When the phenotype and the genotype do not match

Dr. Asaf Danon,

Director, Electrophysiology lab,

Inherited arrhythmia clinic,

Cardiology department,

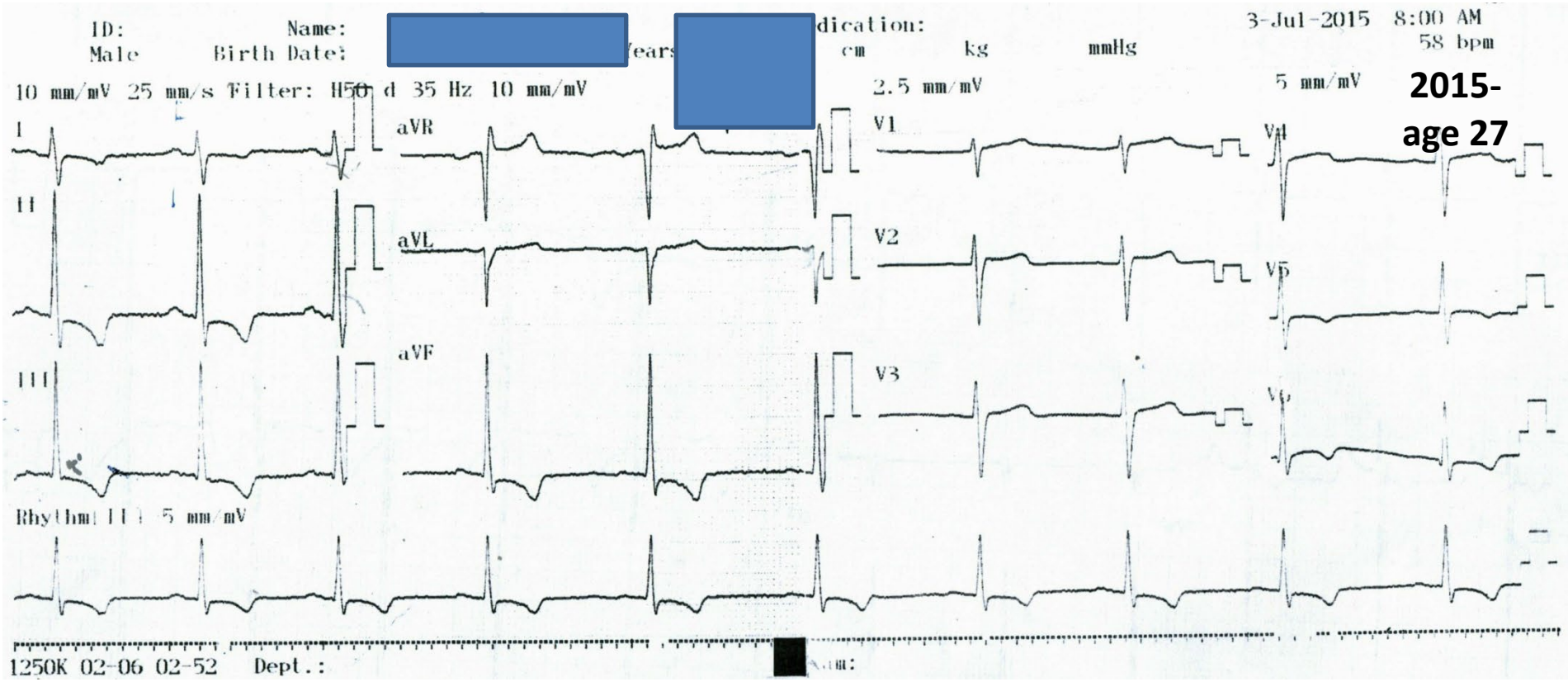
Carmel Medical Center, Haifa, Israel.

Ruth and Bruce Rappaport Faculty of Medicine,

Technion- Israeli Institute of Technology, Haifa, Israel.

