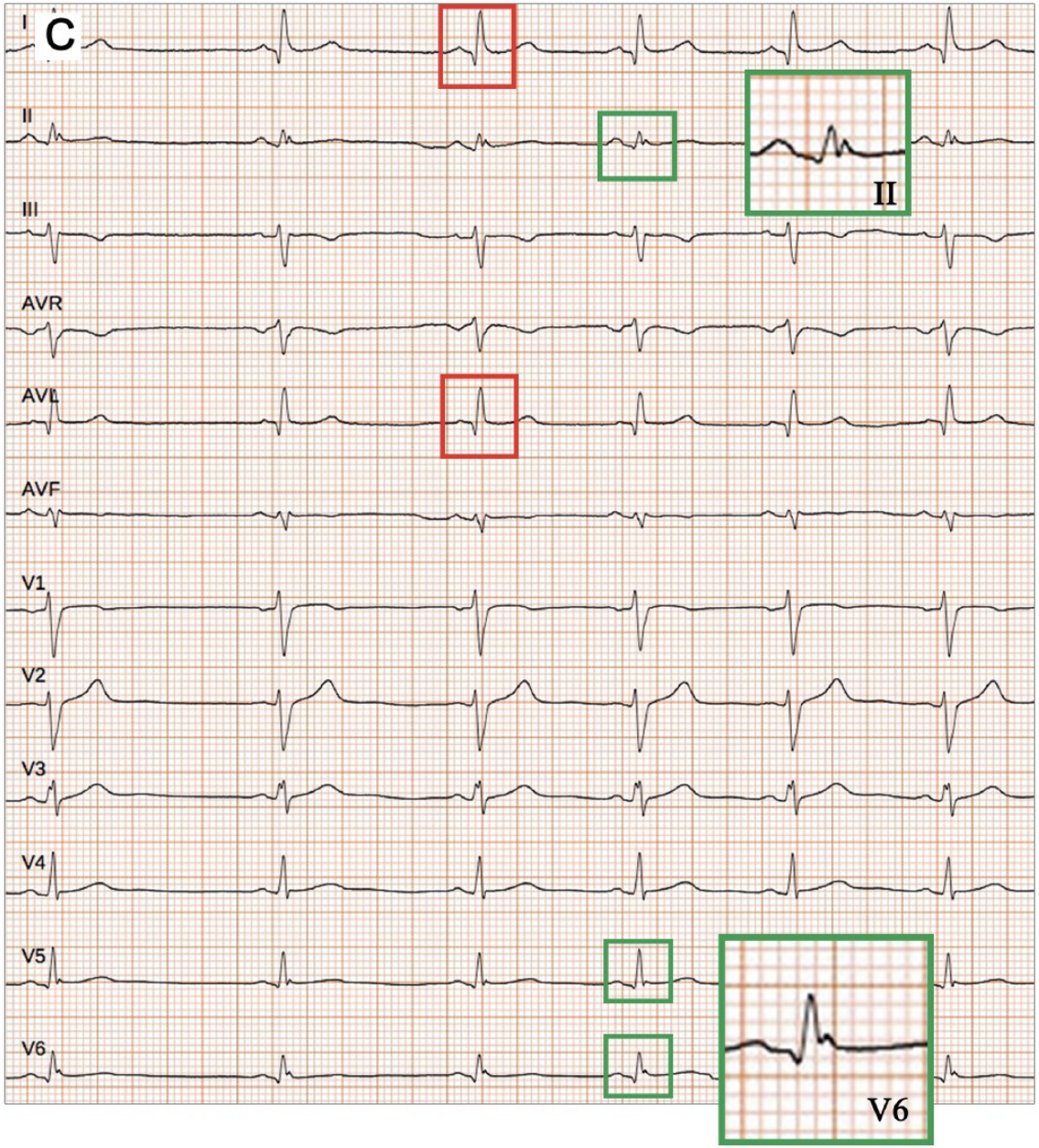
Patient #20, 23-year-old woman with a pathogenic variant in desmoplakin (c.5210del, p.Gly1737AspfsTer16)

ECG characteristics of the control group and study population

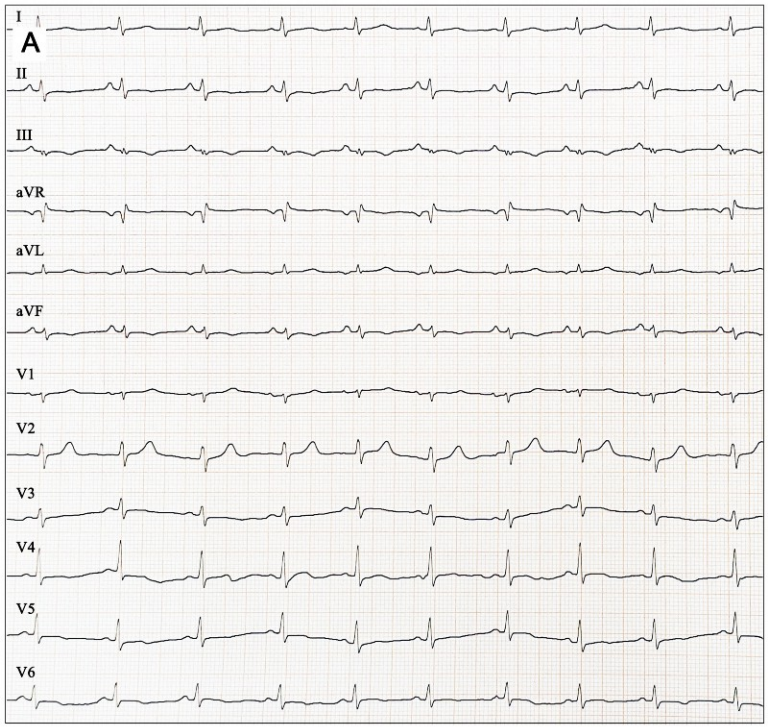
	Controls (n=84)	ALVC (n=54)	P Value
QRS (msec)	91±10	95±14	0.15
First degree AV block	3 (3.6)	5 (9.3)	0.42
NSICD	0	2 (3.7)	0.30
RBBB	1 (1.2)	0	0.99
LAFB	1 (1.2)	4 (7.4)	0.15
LPFB	0	11 (20.4)	**<0.0001**
LBBB	0	0	0
Pathological Q waves	0	18 (33.3)	**<0.0001**
Lateral distribution	0	7 (13.0)	**0.003**
Inferior distribution	0	8 (14.8)	**0.0012**
Precordial distribution	0	1 (1.9)	0.82
More 2 localizations	0	2 (3.7)	0.30
Fragmented QRS	9 (10.7)	19 (35.2)	**0.001**
Lateral distribution	0	1 (1.9)	0.82
Inferior distribution	9 (10.7)	10 (18.5)	0.31
Precordial distribution	0	1 (1.9)	0.82
More 2 localizations	0	7 (13.0)	**0.003**
TWI	1 (1.2)	31 (57.4)	**<0.0001**
Inferolateral TWI	0	6 (11.1)	**0.007**
Anterior TWI	1 (1.2)	6 (11.1)	**0.028**
Inferior TWI	0	4 (7.4)	**0.044**
Lateral TWI	0	6 (11.1)	**0.007**
Anterolateral TWI	0	6 (11.1)	**0.007**
Inferior-anterior-lateral TWI	0	3 (5.6)	0.11
NEW ECG CRITERIA			
SV1+RV6 ≤12 (mm)	12 (14.3)	30 (55.6)	**<0.0001**
RI + RII ≤8 (mm)	2 (2.4)	31 (57.4)	**<0.0001**
SV1+RV6 ≤12 and RI + RII ≤8 (mm)	0	24 (44.4)	**<0.0001**
Global LQRSV	0	4 (7.4)	**0.044**
LQRSV in limb leads	0	8 (14.8)	**0.0011**
Local LQRSV			
Lateral distribution	16 (18.8)	13 (24.1)	0.52
Inferior distribution	11 (12.9)	8 (14.8)	0.75
Inferolateral distribution	0	3 (5.6)	0.11
Precordial and local distribution	3 (3.5)	8 (14.8)	**0.017**
Epsilon Wave	0	1 (1.9)	0.82
Epsilon-like Wave in inferior leads	0	3 (5.6)	0.11
QTc (msec)	405±19	407±26	0.49
QTc ≥440 msec	0	4 (7.4)	**0.044**
Tzou criteria *	15 (17.6)	10 (18.5)	0.89
R >3 mm V1	1 (1.2)	6 (11.1)	**0.028**
R/S ratio ≥0.5 in V1	1 (1.2)	13 (24.1)	**<0.0001**
R/S ratio ≥1 in V1	0	6 (11.1)	**0.007**
Bayés de Luna criteria †	1 (1.2)	3 (5.6)	0.33

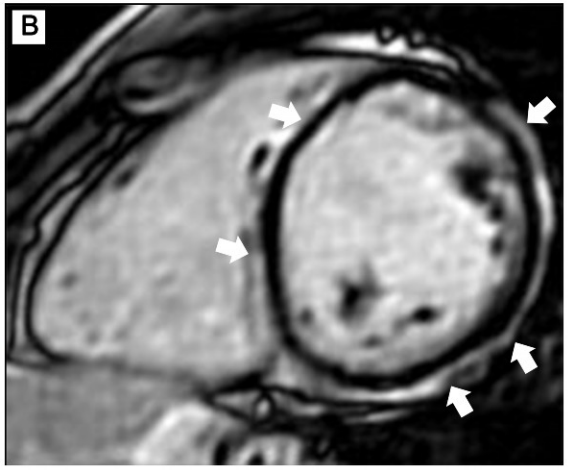
Sensitivity, specificity, PPV and NPV value of new and known ECG parameters for ALVC diagnosis

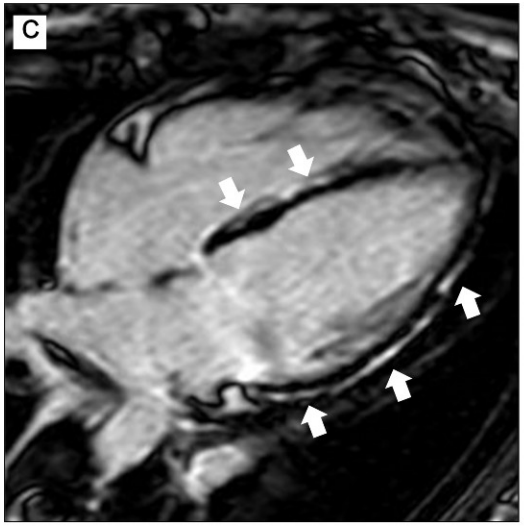
	ALVC (n=54)	Controls (n=84)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Single ECG Parameters							
LPFB	11	0	20.4	100	100	66.1	68.8
Pathologic Q waves	18	0	33.3	100	100	70.0	73.9
TWI	31	1	57.4	98.8	96.9	78.3	82.6
LQRSV in limb leads	8	0	14.8	100	100	64.6	66.7
Global LQRSV	4	0	7.4	100	100	62.7	63.8
R >3 mmV1	6	1	11.1	98.8	85.7	63.4	64.5
R/S ratio ≥0.5 in V1	13	1	24.1	98.8	92.9	66.9	69.6
SV1+RV6 ≤12	30	12	55.6	85.7	71.4	75.0	73.9
RI+ RII ≤8	31	2	57.4	97.6	93.9	78.1	81.9
Combined ECG Parameters							
Known ECG criteria							
TWI or **LQRSV in limb leads**	35	1	64.8	98.8	97.2	81.4	85.5
TWI or **LQRSV (limb leads and global)**	37	1	68.5	98.8	97.4	83.0	86.9
New ECG criteria							
SV1+RV6 ≤ 12 and RI + RII ≤8	24	0	44.4	100	100	73.7	78.3
LPFB or **Q** or **R/S ratio ≥0.5 in V1**	30	1	55.6	98.8	96.8	77.6	81.9
LPFB or **Q** or **R/S ratio ≥0.5 in V1** or **[SV1+RV6 ≤12 and RI + RII ≤8]**	35	1	64.8	98.8	97.2	81.4	85.5
Know and New ECG criteria							
TWI or **LPFB** or **Q**	38	1	70.4	98.8	97.4	83.8	87.7
TWI or **LPFB** or **Q** or **[SV1+RV6 ≤12 and RI + RII ≤8]**	44	1	81.5	98.8	97.8	89.3	92.0
TWI or **LPFB** or **Q** or **R/S ratio ≥0.5 in V1** or **[SV1+RV6 ≤12 and RI + RII ≤8]** or **LQRSV in limb leads**	47	2	87.0	97.6	95.9	92.1	93.5



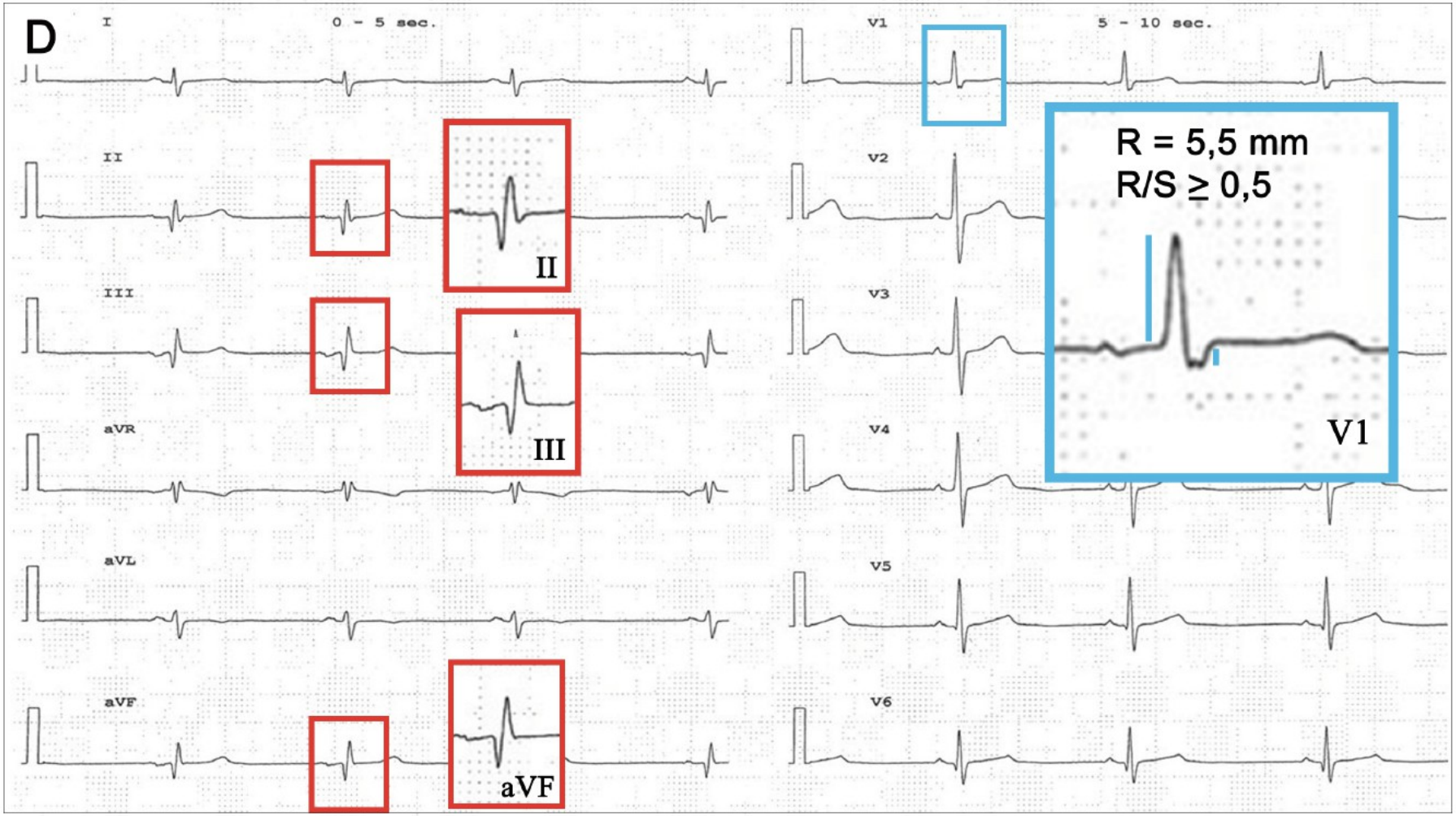
Patient #8, 20-year-old man, pathogenic variant in desmoplakin (c.5851 C>T, p.Arg1951Ter)



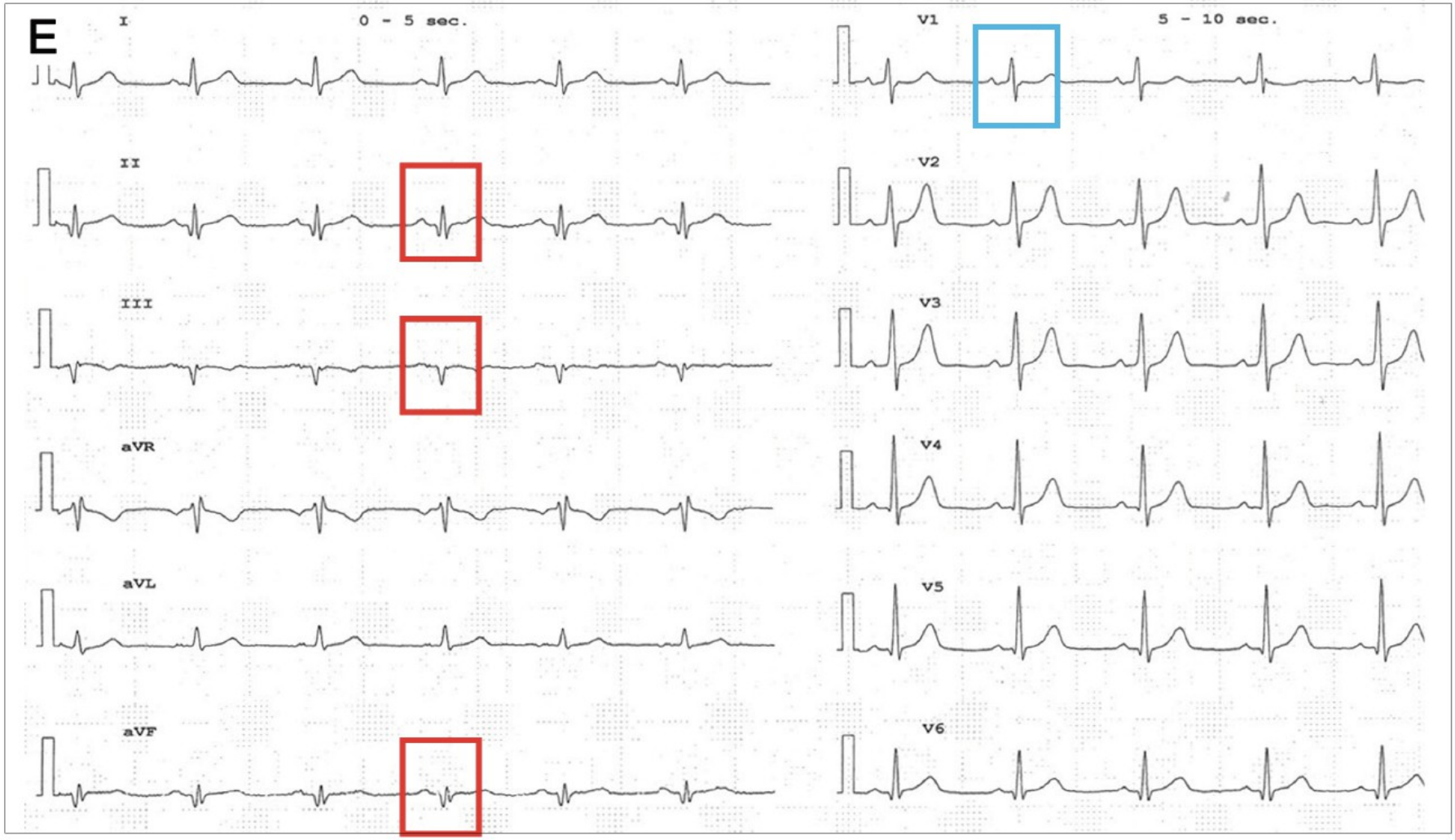




Patient #15 is a18-year-old woman with a likely pathogenic variant in desmoplakin (c.1351C>T, p.Arg451Cys).



Patient #35, 42-year-old man), pathogenic variant in desmoglein-2 (c.1912G>A, p.Gly638Arg)



The family member (Patient #36, 37-year-old man) has the same pathogenic variant in desmoglein-2 (c.1912G>A, p.Gly638Arg)

The Distinctive Electrocardiogram of Duchenne's Progressive Muscular Dystrophy*

An Electrocardiographic-Pathologic Correlative Study

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WILLIAM C. ROBERTS, M.D., *Bethesda, Maryland*
ANTONIO C. DE LEON, JR., M.D. *and* DESMOND O'DOHERTY, M.D. *Washington, D. C.*

The clinical, electrocardiographic, hemodynamic and cardiac pathologic features are described in two patients with the rapidly progressive, pseudohypertrophic, sex-linked form of Duchenne's muscular dystrophy. Previous studies have shown that the electrocardiogram is distinctive enough to aid in identifying this particular type of heredofamilial myopathic disorder even when the clinical features of the systemic myopathy are inconclusive. Tall right precordial R waves and deep limb lead and left precordial Q waves characterize these electrocardiograms. Information thus far has not provided explanations for either the distinctive morphology of the Duchenne electrocardiogram or for the variety of rhythm disturbances that have been observed. Accordingly, an electrocardiographic-pathologic correlative study was undertaken in order to determine whether a relationship existed between the distribution of myocardial dystrophy, the presence of an unusual type of small vessel coronary arteriopathy, and the electrocardiographic abnormalities of both QRS configuration and rhythm.

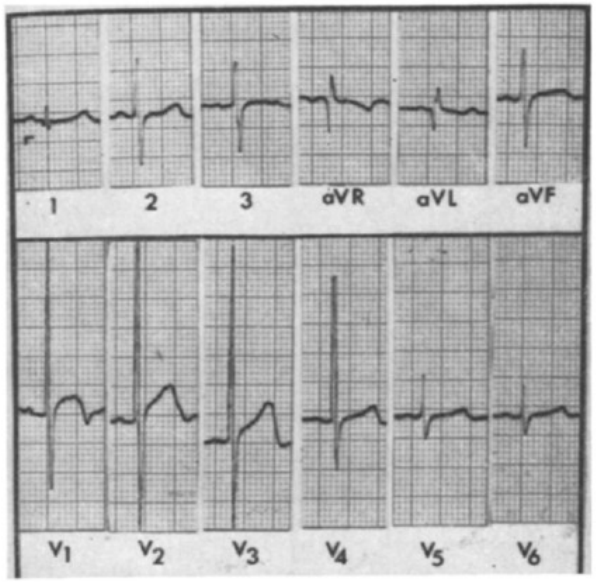


FIG. 1A. Case 1. Electrocardiogram obtained at twelve years of age shows a marked increase in the amplitude of the R wave in lead V_1, but a significant Q wave only in lead aVL.

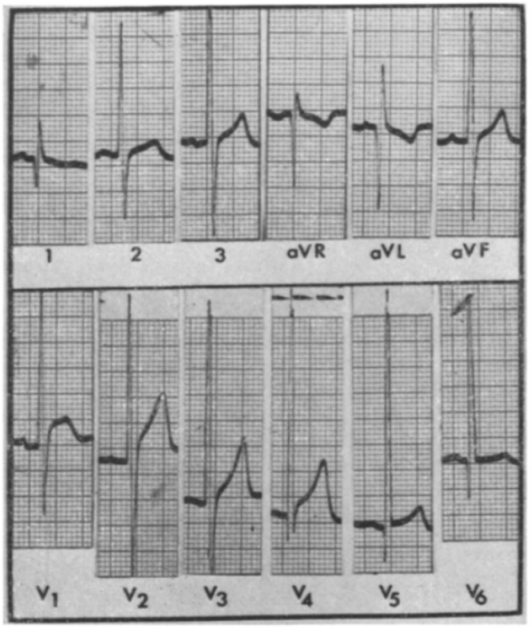


FIG. 1B. Case 1. Electrocardiogram obtained at seventeen years of age (similar to subsequent tracings except for preterminal atrial flutter). The tall R wave in lead V_1 persists. Deep Q waves have now appeared in leads I, aVL, and V_5 to V_6. The amplitude of the R waves in leads V_4 to V_6 has substantially increased.

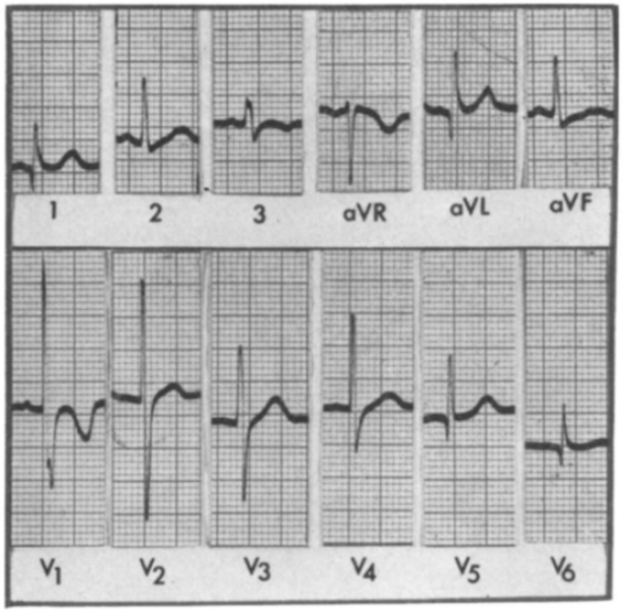


FIG. 2. Case 2. Electrocardiogram obtained at twelve years of age shows a tall R wave in lead V_1 in addition to deep Q waves in leads I and aVL. Leads V_5 to V_6 display moderately deep Q waves that were not present at nine years of age.

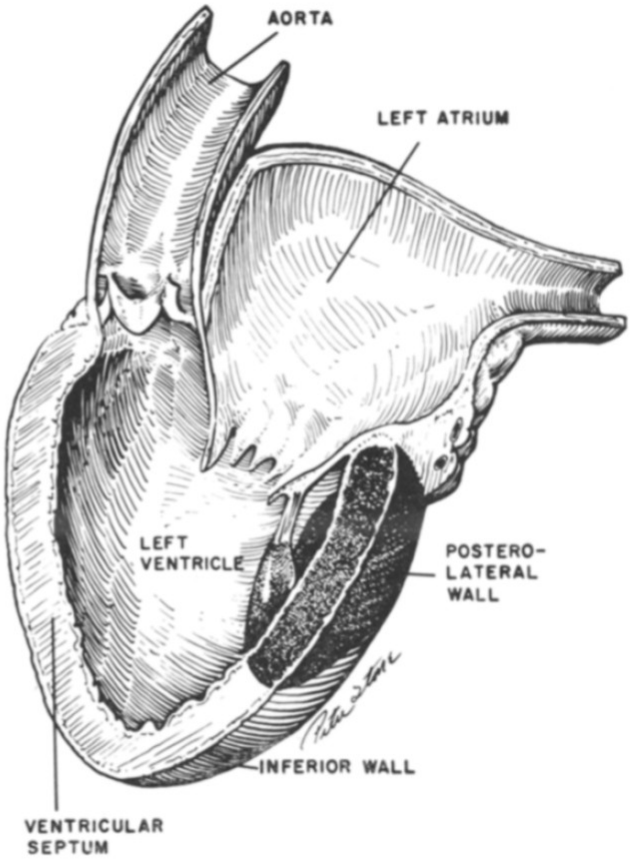
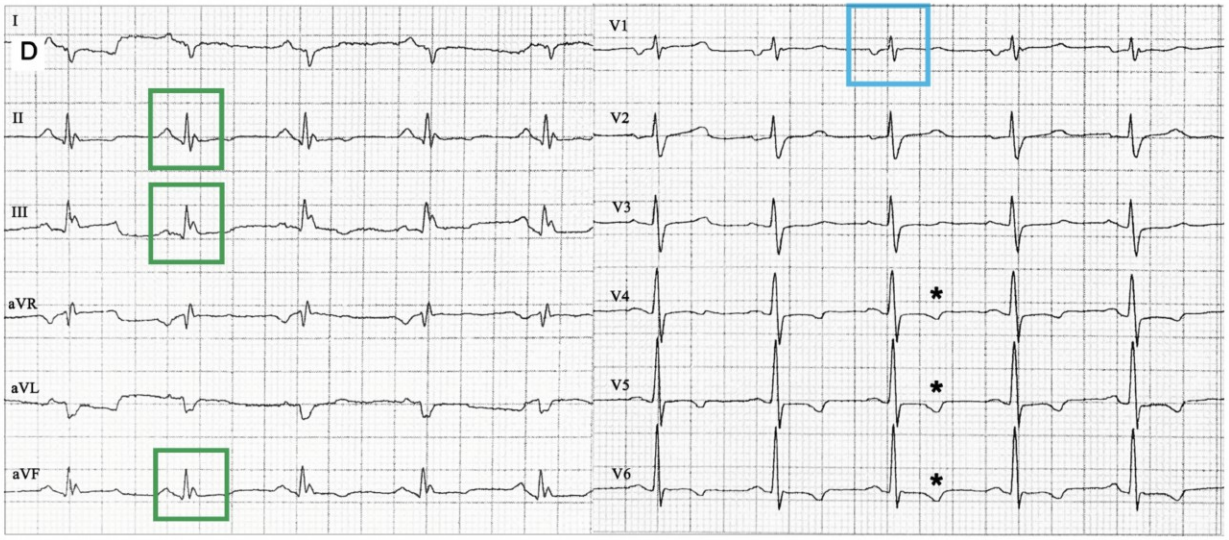
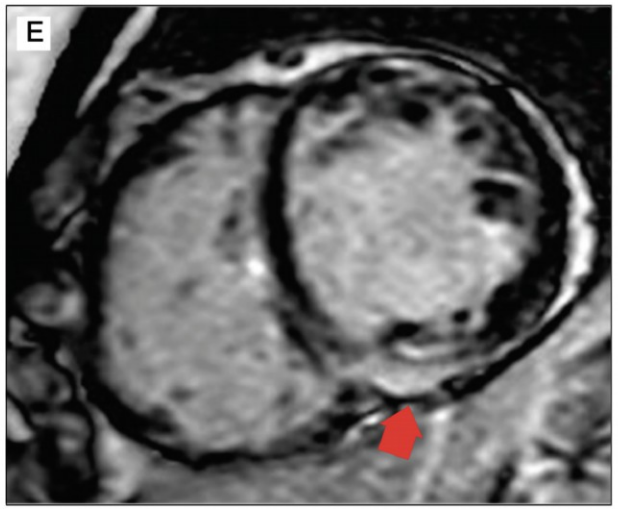
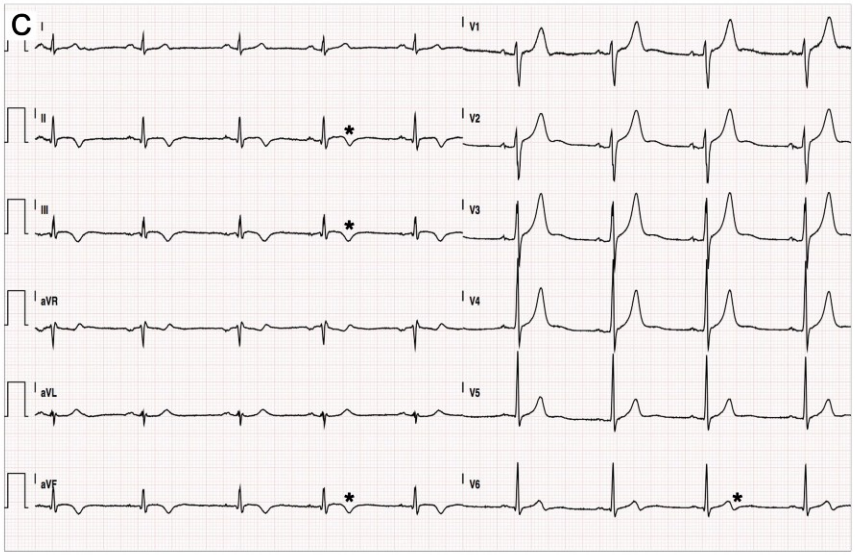


FIG. 3. Diagram of the left side of the heart illustrating the distribution of the fibrous scarring in the two patients. The scarring was focal and limited to the posterolateral free wall of the left ventricle. No scarring was observed in the diaphragmatic or inferior free wall or in the ventricular septum. A papillary muscle was involved in one patient (Case 1) who had clinical mitral incompetence.





Patient #9 is a 33-year-old woman with a pathogenic variant in desmoplakin (c.5851 C>T, p.Arg1951Ter).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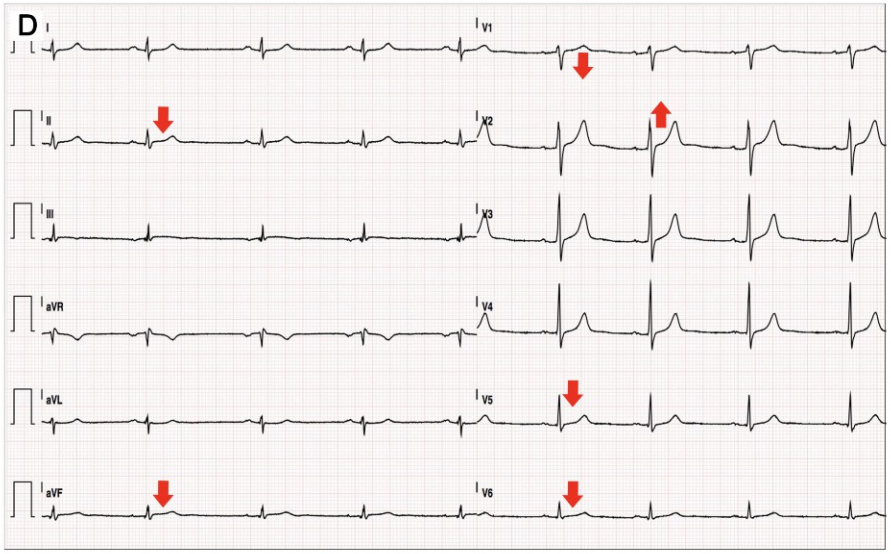
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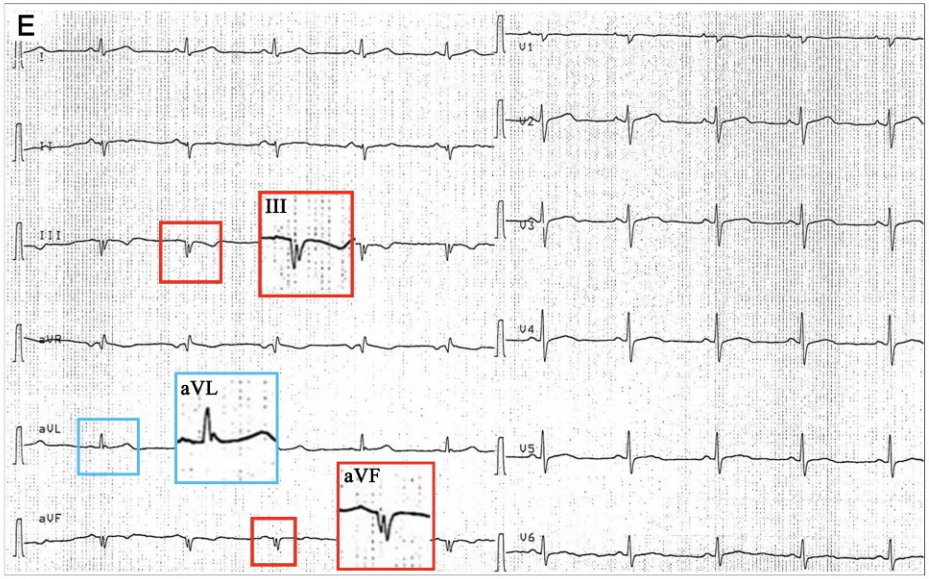
E
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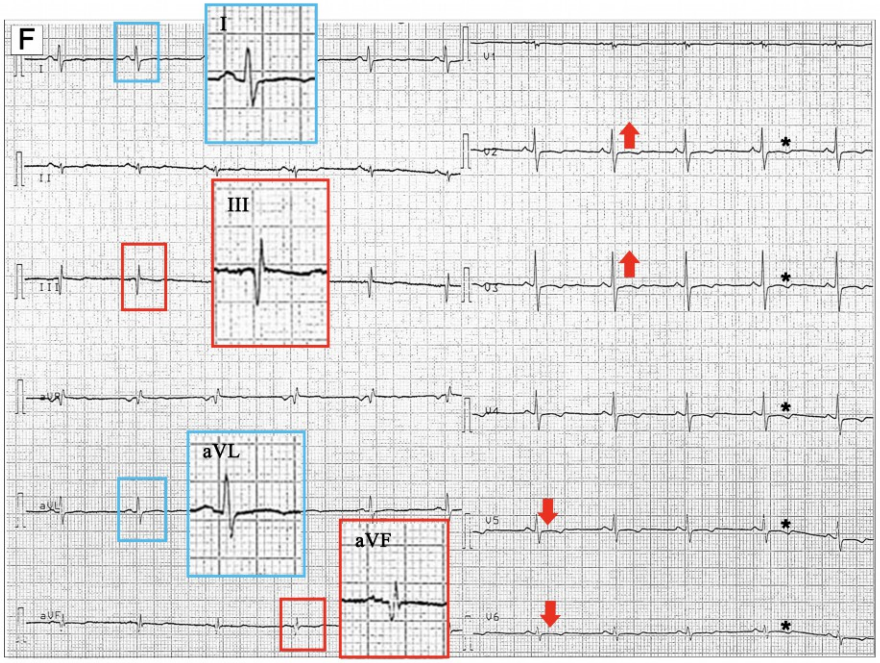
F
I
III
aVL
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	Major Arrhythmic Events (n=15)	No Major Arrhythmic Events (n=39)	P Value
Age at diagnosis, years	43±15	38±15	0.28
Male gender	13 (86.7)	19 (48.7)	**0.011**
Proband	13 (86.7)	27 (69.2)	0.19
Family history of DCM	5 (33.3)	18 (46.2)	0.39
Family history of SCD	3 (20.0)	15 (38.5)	0.20
NYHA class I-II	13 (86.7)	39 (100)	0.22
NYHA class III	2 (13.3)	0	**0.0215**
Atrial fibrillation	2 (13.3)	2 (5.1)	0.31
Unexplained syncope	6 (40.0)	2 (5.1)	**0.001**
NSVT	8 (53.3)	18 (46.2)	0.64
Cardiac magnetic resonance			
LVEDVi (ml/m2)	99.9±19.7	96.8±26.1	0.68
LVEF, %	46.3±6.1	50.8±10.9	0.14
LVEF <50%	10 (66.7)	13 (33.3)	**0.0276**
RVEDVi (ml/m2)	87.2±20.9	85.4±18.4	0.76
RVEF, %	52.6±9.8	54.9±9.2	0.42
Segments with LGE	6±3; 6 (4-7)	6±4; 6 (4-8)	1.0
LGE pattern			
- Ringlike	8 (53.3)	20 (51.3)	0.89
LGE distribution			
- Subepicardial	7 (46.7)	28 (71.8)	**0.09**
- Midmural	2 (13.3)	8 (20.5)	0.55
- Transmural	6 (40.0)	3 (7.7)	**0.0047**
Genetic testing			
Pathogenic/likely pathogenic variant	12/15 (80.0)	36/39 (92.3)	0.20
DSP	6/12 (50.0)	29/36 (80.6)	0.64
Non-DSP *	6/12 (50.0)	7/36 (19.4)	**0.026**
ECG			
QRS (msec)	97±13	95±13	0.61
First degree AV block	1 (6.7)	4 (10.3)	0.68
NSICD	0	2 (5.1)	0.37
RBBB	0	0	-
LAFB	0	4 (10.3)	0.20
LPFB	6 (40.0)	5 (12.8)	**0.028**
LBBB	0	0	-