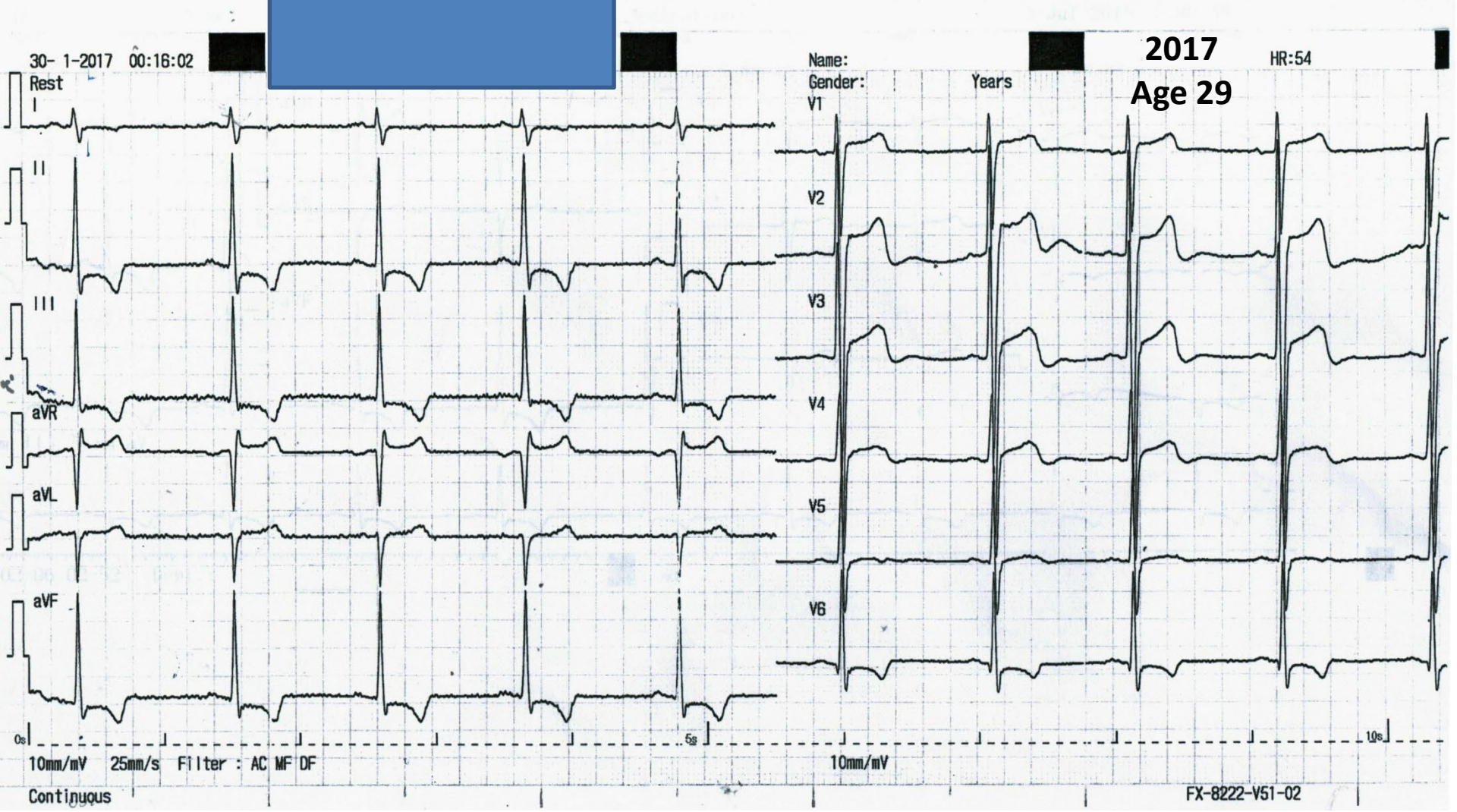
Tel: +972-55-8867102

Department: +972-4-8250801



2015- age 27

- Atypical chest pain (possible mild pericarditis) at the age of 13
- Remain in follow up due to abnormal ECG
- Normal Echo
- Asymptomatic