	Major Arrhythmic Events (n=15)	No Major Arrhythmic Events (n=39)	P Value
Pathological Q waves	5 (33.3)	13 (33.3)	1.0
Lateral distribution	2 (13.3)	5 (12.8)	0.96
Inferior distribution	2 (13.3)	6 (15.4)	0.84
Precordial distribution	0	1 (2.6)	0.53
More 2 localizations	1 (6.7)	1 (2.6)	0.48
Fragmented QRS	4 (26.7)	15 (38.5)	0.42
Lateral distribution	0	1 (2.6)	0.53
Inferior distribution	1 (6.7)	9 (23.1)	0.17
Precordial distribution	1 (6.7)	0	0.11
More 2 localizations	2 (13.3)	5 (12.8)	0.96
Global LQRSV	1 (6.7)	3 (7.7)	0.90
LQRSV in limb leads	1 (6.7)	7 (17.9)	0.31
Local LQRSV			
Lateral distribution	4 (26.7)	9 (23.1)	0.78
Inferior distribution	2 (13.3)	6 (15.4)	0.84
Inferolateral distribution	2 (13.3)	1 (2.6)	0.13
Precordial and local distribution	1 (6.7)	4 (10.3)	0.69
QTc (msec)	401±27	409±26	0.32
QTc ≥440 msec	0	4 (10.3)	0.20
Tzou criteria †	6 (40.0)	4 (10.3)	**0.01**
R >3 mm V1	3 (20.0)	3 (7.7)	0.20
R/S ratio ≥0.5 in V1	9 (60.0)	4 (10.3)	**0.0002**
R/S ratio ≥1 in V1	6 (40.0)	0	**<0.0001**
Bayés de Luna criteria ‡	3 (20.0)	0	**0.0044**
TWI	11 (73.3)	20 (51.3)	0.15
Inferolateral TWI	4 (26.7)	2 (5.1)	**0.025**
Anterior TWI	2 (13.3)	4 (10.3)	0.76
Inferior TWI	2 (13.3)	2 (5.1)	0.31
Lateral TWI	2 (13.3)	4 (10.3)	0.76
Anterolateral TWI	1 (6.7)	5 (12.8)	0.53
Inferior-anterior-lateral TWI	0	3 (7.7)	0.27
NEW ECG CRITERIA			
SV1+RV6 ≤12 (mm)	10 (66.7)	20 (51.3)	0.31
RI + RII ≤8 (mm)	7 (46.7)	24 (61.5)	0.33
SV1+RV6 ≤12 and RI + RII ≤8 (mm)	7 (46.7)	17 (43.6)	0.84

Probability of major arrhythmic events in relation to clinical, electrocardiographic and structural parameters

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P value*	OR	95% CI	*P value*
Clinical parameters						
Age	1.0	0.9-1.1	0.317			
Sex	6.8	1.4-34.4	**0.020**			
Unexplained syncope	12.3	2.1-71.5	**0.005**	**8.9**	**1.1-70.6**	**0.037**
Structural parameters						
Transmural LGE	8.0	1.7-38.2	**0.009**			
LVEF <50%	4.0	1.1-14.1	**0.031**			
ECG parameters						
LPFB	4.5	1.1-18.3	**0.034**			
R/S ratio in V1 ≥0.5	13.1	3.0-56.6	**0.001**	**6.8**	**1.4-34.4**	**0.020**
Inferolateral TWI	6.7	1.1-41.8	**0.041**			
SV1+RV6 ≤12 mm	1.9	0.5-6.6	0.312			
RI+ RII ≤8 mm	0.6	0.2-1.8	0.325			

Unrecognized cases of prominent R-wave in V1 detected in the iconography of published papers

Case ID	References	Figure	12 lead ECG findings	Genetic analysis	CMR data	Endomyocardial biopsy data/ Histologic data
Case 1	Rubino M et al [1] *Genes 2021*	Fig.1	**Prominent R V1 (>3mm)** Inferolateral TWI Pathological Q in I-aVL	DSP (c.5428C>T, p.Gln1810Ter)	Subepicardial circumferential LGE involving the entire LV	Not available
Case 2	Zorzi A et al [2] *Circ Arrhythm Electrophysiol. 2016*	Fig. 4	LPFB Inferolateral TWI Pathological Q II-III-aVF **Prominent R V1 (>3 mm)** LQRSV in left precordial leads	Not performed	Sub/midmyocardial LGE with a stria pattern involving the infero-lateral LV wall	Extensive fibrosis in the sub- and midmyocardial layers (inferolateral LV), focal and patchy fatty infiltration. Cardiomyocytes hypertrophic with dysmetric and dysmorphic nuclei, with cytoplasmic vacuolization.
Case 3	Oloriz T et al [3] *Europace. 2016*	Fig. 1-right panel	LPFB - **R/S ratio V1 ≥0.5**	Not performed	Infero-lateral scar	Not performed
Case 4	Sakamoto N et al [4] *Circ Cardiovasc Imaging. 2019*	Fig.1	**R/S ratio V1 ≥1** Inferolateral TWI LQRSV in limb leads	DSP (c.4650delTG, p.V1551E fs74X) and MYBPC3 (c.2459G>A, p.R820Q)	LGE in the mid-myocardial septum and subepicardial anterolateral LV myocardium.	Fibrofatty replacement, mild hypertrophy, and disarrangement of the myocytes. Electron microscopy of the intercalated discs showed disarrangement of the filaments and widening of the fascia adherens gap
Case 5	Tsuruta Y et al [5] *Heart Fail. 2020*	Fig.1	**R/S ratio V1 ≥1** Inferolateral TWI LQRSV in limb leads	Nonsense mutation in DSP (c.5212C > T, p.R1738*)	Fat signals LGE in the mid-wall to subepicardial layers in the LV myocardium	Moderate fibrofatty replacement and mild hypertrophy
Case 6	Groeneweg JA et al [6] *Heart Rhythm. 2013*	Fig.4	**R/S ratio V1 ≥1** TWI in II and anterolateral leads	PKP2 variant c.419C4T and the PLN mutation c.40_42delAGA	LGE in the lateral wall of the LV	Normal myocardium,with locally some (<10%) subendocardial fibrosis.
Case 7	Blom LJ et al [7] *Heart Rhythm Case Rep. 2018*	Fig.2	LPFB TWI V5-V6, I, II, aVF **R/S ratio V1 ≥1**	Unclassified variant PKP2 gene and a pathogenic c.4042delAGA mutation in the PLN gene.	Not performed	Normal
Case 8	Singh SM et al [8] *JACC Case Rep. 2021*	Fig.3 (C)	LPFB - **R/S ratio V1 ≥1**	Not performed	Biventricular apical and anterolateral LGE in the epi- to mid-myocardium	Not performed
Case 9	Norman M et al [9] *Circulation 2005*	Fig.3	**R/S ratio V1 ≥0.5** Inferolateral TWI	DSP gene identified insertion of a single adenine base (2034insA)	Not performed	Not performed
Case 10	Chen P et al [10] *Int J Cardiol. 2020*	Fig. 2 (A)	LPFB. TWI V1-V3. **R/S ratio V1 ≥1**	DSG2 p.Leu237Ter mutation	Dilation of both ventricles	Not performed
Case 11	Pilichou K et al [11] *Circulation 2014*	Fig.3	**R/S ratio V1 ≥1**	DSP c.448C>T mutation	Focal bulging on anterolateral RV apex. LGE (midepicardial stria) in the inferior LV wall	Not performed

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The end of an electrocardiographic dogma: a prominent R wave in V_1 is caused by a lateral not posterior myocardial infarction—new evidence based on contrast-enhanced cardiac magnetic resonance—electrocardiogram correlations

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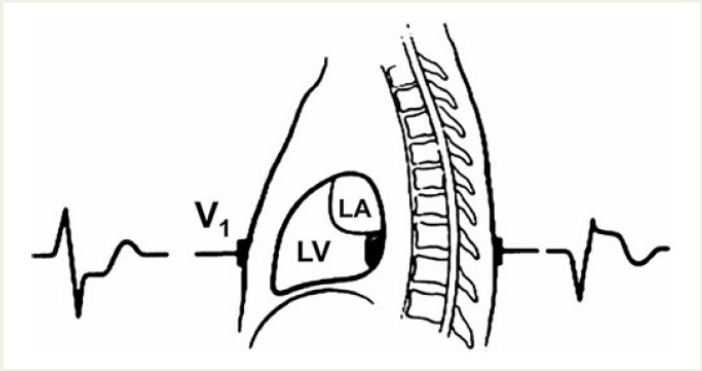


Figure 1 Original drawing of true posterior infarction with the QRS morphology according to Perloff.[1]

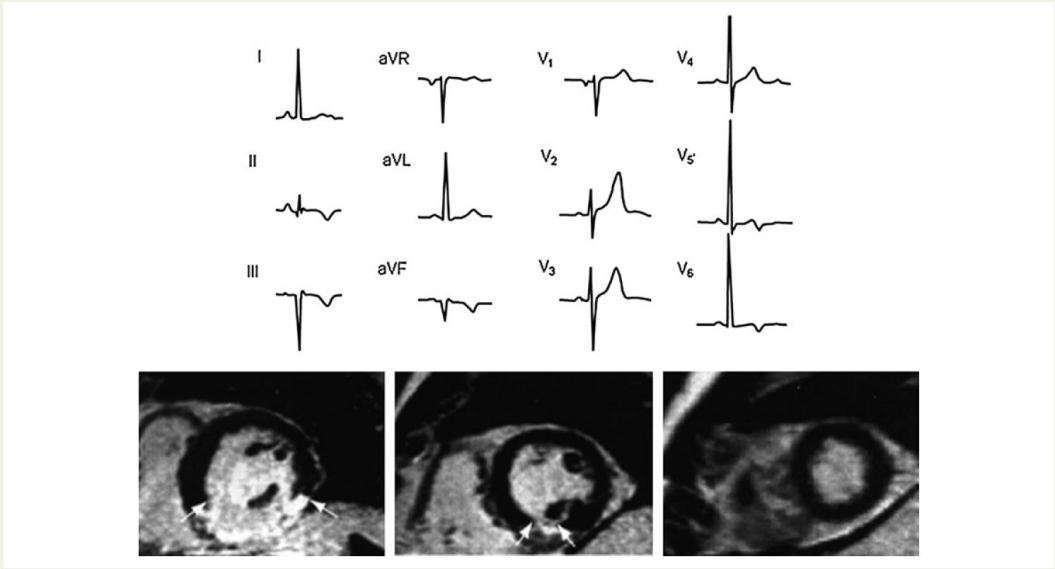


Figure 2 Electrocardiographic and cardiac magnetic resonance images of an inferior infarct. Despite the clear infero-basal location of infarction at contrast-enhanced cardiac magnetic resonance (left-hand panel, between the white arrows), lead V_1 does not show a prominent R wave but an rS morphology.

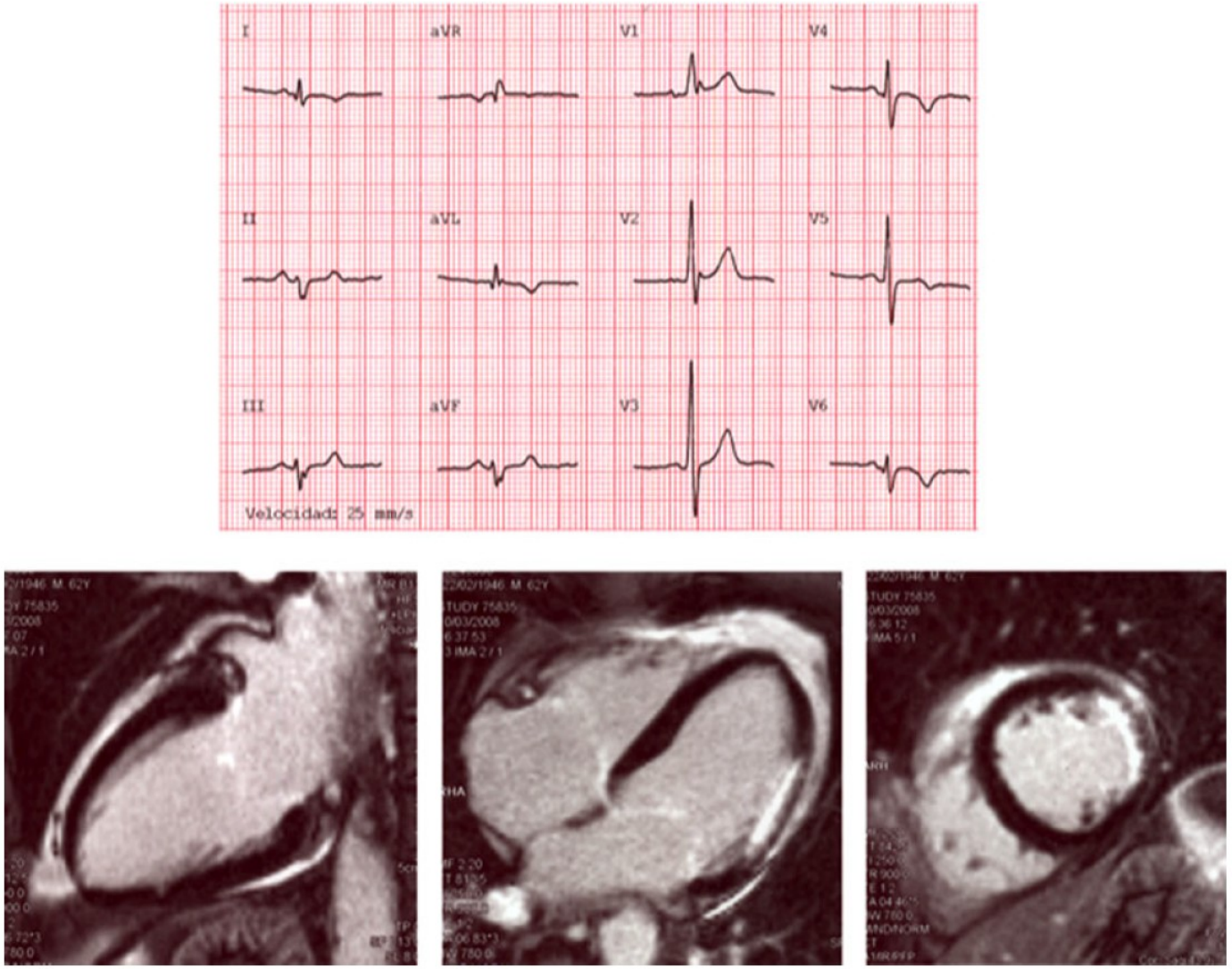


Figure 3 Electrocardiographic and cardiac magnetic resonance images of a lateral infarct. A tall R wave in V_1 corresponds to a lateral infarct at contrast-enhanced cardiac magnetic resonance (lower central and right-hand panels). Of note, the infero-basal segment (segment 4) does not present any sign of necrosis (lower left and right panels).

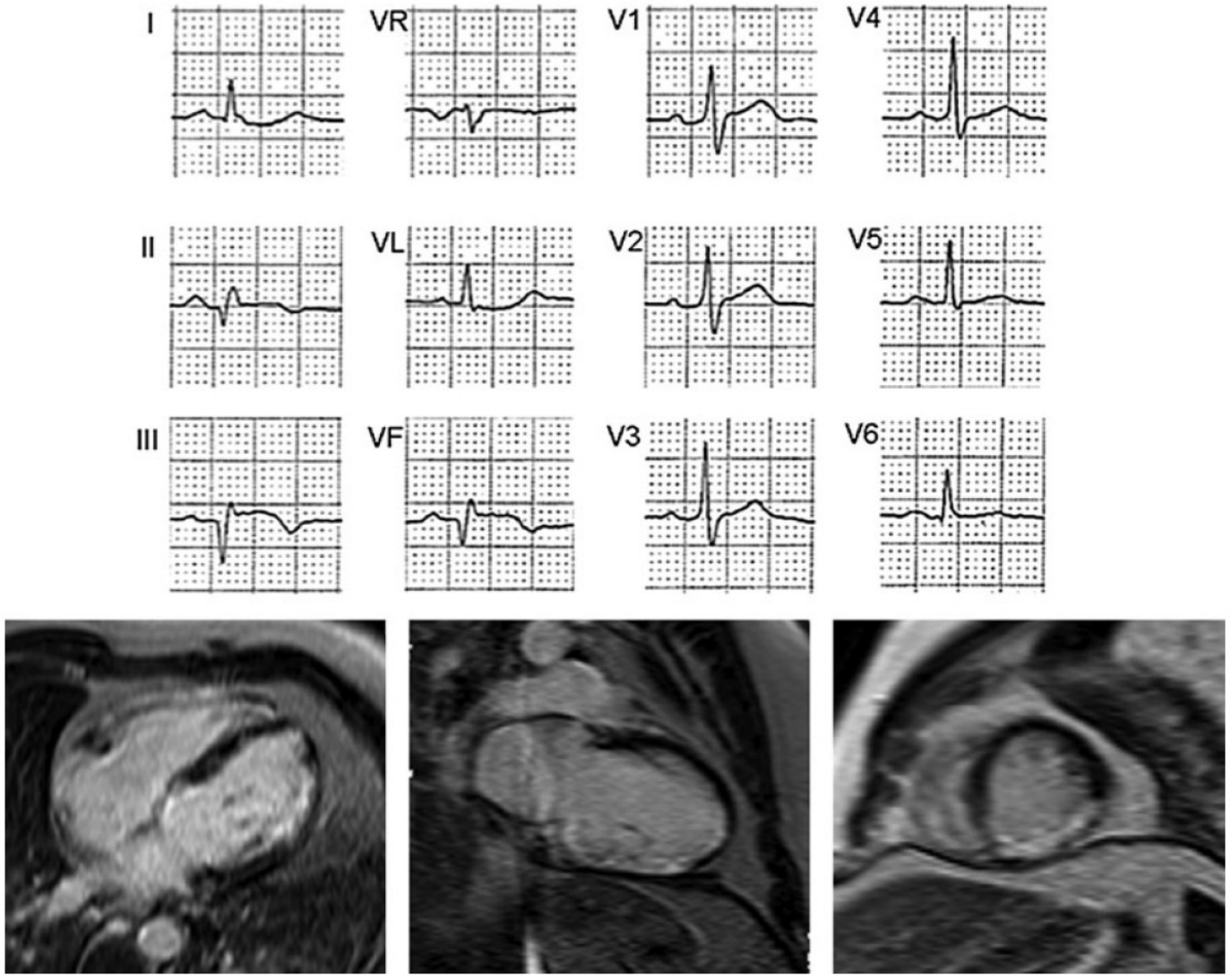
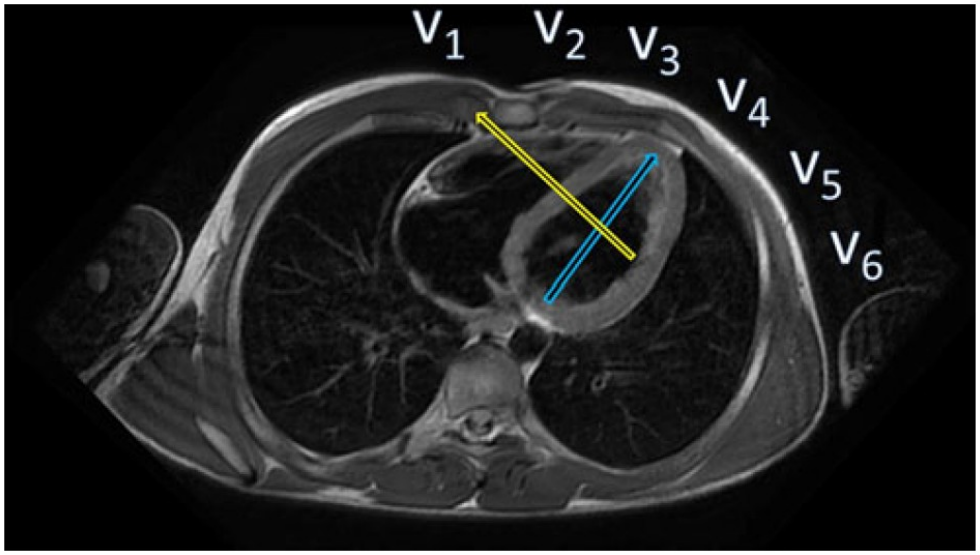
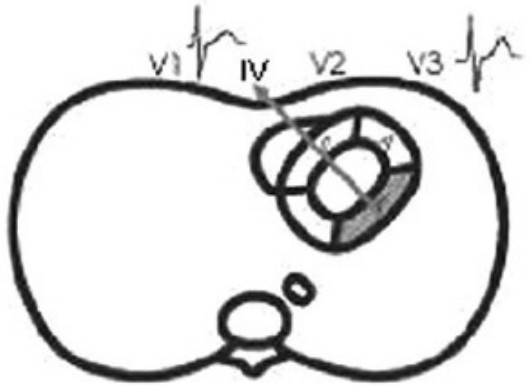


Figure 4 Electrocardiographic and cardiac magnetic resonance images of an infero-lateral infarct. Q waves of necrosis are present in leads II, III, and aVF (inferior necrosis); an R $\geq$ S morphology is present in lead V_1 (lateral necrosis). Contrast-enhanced cardiac magnetic resonance (four-chamber, long-, and short-axis views) clearly shows an infero-lateral necrosis.

Transverse plane of the thorax at cardiac magnetic resonance





The infarction vector produced by involvement of the wall formerly termed posterior (blue arrow) is directed towardsV3–V4, while the infarction vector generated by the lateral wall (yellow arrow) is directed towards V1

Unrecognized LPFB cases noted in the iconography of published papers

Case ID	References	Figure	12 lead ECG findings	Genetic analysis	CMR data	Endomyocardial biopsy data/ Histologic data
Case 1	Protonotarios A et al [1] *J Electrocardiol. 2013*	Fig. 1	**LPFB,** LQRSV in limb and left precordial leads, TWI V5-V6, fQRS in lead V1.	Not performed	Not performed	Fibrotic subepicardial and midwall bands on anterolateral and postero-apical LV walls and on the interventricular septum. Myocyte loss with fibro-fatty replacement and myocyte abnormalities
Case 2	Zorzi A et al [2] *Circ Arrhythm Electrophysiol. 2016*	Fig. 4	**LPFB** Inferolateral TWI Pathological Q in II-III-aVF Prominent R wave V1 LQRSV in left precordial leads	Not performed	Sub/midmyocardial LGE with a stria pattern involving the infero-lateral LV wall	Extensive fibrosis in the sub- and midmyocardial layers (inferolateral LV), focal and patchy fatty infiltration. Cardiomyocytes hypertrophic with dysmetric and dysmorphic nuclei, with cytoplasmic vacuolization.
Case 3	Oloriz T et al [3] *Europace. 2016*	Fig. 1 -right panel	**LPFB** - R/S ratio V1 ≥0.5	Not performed	Infero-lateral scar	Not performed
Case 4	Miles C et al [4] *Circulation. 2019*	Fig. 4	**LPFB** – fQRS inf-septal leads First-degree AV block, Inferolateral TWI – LQRSV in limb leads, prolonged terminal activation duration in V1	Not performed	Extensive LV LGE, including near transmural LGE of lateral wall and midwall of anterior wall.	Myocyte degeneration and fibrofatty infiltration within the posterolateral wall of the LV (extending transmurally).
Case 5	Saguner AM et al [5] *Circulation. 2015*	Fig. 2	**LPFB** Early repolarization in the inferior leads and QRS fragmentation in aVL	Heterozygous pathogenic variant in the plakophilin-2 (c.2392A>G, p.T798A) and desmoglein-2 (c.877A>G, p.I293V) genes.	Fibrofatty infiltration involving epi- and midmyocardial layers of the inferolateral, antero-lateral, and septal LV wall.	Unremarkable
Case 6	d'Amati G et al [6] *Int J Cardiol. 2016*	Fig. 1	**LPFB**	Not pathogenic mutation	Not performed	Fibro-adipose replacement (LV postero-lateral wall). Myocytes enlarged, dysmorphic nuclei
Case 7	Blom LJ et al [7] *Heart Rhythm Case Rep. 2018*	Fig. 1	**LPFB** - Intra-ventricular conduction delay, J-point elevation in inferior leads	Unclassified variant in the DSG2 gene and a p.Leu729del mutation in the gene SCN5A.	Not performed	Normal
Case 8	Blom LJ et al [7] *Heart Rhythm Case Rep. 2018*	Fig.2	**LPFB** TWI V5-V6, I, II, aVF R/S ratio V1 ≥1	Unclassified variant plakophilin-2 gene and a pathogenic c.40-42delAGA mutation in the phospholamban (PLN) gene.	Not performed	Normal
Case 9	Singh SM et al [8] *JACC Case Rep. 2021*	Fig.3 (C)	**LPFB** - R/S ratio V1 ≥1	Not performed	Biventricular apical and anterolateral LGE in the epi- to mid-myocardium	Not performed
Case 10	Piriou N et al [9] *ESC Heart Fail. 2020*	Fig.2 (B)	**LPFB** - TWI V4-V6 LQRSV in limb leads	Pathogenic variant in desmoplakin c.3924del	High T2 intensity and subepicardial circumferential LGE.	Not performed
Case 11	Reichl K et al [10] *Circ Genom Precis Med. 2018*	Fig.1 (A)	**LPFB**	Heterozygous variant was identified in exon 23 of the DSP gene—c.3415_3417del TATinsG.	Epi- and midmyocardial LGE and fatty replacement in anterior, lateral and inferior LV and basal inferior RV segments.	Not performed
Case 12	Chmielewski P et al [11] *Diagnostics 2020*	Fig.2 (A)	**LPFB** TWI V1-V3 LQRSV, prolonged terminal activation duration in V1, fQRS II-III- aVF.	DSP NM_004415.4:c.3737dupA (p.Asn1246Lysfs Ter7) PKP2 NM_004572.3:c.2636T>C (p.Leu879Pro) NLRP3 NM_004895.4:c.1469G>A (p.Arg490Lys)	Moderate subepicardial and midwall areas of LGE with a ringlike pattern	
Case 13	Poller W et al [12] *J Am Heart Assoc. 2020*	Fig.3 (C)	**LPFB** TWI inferolateral leads	Dystrophin c.3970C>T, p.Arg1324Cys, desmoplakin c.4372C>T, p.Arg1458Ter, nexilin F-actin–binding protein c.154G>C, p.Asp52His	Multifocal subepicardial posteroseptal and lateral LGE.	Low-level immune cell infiltration in the absence of intramyocardial virus genomes
Case 14	Vahidnezhad H et al [13] *Sci Rep. 2020*	Fig.2 (A)	**LPFB**, TWI V1-V3 Prolonged V3 terminal QRS duration- LQRSV limb leads	JUP mutation	Normal	Not performed
Case 15	Chen P et al [14] *Int J Cardiol. 2020*	Fig. 2 (A)	**LPFB**, TWI V1-V3. R/S ratio V1 ≥1	DSG2 p.Leu237Ter mutation	Dilation of both ventricles	Not performed
Case 16	Protonotarios N et al [15] *Br Heart J. 1986*	Fig. 3 (A)	**LPFB**, QRS prolongation, LQRSV, TWI precordial leads.	Not performed (JUP mutation?)	Not performed	Not performed
Case 17	Chen V et al [16] *Eur Heart J Case Rep 2022*	Fig 2	**LPFB**	Pathogenic heterozygous DSP gene truncation variant (p.R1951X) and the pathogenic HFE variant (p.H63D).	Subepicardial basal-anterior, basal anterolateral, mid-inferior and mid-anteroseptal areas of LGE.	Mild lymphocytic myocarditis, interstitial fibrosis, and myocyte hypertrophy

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CLINICAL RESEARCH

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

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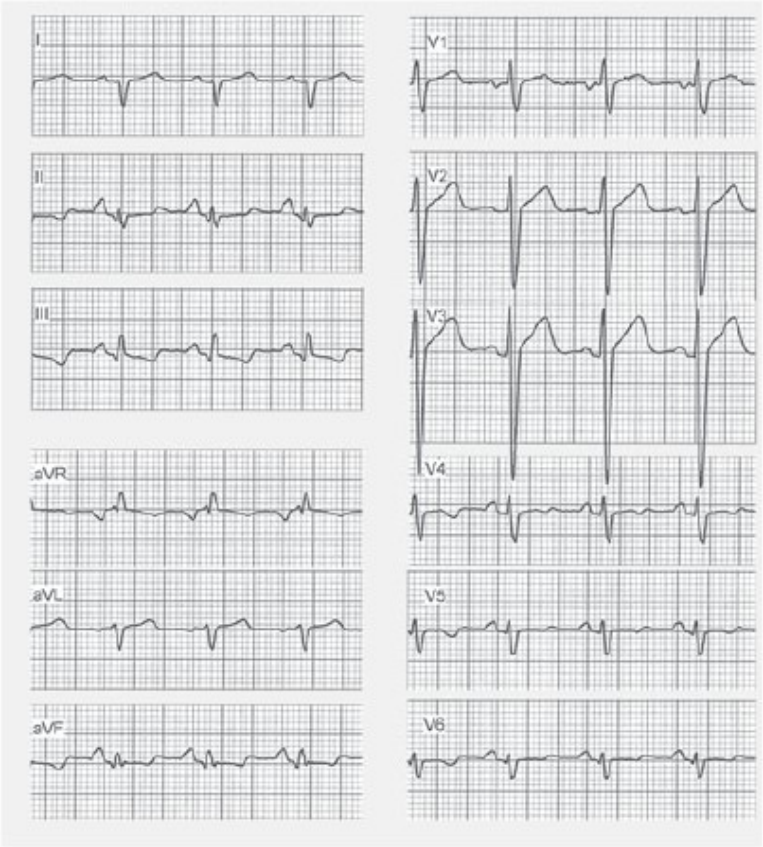
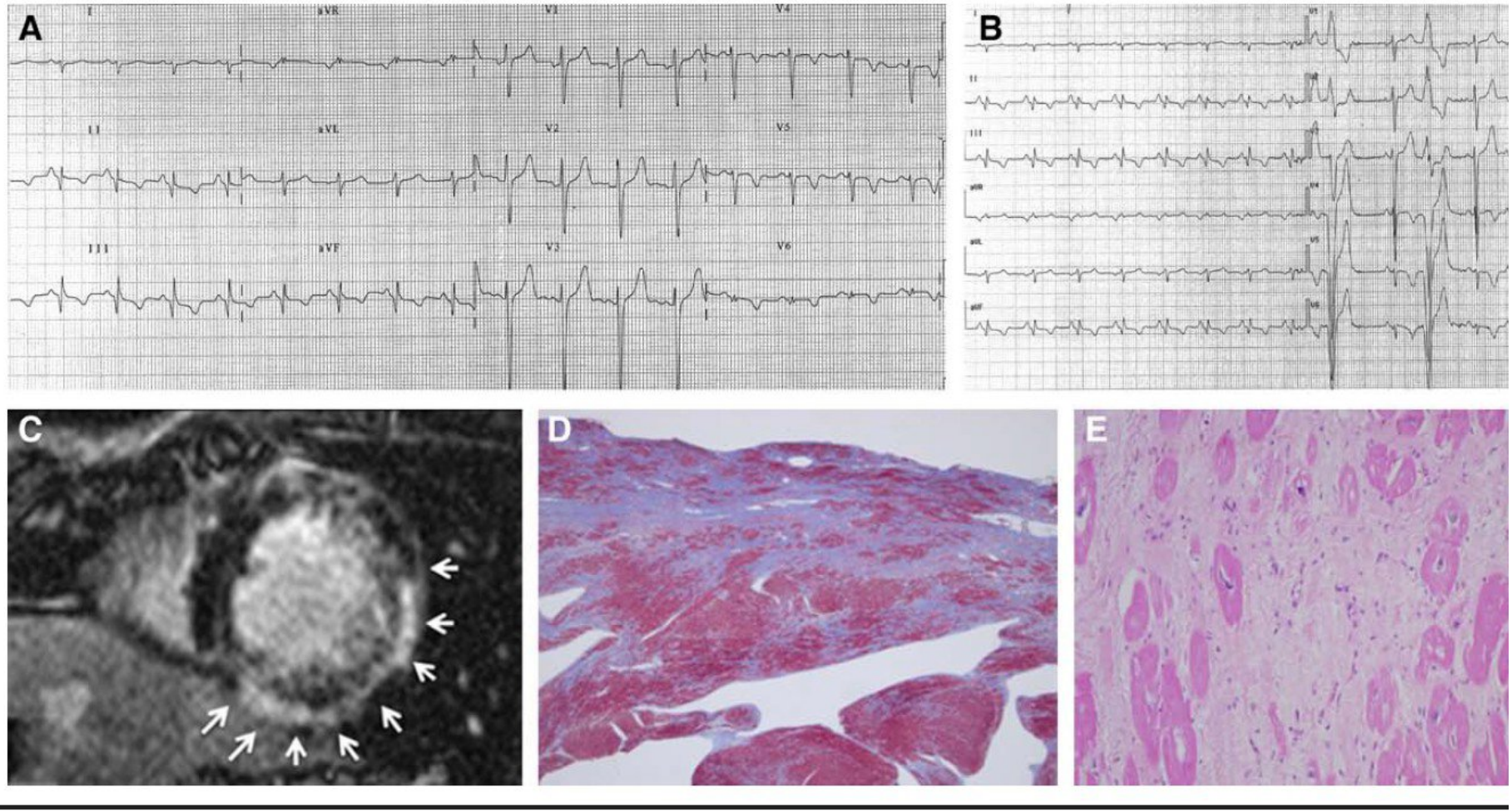