29M, recreational athlete

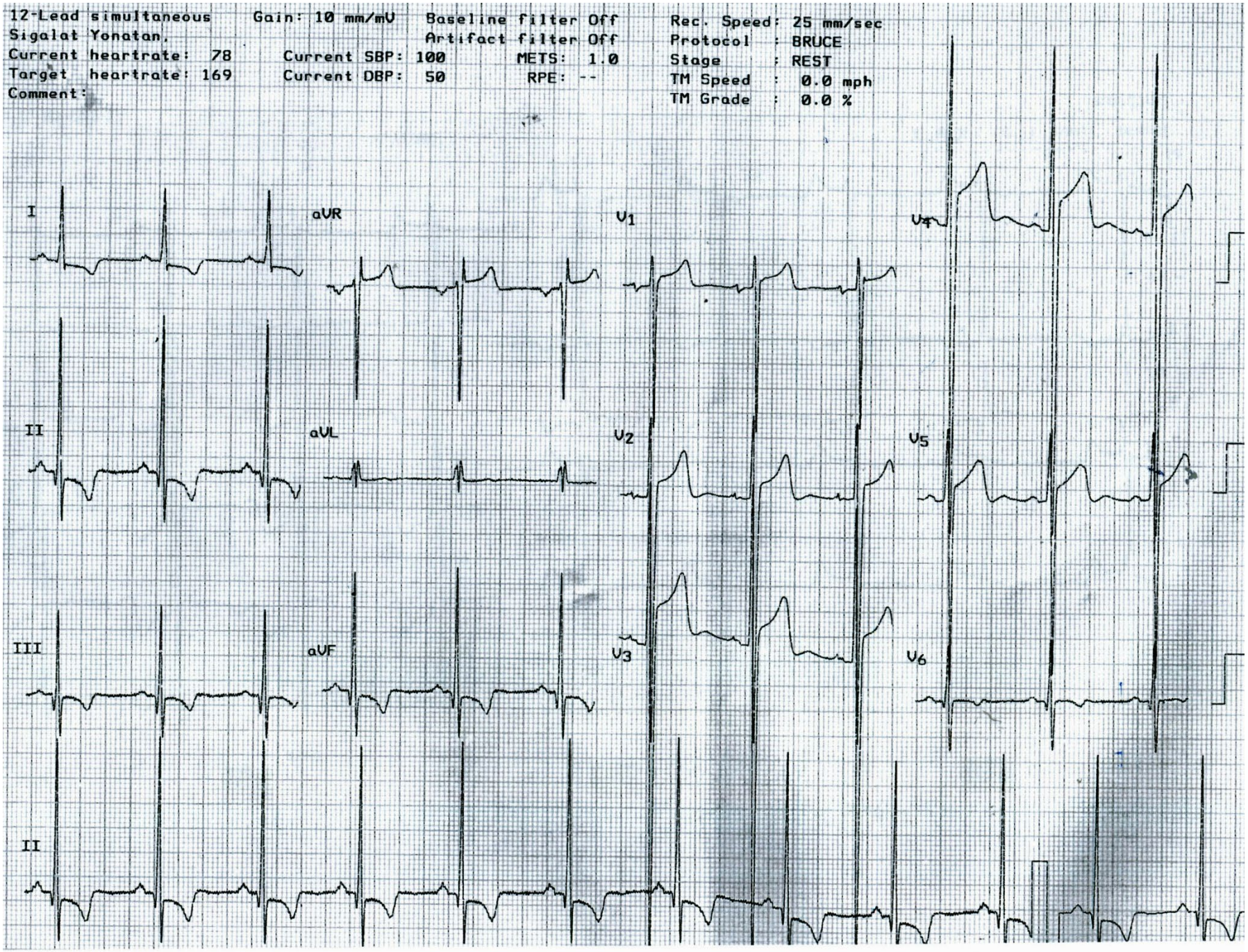
Paternal Uncle died at the age of 36 after/during? sport activity in the beach