OPEN

Nonischemic Left Ventricular Scar as a Substrate of Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death in Competitive Athletes

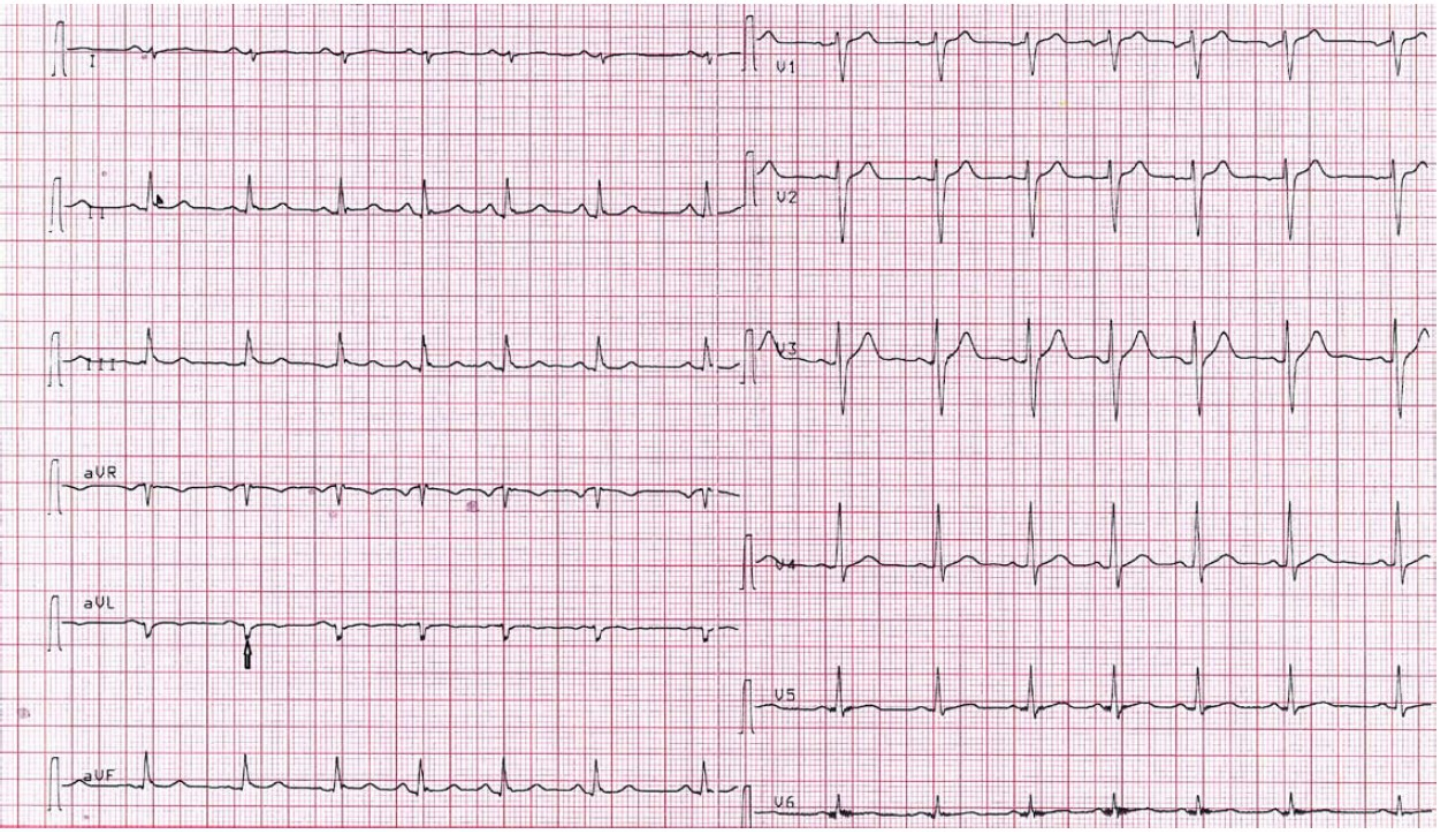
Alessandro Zorzi, MD*; Martina Perazzolo Marra, MD, PhD*; Ilaria Rigato, MD, PhD; Manuel De Lazzari, MD; Angela Susana, MD; Alice Niero, MD; Kalliopi Pilichou, BS, PhD; Federico Migliore, MD, PhD; Stefania Rizzo, MD, PhD; Benedetta Giorgi, MD; Giorgio De Conti, MD; Patrizio Sarto, MD; Luis Serratosa, MD; Giampiero Patrizi, MD; Elia De Maria, MD; Antonio Pelliccia, MD; Cristina Basso, MD, PhD; Maurizio Schiavon, MD; Barbara Bauce, MD, PhD; Sabino Iliceto, MD; Gaetano Thiene, MD; Domenico Corrado, MD, PhD

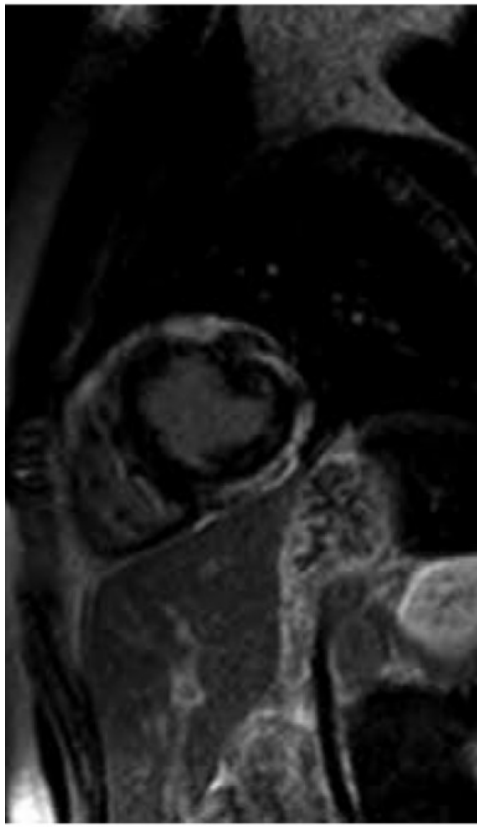


Arrhythmogenic Left Ventricular Cardiomyopathy

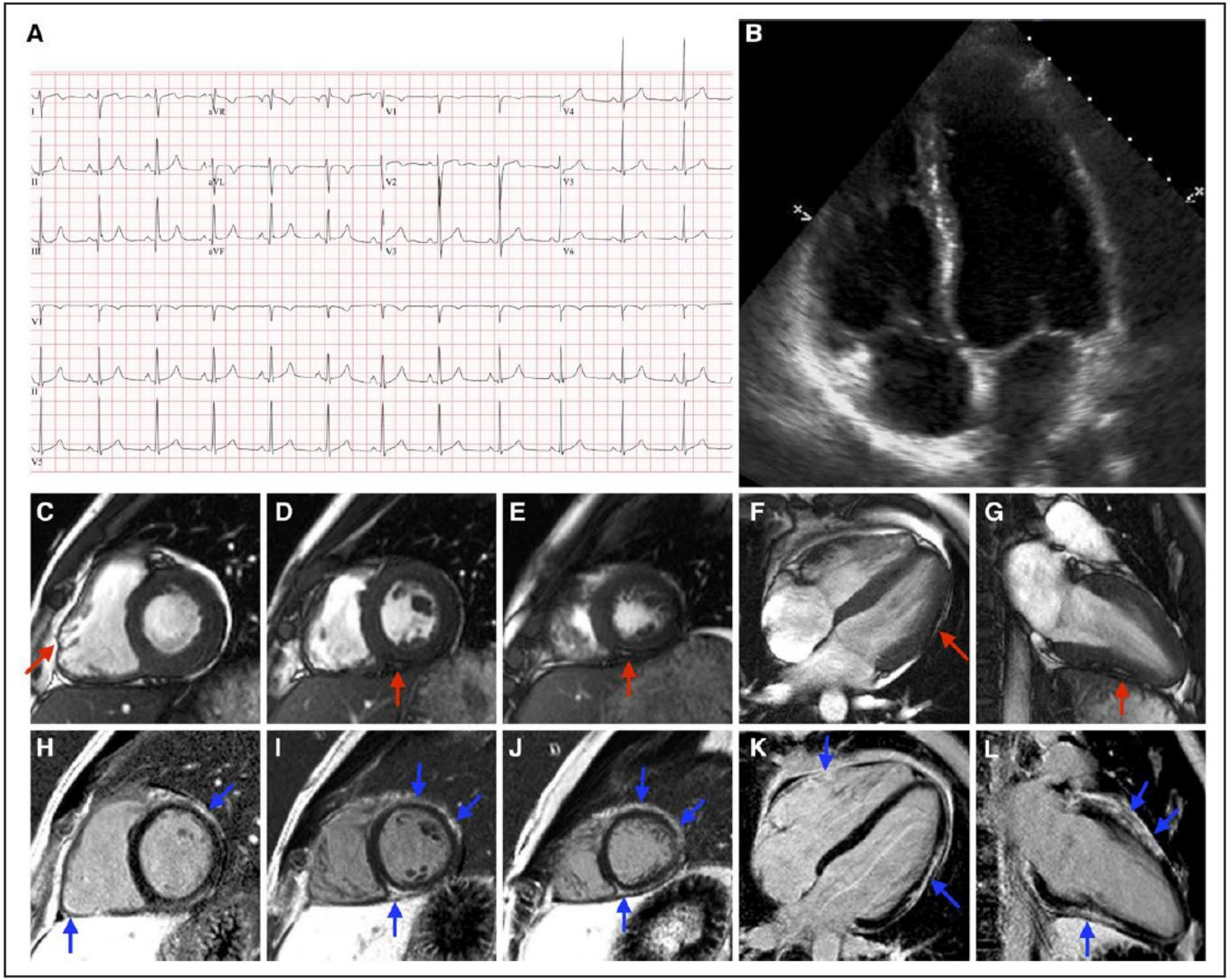
Suspected by Cardiac Magnetic Resonance Imaging, Confirmed by Identification of a Novel Plakophilin-2 Variant

Ardan M. Saguner, MD; Beate Buchmann, MD; Daniel Wyler, MD; Robert Manka, MD; Alexander Gotschy, MD; Argelia Medeiros-Domingo, MD, PhD; Corinna Brunckhorst, MD; Firat Duru, MD; Kurt A. Mayer, MD





(Circulation. 2015;132:e38-e40. DOI: 10.1161/CIRCULATIONAHA.115.017284.)



Reichl et al; Desmoplakin AC Presenting as Acute Myocarditis. Circ Genom Precis Med. 2018;11:e002373. DOI: 10.1161/CIRCGEN.118.002373

Late evolution of arrhythmogenic cardiomyopathy in patients with initial presentation as idiopathic ventricular fibrillation

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Richard N.W. Hauer, MD, PhD,* Rutger J. Hassink, MD, PhD*

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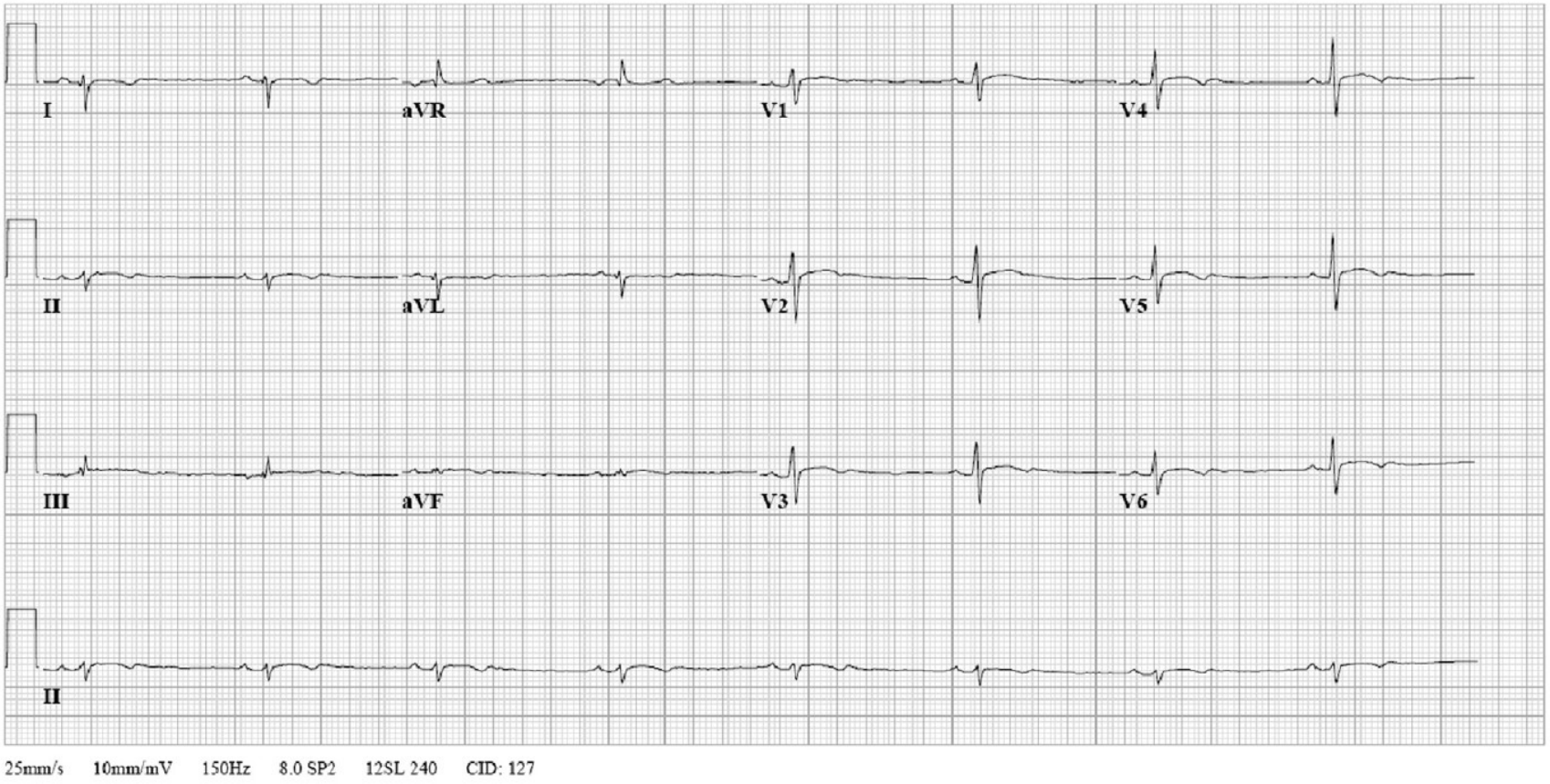


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JACC: CASE REPORTS VOL. 3, NO. 15, 2021

CASE REPORT

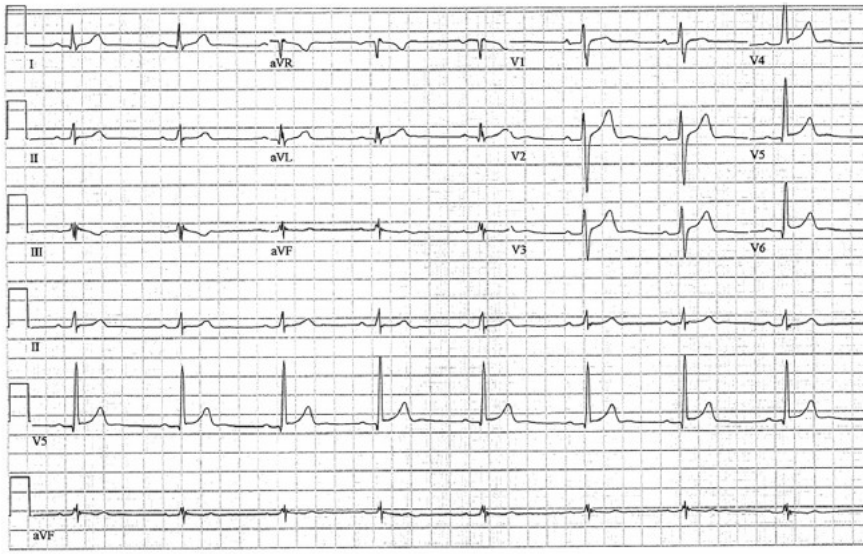
ADVANCED

CLINICAL CASE SERIES

Acute Myocardial Infarction-Like Events in Related Patients With a Desmoplakin-Associated Arrhythmogenic Cardiomyopathy

Sajya M. Singh, BS,[a] Scott W. Sharkey, MD,[a] Susan A. Casey, RN,[a] Kevin M. Harris, MD,[a] Christina M. Thaler, MD,[a] Mina Chung, MD,[b] Allison Berg, MS, CGC,[c] Mosi K. Bennett, MD,[a] Emily R. Ducanson, MD,[d] Shannon Mackey-Bojack, MD,[d] Jay D. Sengupta, MD[a]

A



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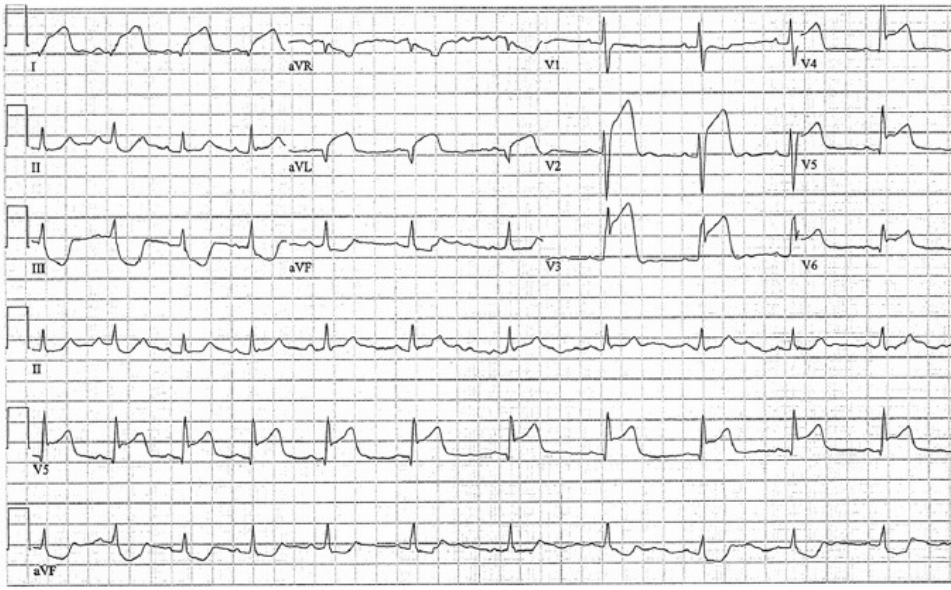

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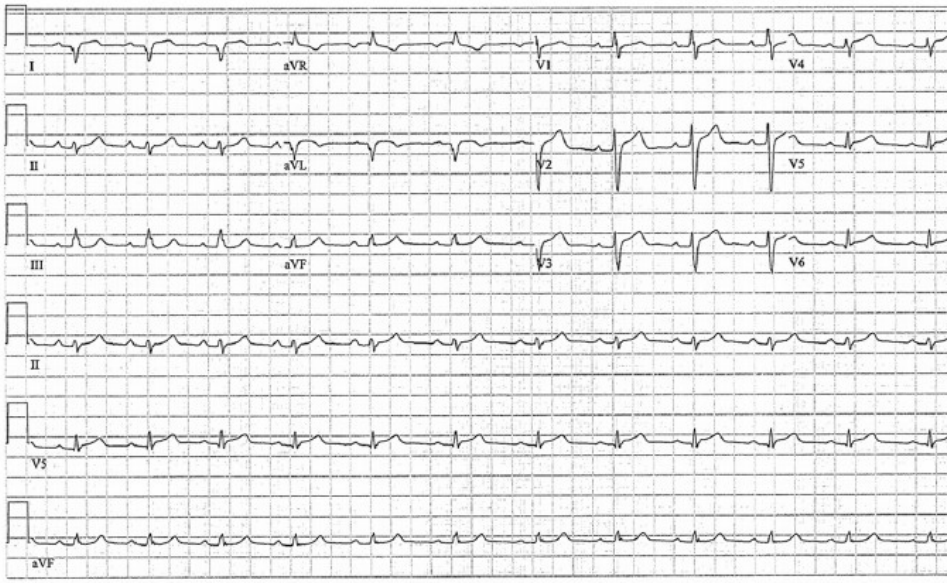
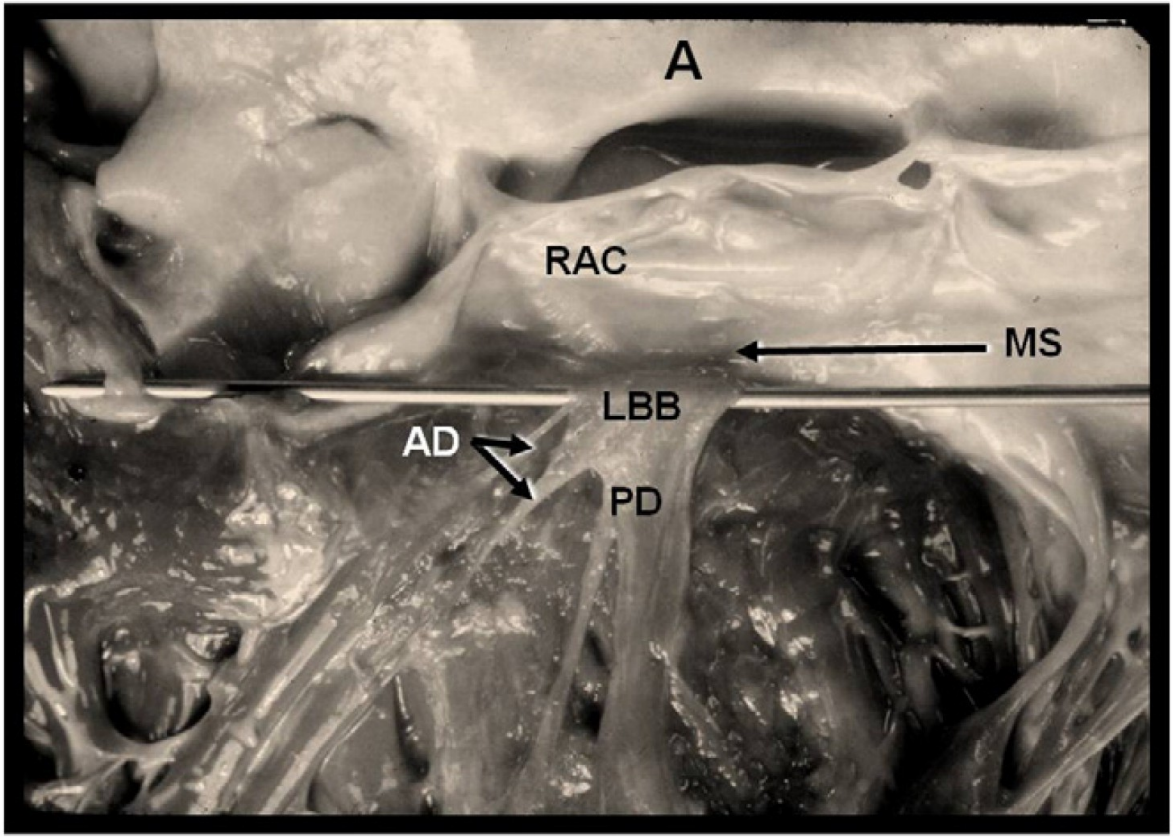
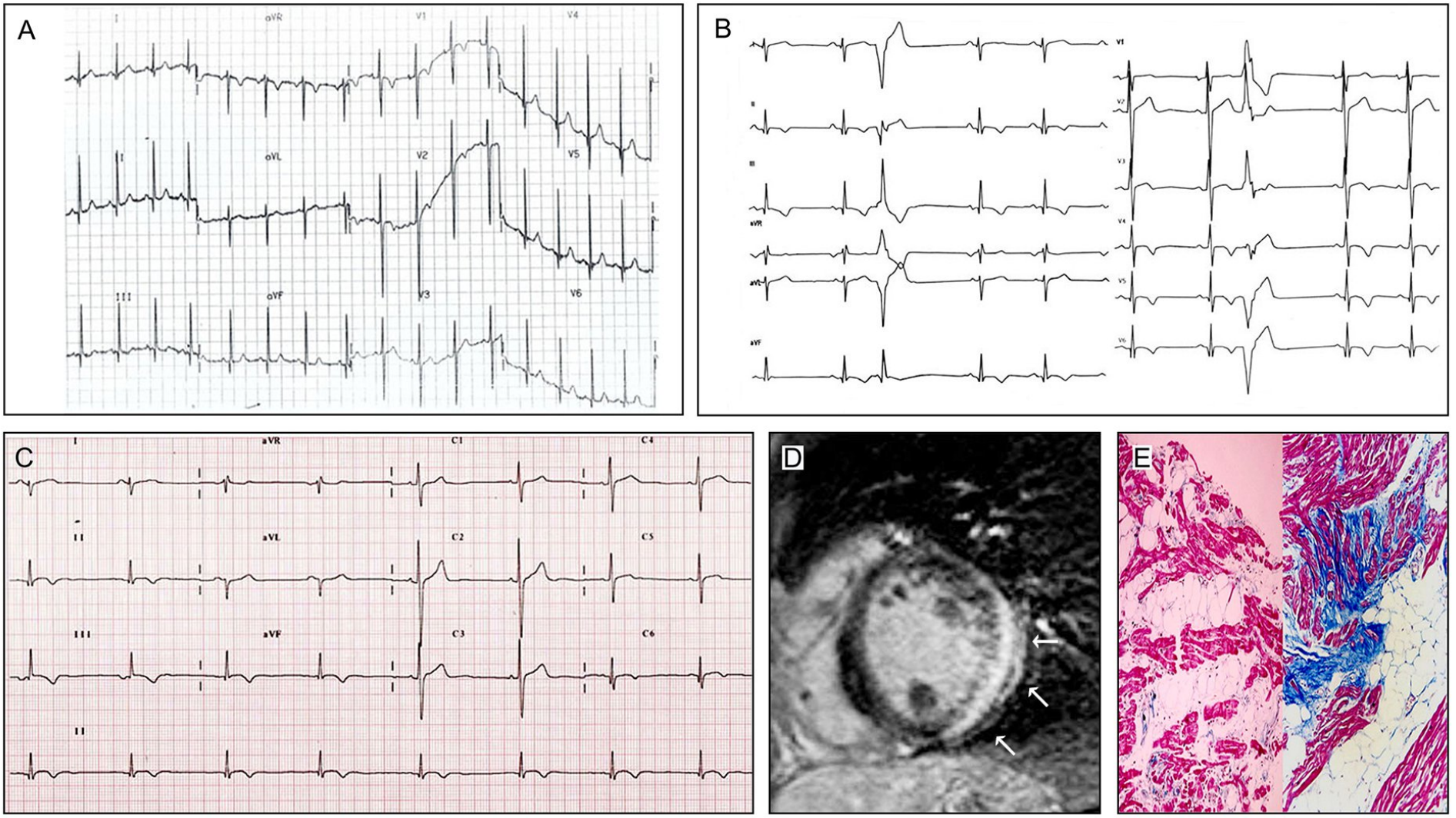




Human heart. The LBB (LBB) emerges in the subaortic region. The membranous septum (MS) is almost absent and the aortic valve lies directly over the LBB,which gives off the anterior division (AD) and posterior division (PD) from its very beginning. The membranous septum is strikingly small or practically absent in this case. The distance between the branching portion of the bundle of His from the aortic valve depends on the size of the MS. The larger the MS, the lesser the possibility that the aortic valve pathology involves this crucial part of the conducting system. A: aorta; RAC right aortic cusp.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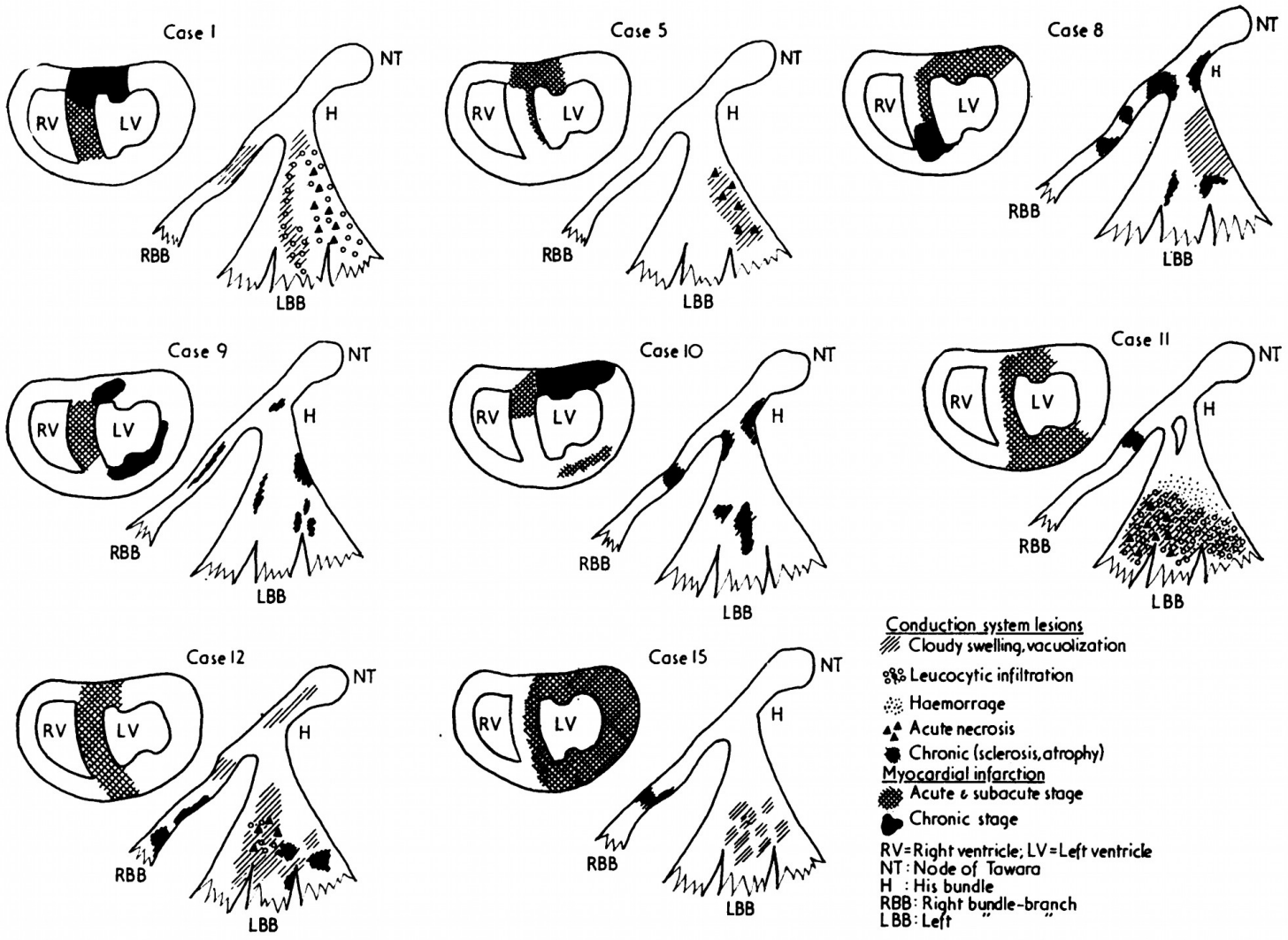
Case 1
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H
RBB
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Case 5
RV
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Case 8
RV
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LBB
Case 9
RV
LV
NT
H
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Case 10
RV
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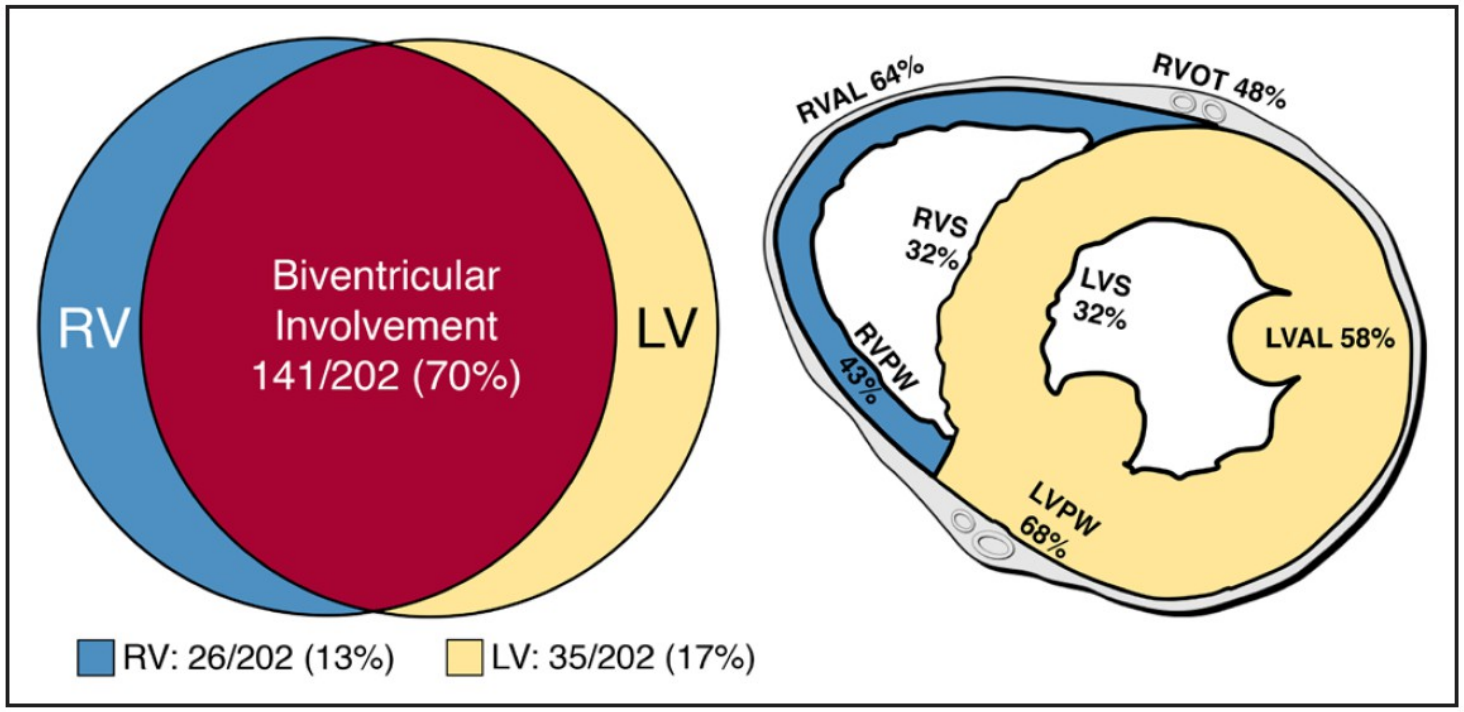
NT
H
RBB
LBB
Case 11
RV
LV
NT
H
RBB
LBB
Case 12
RV
LV
NT
H
RBB
LBB
Case 15
RV
LV
NT
H
RBB
LBB
Conduction system lesions
Cloudy swelling, vacuolization
Leucocytic infiltration
Haemorrage
Acute necrosis
Chronic (sclerosis, atrophy)
Myocardial infarction
Acute & subacute stage
Chronic stage
RV=Right ventricle; LV=Left ventricle
NT: Node of Tawara
H : His bundle
RBB: Right bundle-branch
LBB: Left

Distribution and location of disease involvement in arrhythmogenic cardiomyopathy



Miles et al Circulation 2019

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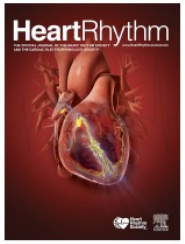

Fascicular heart blocks and risk of adverse cardiovascular outcomes: results from a large primary care population.