Paternal grandfather died at the age of 60 during sleep

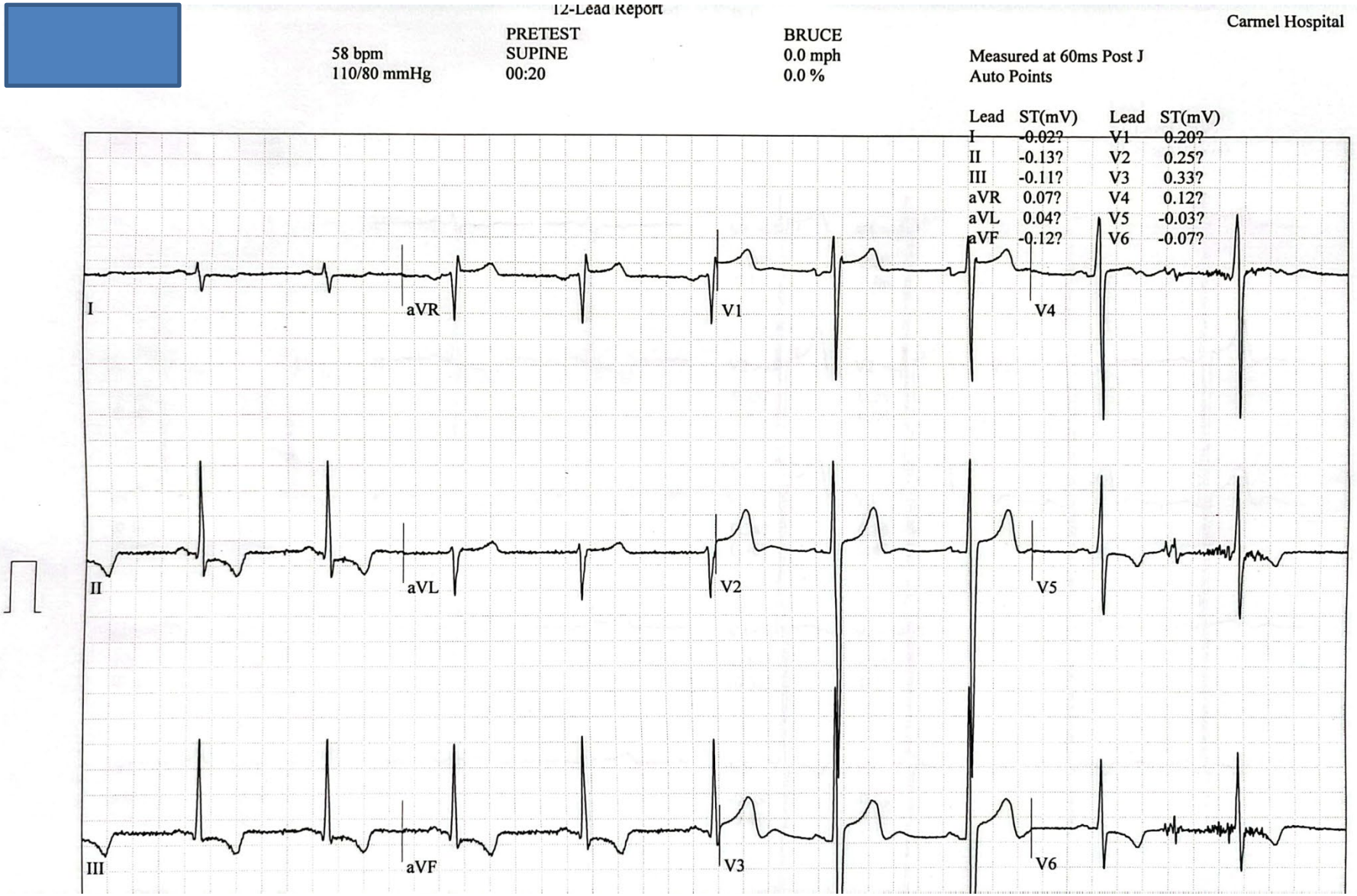
Asymptomatic

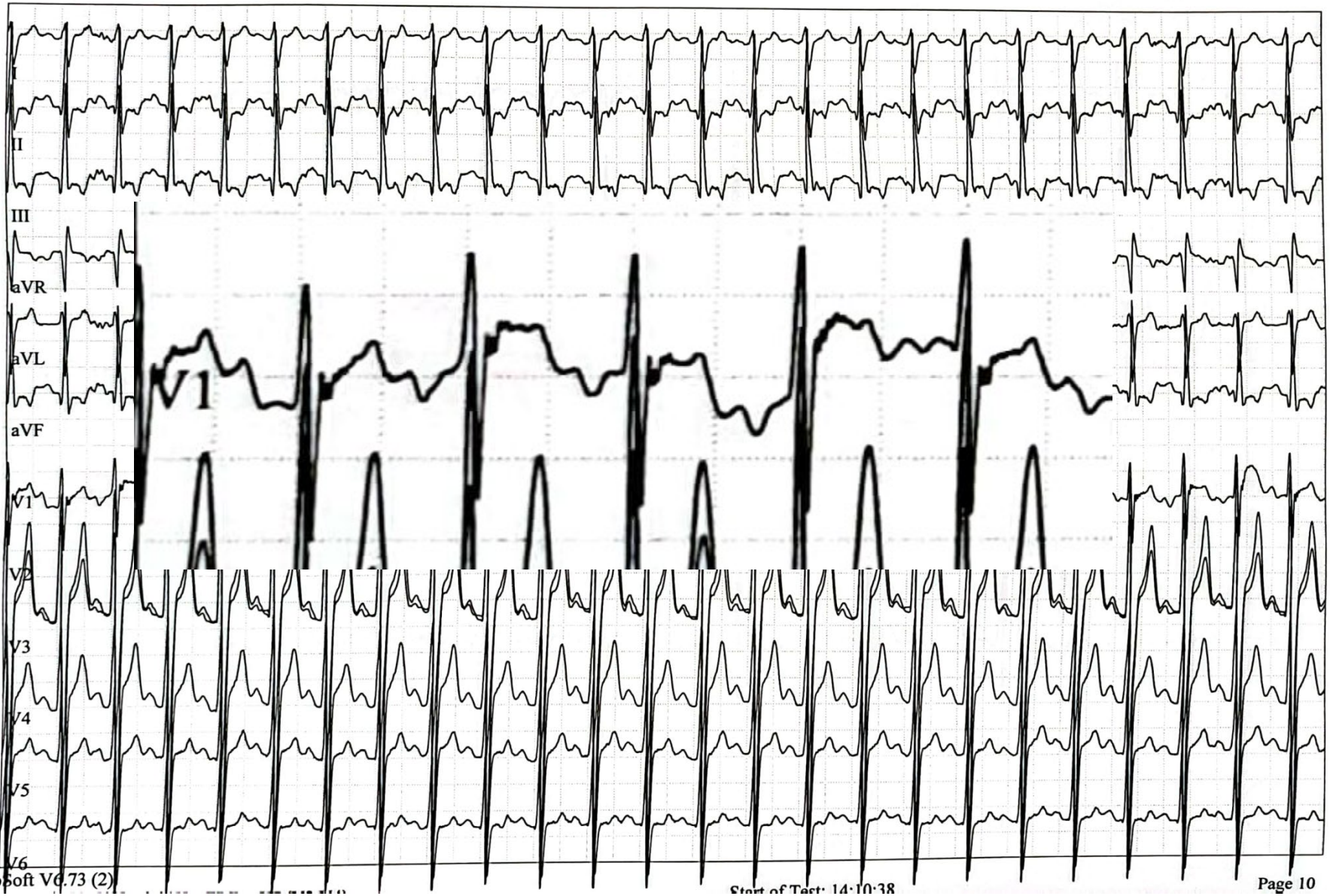
Normal echo and stress test

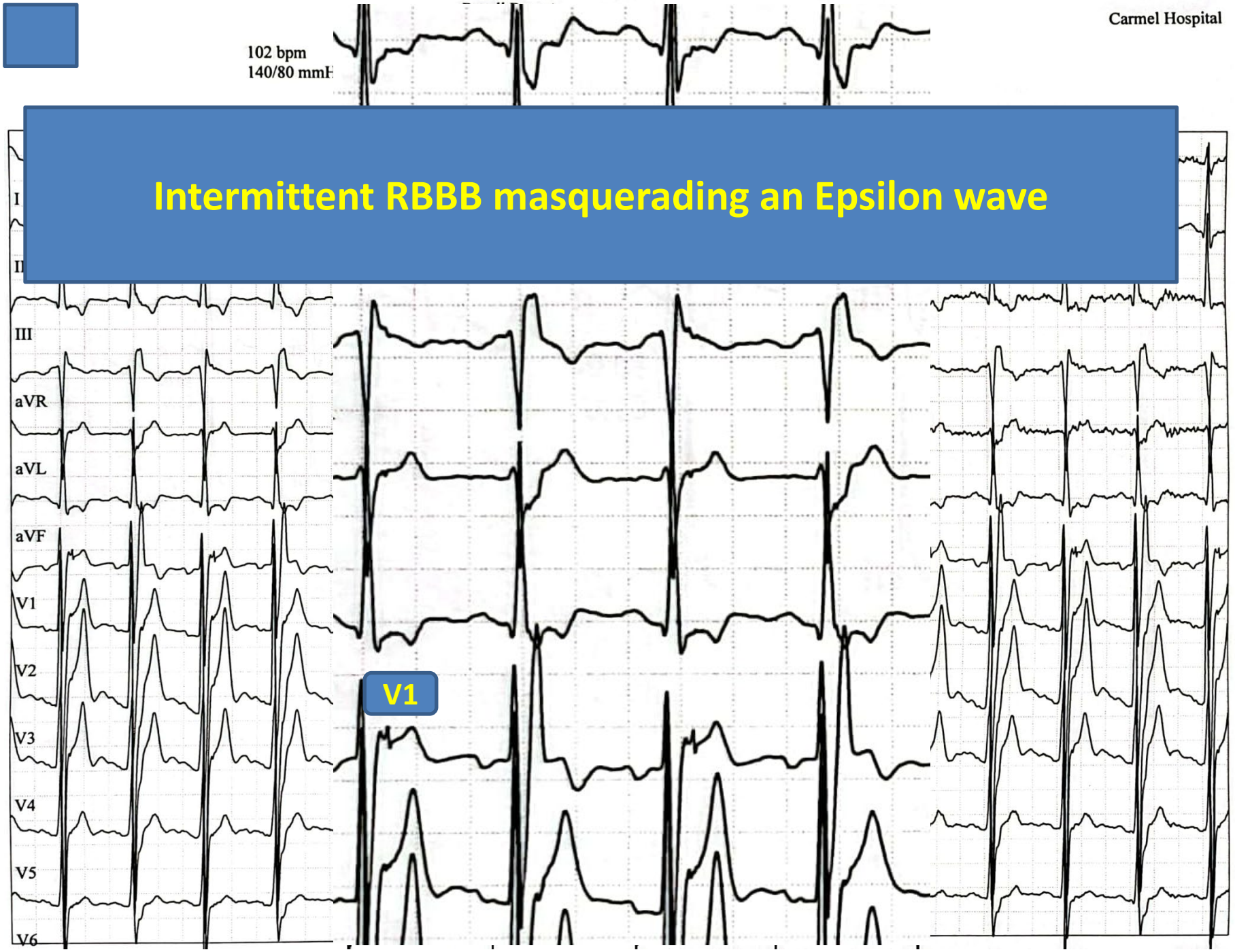
Cardiac MRI- 2017- hypertrabeculation not meeting LVNC criteria


12-Lead simultaneous
Gain: 10 mm/mV
Baseline filter Off
Artifact filter Off
Rec. Speed: 25 mm/sec
Sigalat Yonatan,
Protocol : BRUCE
Current heartrate: 78
Current SBP: 100
METS: 1.0
Stage : REST
Target heartrate: 169
Current DBP: 50
RPE: --
TM Speed : 0.0 mph
Comment:
TM Grade : 0.0 %
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Follow up – 2023: Asymptomatic. Normal echo