Benjamin Chris Nyholm, MD, Jonas Ghouse, MD, PhD, Christina Ji-Young Lee, MD, PhD, Peter Vibe Rasmussen, MD, Adrian Pietersen, MD, Steen Møller Hansen, MD, PhD, Christian Torp-Pedersen, MD, DMSci, Lars Køber, MD, DMSci, Stig Haunsø, MD, DMSci, Morten Salling Olesen, MSc, PhD, Jesper Hastrup Svendsen, MD, DMSci, Claus Graff, MSc, PhD, Anders Gaarsdal Holst, MD, PhD, Jonas Bille Nielsen, MD, PhD, Morten Wagner Skov, MD, PhD

PII: S1547-5271(21)02216-5

DOI: https://doi.org/10.1016/j.hrthm.2021.09.041

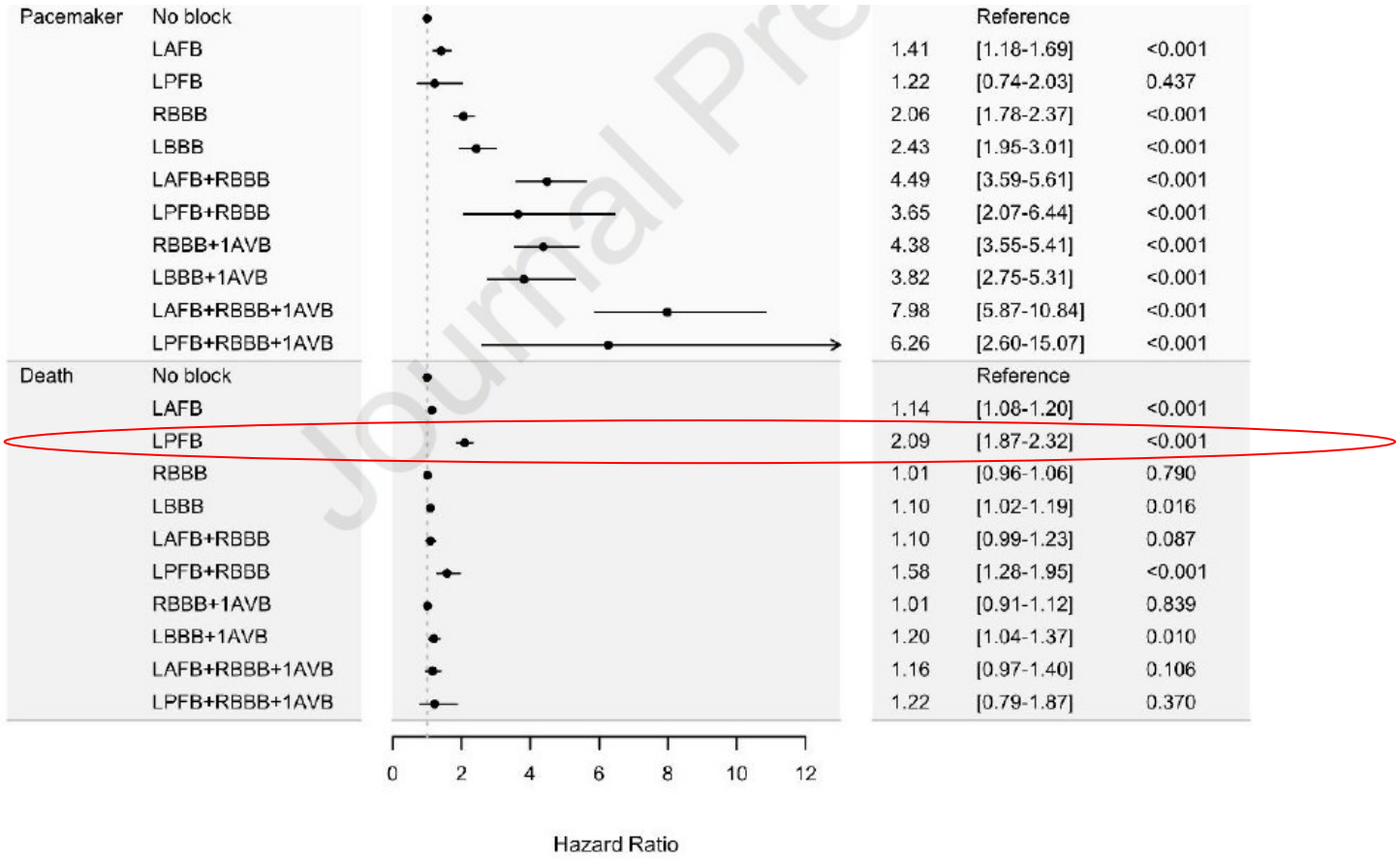

Table 1. Baseline characteristics

Fascicular block subtype	No conduction defects		LAFB		LPFB		RBBB		LBBB		RBBB + LAFB		RBBB + LPFB		RBBB + 1AVB		LBBB + 1AVB		RBBB + LAFB + 1AVB		RBBB + LPFB + 1AVB	
n (%)	**345,315**	**(96.2)**	**3,526**	**(0.98)**	**2,889**	**(0.80)**	**3,910**	**(1.09)**	**1,390**	**(0.39)**	**570**	**(0.16)**	**196**	**(0.05)**	**643**	**(0.18)**	**304**	**(0.08)**	**176**	**(0.05)**	**32**	**(0.01)**
Age, years, median (IQR)	54	(41-66)	71	(60-80)	35	(26-51)	69	(58-79)	75	(64-82)	76	(68-83)	66	(53 -78)	77	(70-84)	80	(72-86)	79	(70-86)	78	(71-84)
Women, n (%)	190,796	55	1,463	41	1,441	50	1,349	35	949	68	169	30	79	40	158	25	136	45	32	18	6	19
Medical history, n (%)																						
Hypertension	66,316	(19)	1,139	(32)	198	(7)	1,349	(35)	625	(45)	241	(42)	48	(25)	333	(52)	174	(57)	101	(57)	15	(47)
Syncope	9,355	(2.7)	135	(3.8)	83	(2.9)	148	(3.8)	60	(4.3)	26	(4.6)	6	(3.1)	37	(5.8)	13	(4.3)	16	(9.1)	<4	(<12.5)*
Atrial fibrillation	5,041	(1.5)	134	(3.8)	38	(1.3)	121	(3.1)	66	(4.8)	20	(3.5)	9	(4.6)	35	(5.4)	27	(8.9)	12	(6.8)	5	(15.6)
Valvular heart disease	1,442	(0.4)	46	(1.3)	10	(0.4)	50	(1.3)	25	(1.8)	12	(2.1)	<4	(<2)*	15	(2.3)	12	(4.0)	<4	(<3)	<4	(<12.5)*
Beta blocker therapy	52,809	(15.3)	736	(20.9)	242	(8.4)	845	(21.6)	408	(29.4)	132	(23.2)	31	(15.8)	193	(30.2)	111	(36.5)	58	(33.0)	11	(34.4)
Charlson Comorbidity Index																						
0 points	265,361	(77)	2,078	(59)	2,413	(84)	2,429	(62)	802	(58)	296	(52)	124	(63)	319	(50)	144	(47)	71	(40)	14	(44)
1 point	41,598	(12)	648	(18)	271	(9)	632	(16)	237	(17)	109	(19)	31	(16)	121	(19)	66	(22)	34	(19)	8	(25)
≥ 2 points	38,356	(11)	800	(23)	205	(7)	849	(22)	351	(25)	165	(29)	41	(21)	203	(31)	94	(31)	71	(40)	10	(31)
ECG variables																						
QRS duration, median (IQR)	92	(84-100)	102	(96-110)	96	(88-104)	136	(128-146)	146	(136-156)	144	(136-154)	140	(130-148)	144	(134-152)	154	(144-164)	151	(142-160)	150	(134-159)
PR interval, median (IQR)	156	(144-172)	168	(152-186)	154	(140-170)	162	(148-178)	168	(154 -180)	170	(156-184)	162	(146-178)	220	(208-242)	218	(208-238)	228	(211-251)	221	(207-242)
Heart rate (IQR)	69	(62-79)	72	(63-82)	71	(62-82)	70	(62-80)	73	(65-83)	71	(64-80)	74	(66-84)	68	(60-78)	70	(62-80)	69	(60-77)	76	(68-86)

TABLE 1: LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; LBBB = left bundle branch block; RBBB = right bundle branch block; 1AVB = first degree atrioventricular block;
*Due to the Act on Processing of Personal Data, we are not allowed to report any number less than four observations.

EDITORIAL COMMENTARY

From Argentina to Denmark—The wine is still good

Reginald T. Ho, MD, FHRS

From the Division of Cardiology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

In 1968, Dr Mauricio Rosenbaum published a book dedicated entirely to the intraventricular conduction system.[1] In this classic monograph and its subsequent English version, he coined the term "hemiblock" and introduced the concept of a trifascicular conduction system after analyzing electrocardiograms from a 58-year-old man who had suffered an anterior myocardial infarction and demonstrated right bundle branch block (RBBB) with alternating left anterior fascicular block (LAFB) and left posterior fascicular block (LPFB) (now called Rosenbaum's syndrome).[2] He referred to the conduction system as a "detector" of the heart, showing the association between various conduction blocks and heart disease (commonly coronary artery disease and Chagas cardiomyopathy in his home country of Argentina). He described the unequal "anatomic vulnerability" of the bundle branches (right more than left; left anterior more than posterior) and the relative "immunity" of the left posterior fascicle because of its thick structure and dual blood supply (indicating that the presence of LPFB generally signified more severe heart disease). His book was followed by a flurry of studies in the mid-1970s and early 1980s evaluating the value of His-ventricular intervals in predicting impending atrioventricular block (AVB) in patients with bifascicular block—research that today remain the foundation for our current pacemaker guidelines.[3] Since then, however, research on the natural history of fascicular block and its progression to AVB has been relatively quiet.

In this issue of *Heart Rhythm Journal*, Nyholm et al[4] breathe new life into the study of fascicular blocks by providing the largest population-based study on its natural progression to AVB. Among 358,958 primary care patients in a large Danish registry (Copenhagen ECG Study), the authors studied 13,636 patients with fascicular block (3.8%) and compared them with a reference group of patients without block. Not surprisingly, RBBB and isolated LAFB were most common. With the longest follow-up approaching 16 years, they found that syncope, pacemaker implantation, and third AVB increased with increasing complexity of fascicular block. Depending on gender and age, the 10-year absolute risk of developing third-degree AVB increased from 0% to 2% (hazard ratio [HR] 1.60) for isolated LAFB to 23% (HR 10.98) for multicombination block (first-degree AVB + RBBB + LAFB). While this dose-response relationship between worsening fascicular block and AVB is not unexpected, their data provide clearer granularity about the long-term risk of developing AVB among 10 different block subtypes. True bilateral BBB (eg, alternating BBB and Rosenbaum's syndrome) was not represented. However, this subtype is already an established high-risk group carrying a class I indication for pacemaker implantation. While a higher burden of comorbidity occurred with increasing block complexity, LAFB was not associated with worse mortality. This has been observed in another study from the same group but not by others.[5–7] Curiously, isolated LPFB was associated with the youngest age group (median age 35 years) and the highest risk of death (HR 2.09). A recent case-control study of 10 young patients (median age 27.5 years) with LPFB and aborted cardiac arrest/sudden cardiac death found left ventricular fibrosis (particularly along the inferolateral wall) in all patients undergoing cardiac magnetic resonance imaging (n = 6) or histopathological analysis/autopsy (n = 4).[8] Further investigation is required into this small but worrisome group of young patients.

In the preface to his book, Dr Rosenbaum wrote "Like good wines, some research improves after resting for a while." By allowing many years for their registry to mature, Nyholm et al have produced an excellent bottle of wine for a slowly aging cellar.

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but not by others.[5–7] Curiously, isolated LPFB was associated with the youngest age group (median age 35 years) and the highest risk of death (HR 2.09). A recent case-control study of 10 young patients (median age 27.5 years) with LPFB and aborted cardiac arrest/sudden cardiac death found left ventricular fibrosis (particularly along the inferolateral wall) in all patients undergoing cardiac magnetic resonance imaging (n = 6) or histopathological analysis/autopsy (n = 4).[8] Further investigation is required into this small but worrisome group of young patients.

Left-Dominant Arrhythmogenic Cardiomyopathy With Heterozygous Mutations in *DSP* and *MYBPC3*

Sakamoto N. et al. Circ Cardiovasc Imaging. 2019;12:e008913

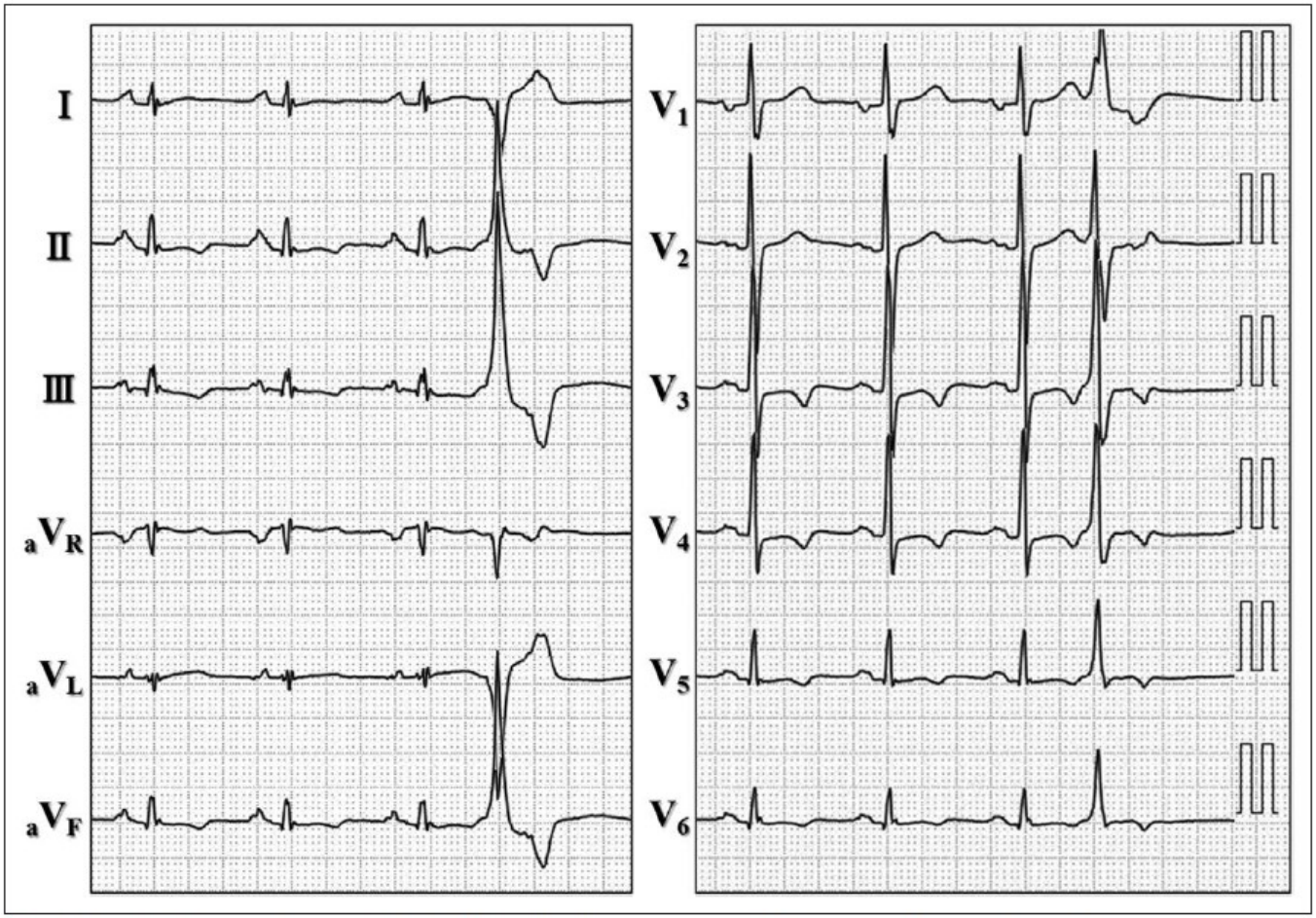


Figure 1. ECG showing T-wave inversion in the left-sided leads and a premature ventricular complex of left ventricular origin.

Pathogenic mutations in desmoplakin (c.4650delTG, p.V1551E fs74X) and myosin-binding protein C gene (c.2459G>A, p.R820Q)

Circulation: Cardiovascular Imaging

LETTER TO THE EDITOR

Letter by Pérez-Riera et al Regarding Article, "Left-Dominant Arrhythmogenic Cardiomyopathy With Heterozygous Mutations in *DSP* and *MYBPC3*"

Andrés Ricardo Pérez-Riera, MD, PhD
Raimundo Barbosa-Barros, MD
Bernard Belhassen, MD

To the Editor:

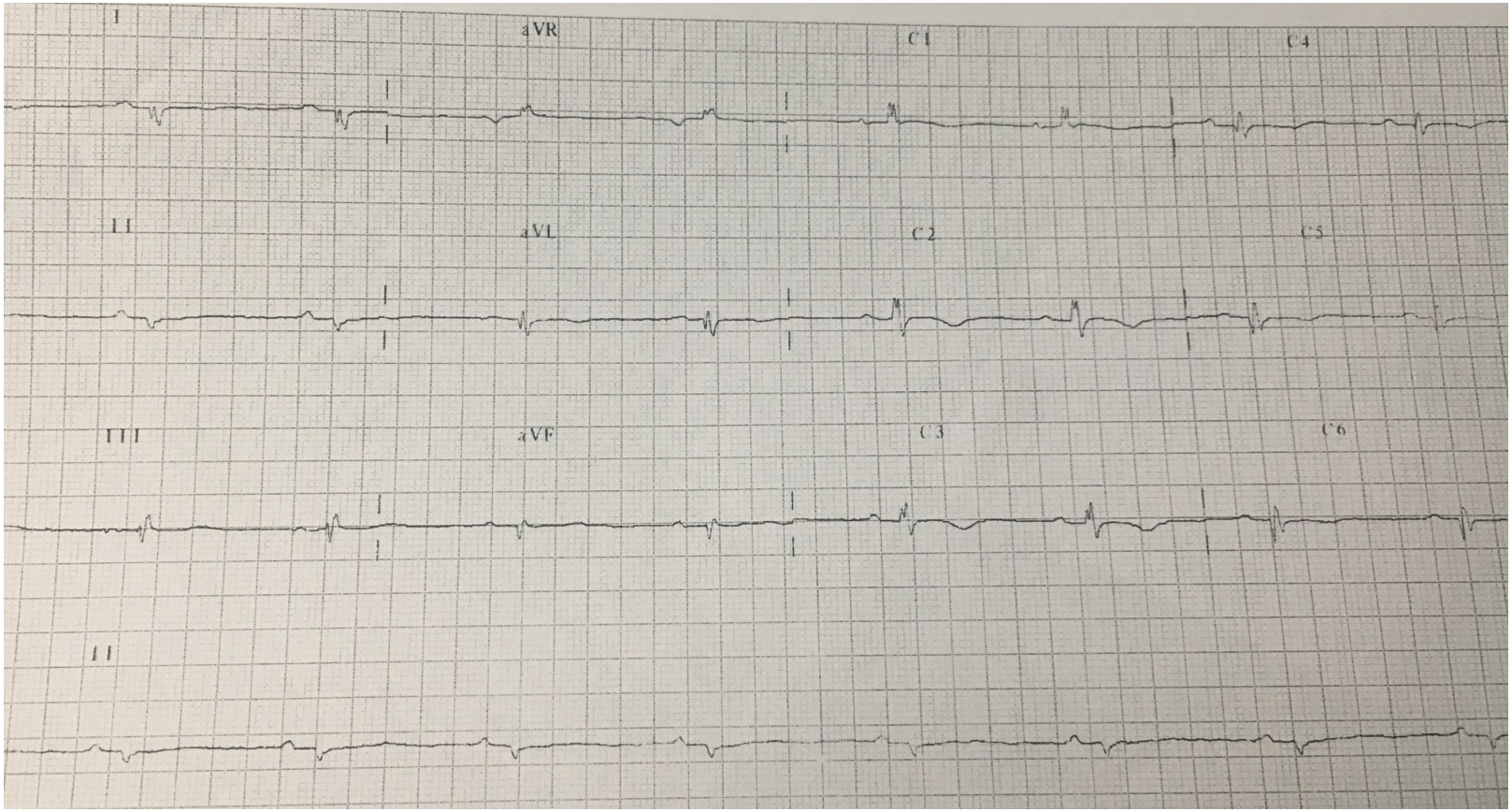
We have read with interest the recent exceptional case report from Dr Sakamoto et al[1] who presented a 46-year-old woman whose main complaint was dyspnea on exertion and in whom the final diagnosis was left-dominant arrhythmogenic cardiomyopathy (ALVC). Genetic screening showed a mutation not reported previously consisting of heterozygous pathogenic mutation in the desmoplakin and myosin-binding protein C.

In their description of the 12-lead ECG, the authors wrote literally: "T-wave inversion in the left-sided leads and a premature ventricular complex of left ventricular origin." We would like to add some additional ECG features of Figure 1,

Finally, early precordial transition was observed in the precordial leads (R/S ratio >1 in V1-V2).

Such prominent anterior QRS forces can be observed in numerous scenarios: normal variant, athlete's heart, misplaced precordial leads, lateral myocardial infarction (previously named dorsal myocardial infarction), right ventricular hypertrophy, left ventricular hypertrophy, biventricular hypertrophy, right bundle branch block, **left septal fascicular block**, ventricular preexcitation with accessory pathway located in the posterior wall, hypertrophic cardiomyopathy, Duchenne's cardiomyopathy, endomyocardial fibrosis, dextroposition, and ALVC.

In the latter case, **early precordial transition indicates fibrosis in the basal-lateral wall of the LV.**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REVIEW

The tetrafascicular nature of the intraventricular conduction system

Andrés R. Pérez-Riera[1] | Raimundo Barbosa-Barros[2] | Rodrigo Daminello-Raimundo[1] | Luiz C. de Abreu[1] | Kjell Nikus[3]

[1]Design of Studies and Scientific Writing Laboratory, ABC Faculty of Medicine, São Paulo, Brazil

[2]Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza, Brazil

[3]Heart Center, Tampere University Hospital and Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

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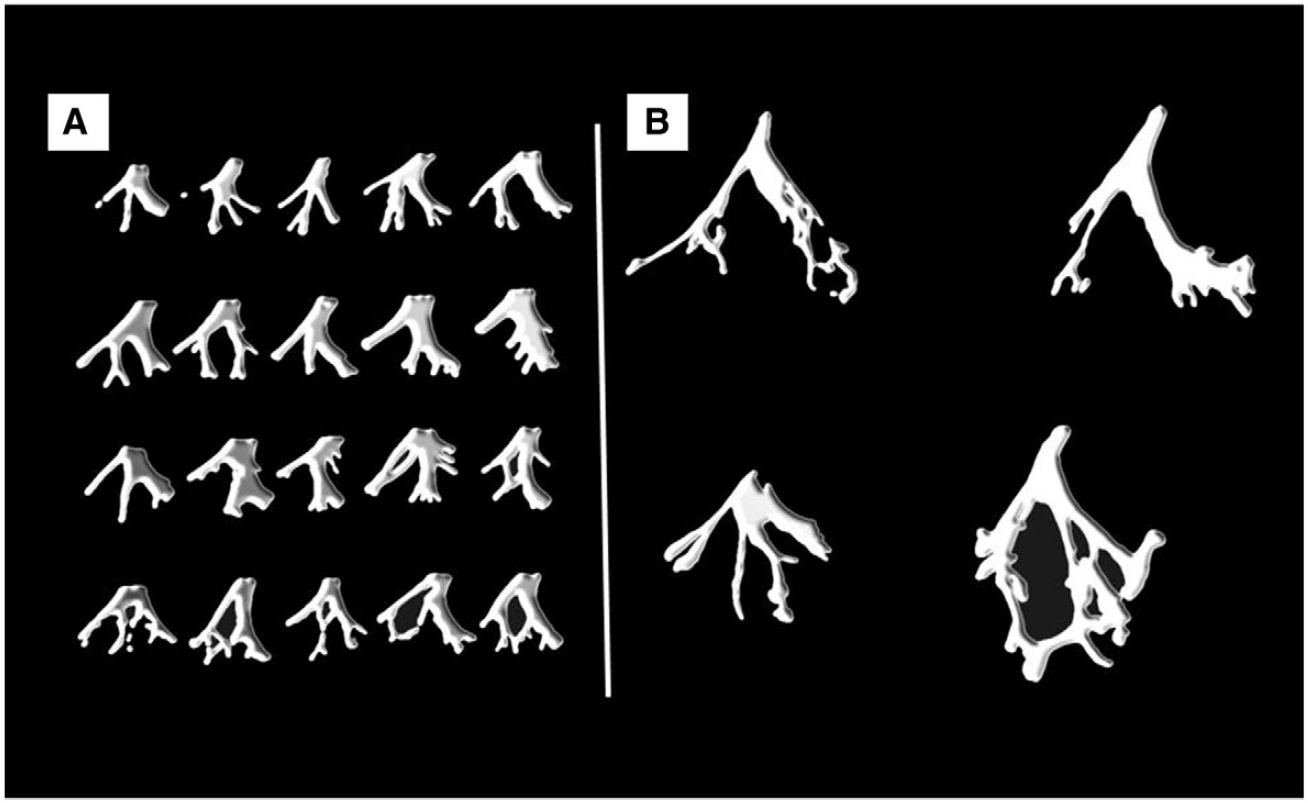
Email: riera@uol.com.br

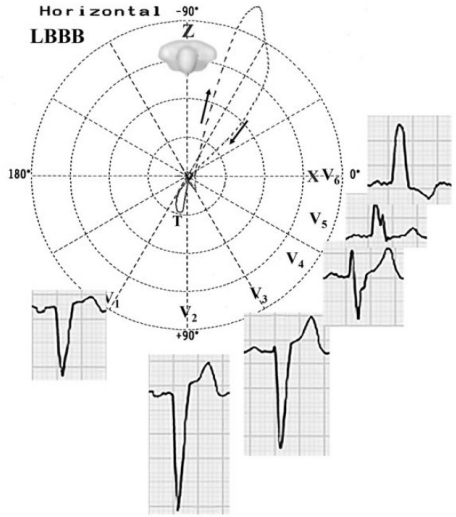
The existence of a tetrafascicular intraventricular conduction system remains debatable. A consensus statement ended up with some discrepancies and, despite agreeing on the possible existence of an anatomical left septal fascicle, the electrocardiographic and vectorcardiographic characteristics of left septal fascicular block (LSFB) were not universally accepted. The most important criteria requested to confirm the existence of LSFB is its intermittent nature. So far, our group has published cases of transient ischemia-induced LSFB and phase 4 or bradycardia-dependent LSFB. Finally, anatomical, anatomopathological, histological, histopathological, electrocardiographic, vectorcardiographic, body surface potential mapping, and electrophysiology studies support the fact that the left bundle branch divides into three fascicles or a "fan-like interconnected network."

KEYWORDS

intraventricular conduction system, left septal fascicle, left septal fascicular block



A. Fig. 2 from Demoulin JC, Kulbertus HE [24]. Diagrammatic sketches of the LBB conduction system in twenty human normal hearts. These sketches depict the anatomy from serial histologic sections of left septal myocardium. The LBB and its subdivisions were identified by their subendocardial location and histological features typical of the conducting fibers. B: Figure 28, Chapter 2 from RosenbaumMB et al. [13]. Four human LBB systems dissected and separated from the heart considered the main prototypes observed in our material. In every case, the main LBB is short and its divisions longer depicting a wider posterior division as compared with the anterior one. The bottom left LBB shows what can be considered a medial left septal fascicle arising at the bifurcation of the LBB, although it actually emerges from a wide posterior division, a pattern that can also be observed in the examples of Fig. 14 A in most cases.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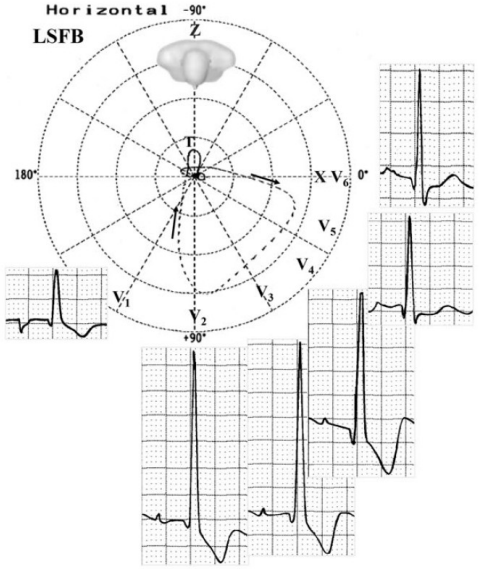
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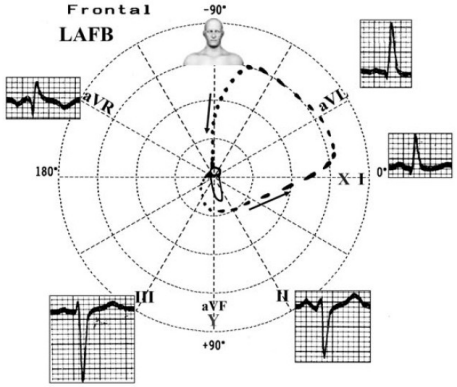
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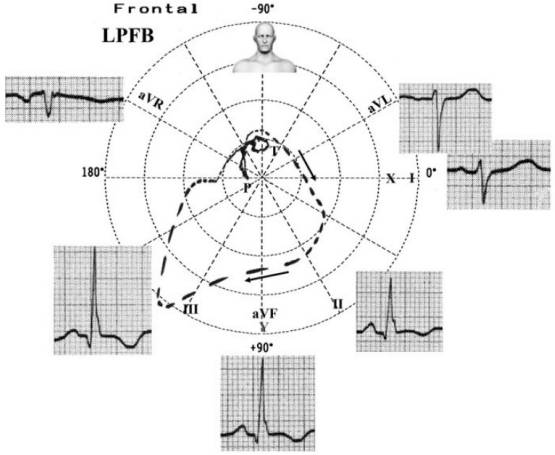
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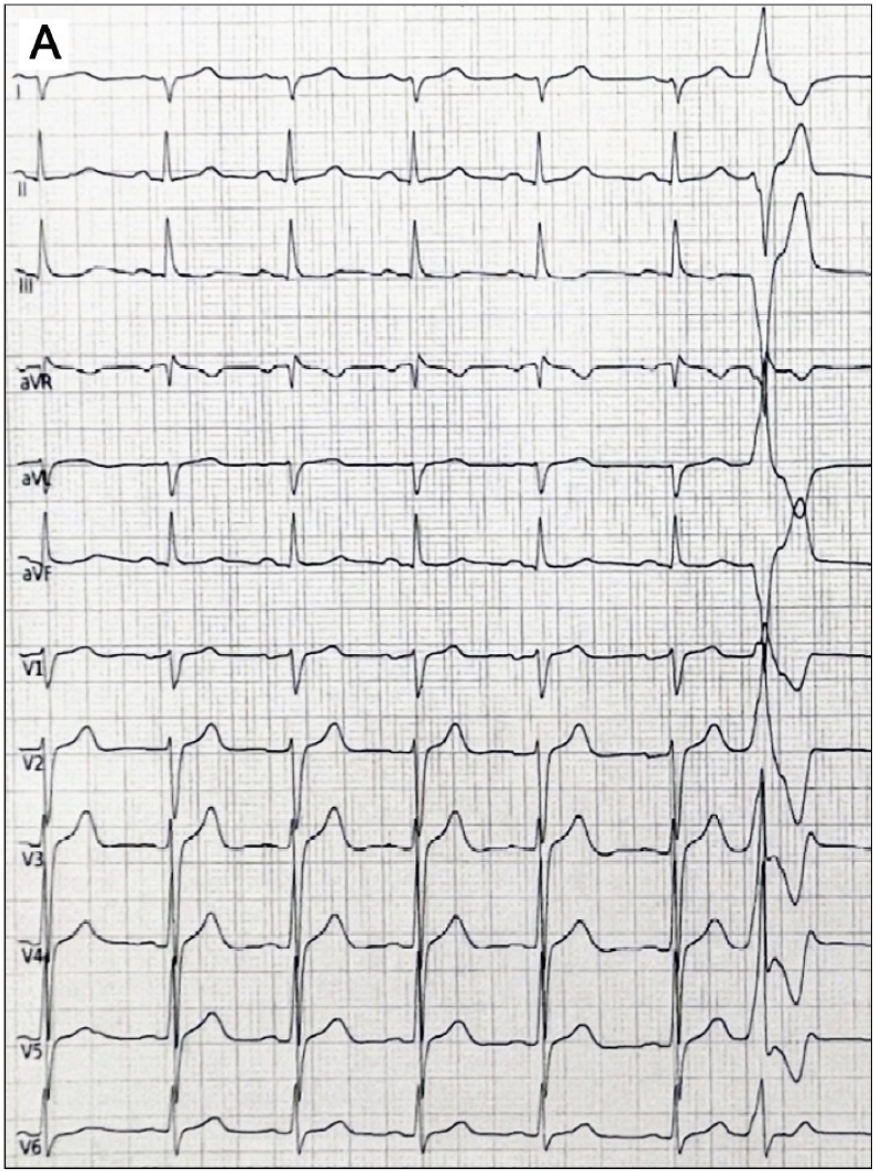

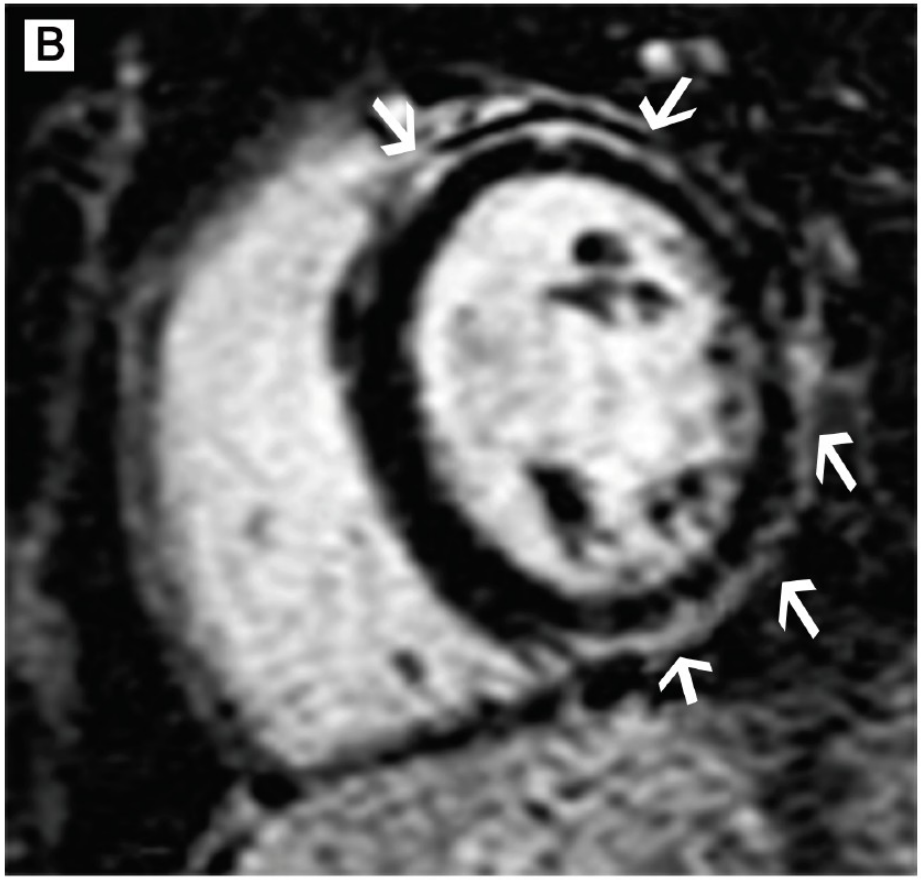

Patient #2, 19-year-old man, pathogenic variant in desmoplakin (c.1707-1708insAC,p.Met571Glnfs*8)