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



Intermittent RBBB masquerading an Epsilon wave

Segalat, Yonatan
Patient ID 3702848
18.06.2023
14:30:57

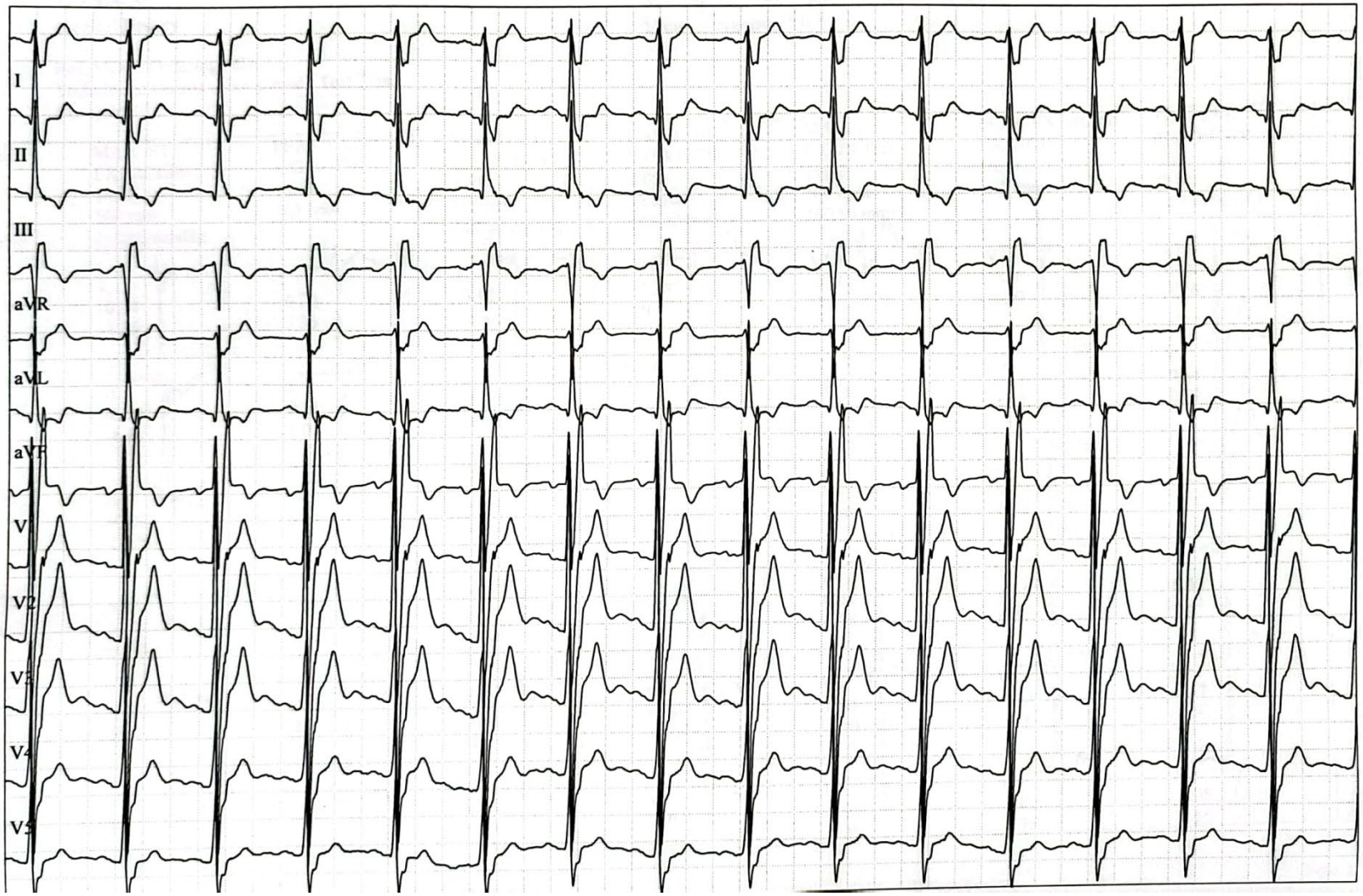
Recall Report

91 bpm
140/80 mmHg

RECOVERY
#3
03:03

BRUCE
0.0 mph
0.0 %

Carmel Hospital



Cardiac MRI 12.2023

Left Ventricle:

Size:	Normal
Wall thickness:	Normal
Global Function:	Normal
Regional Function:	
	hypokinesis of basal anterior segment
LV thrombus:	Absent
Trabeculation pattern:	Normal

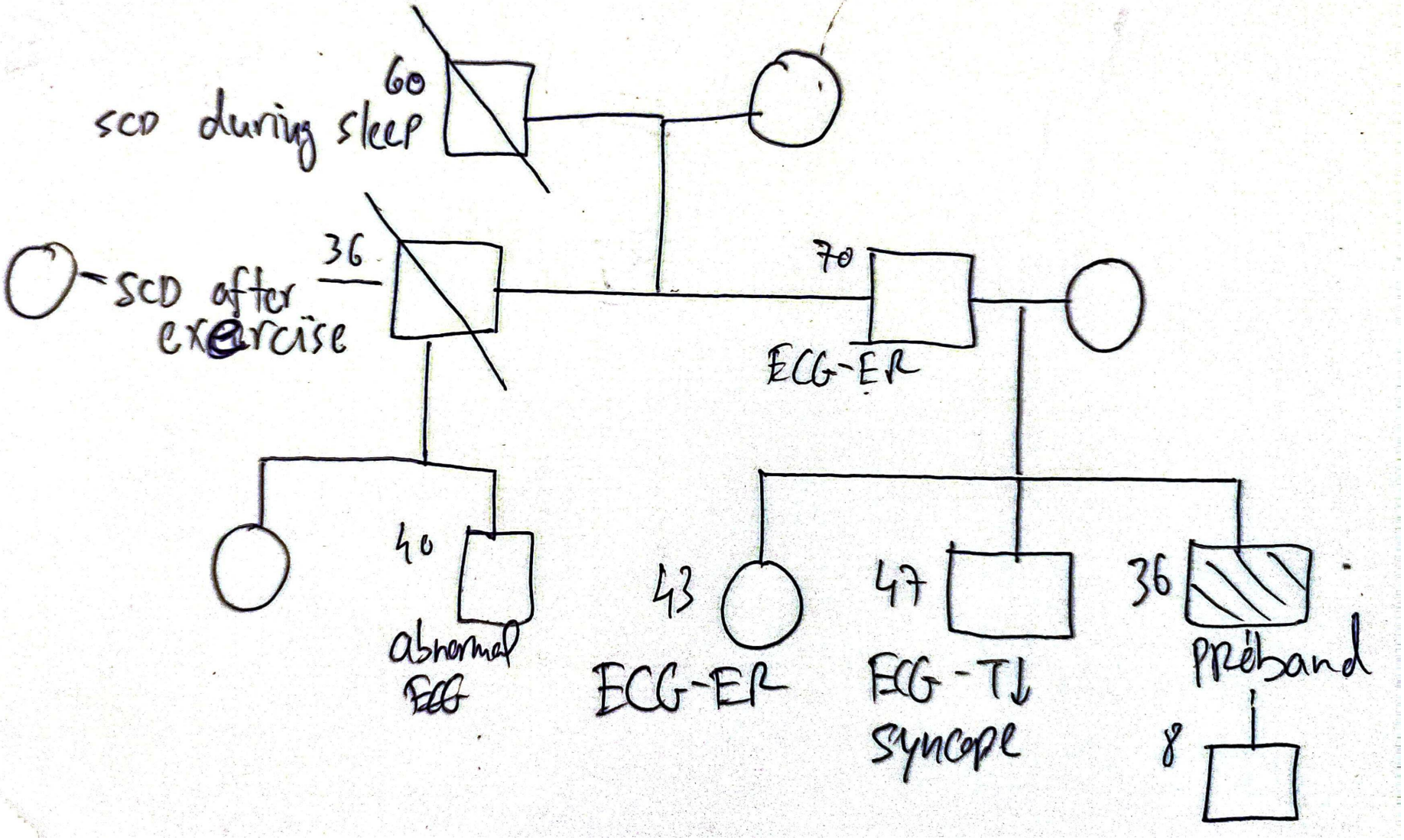
Global 2D Measurements:

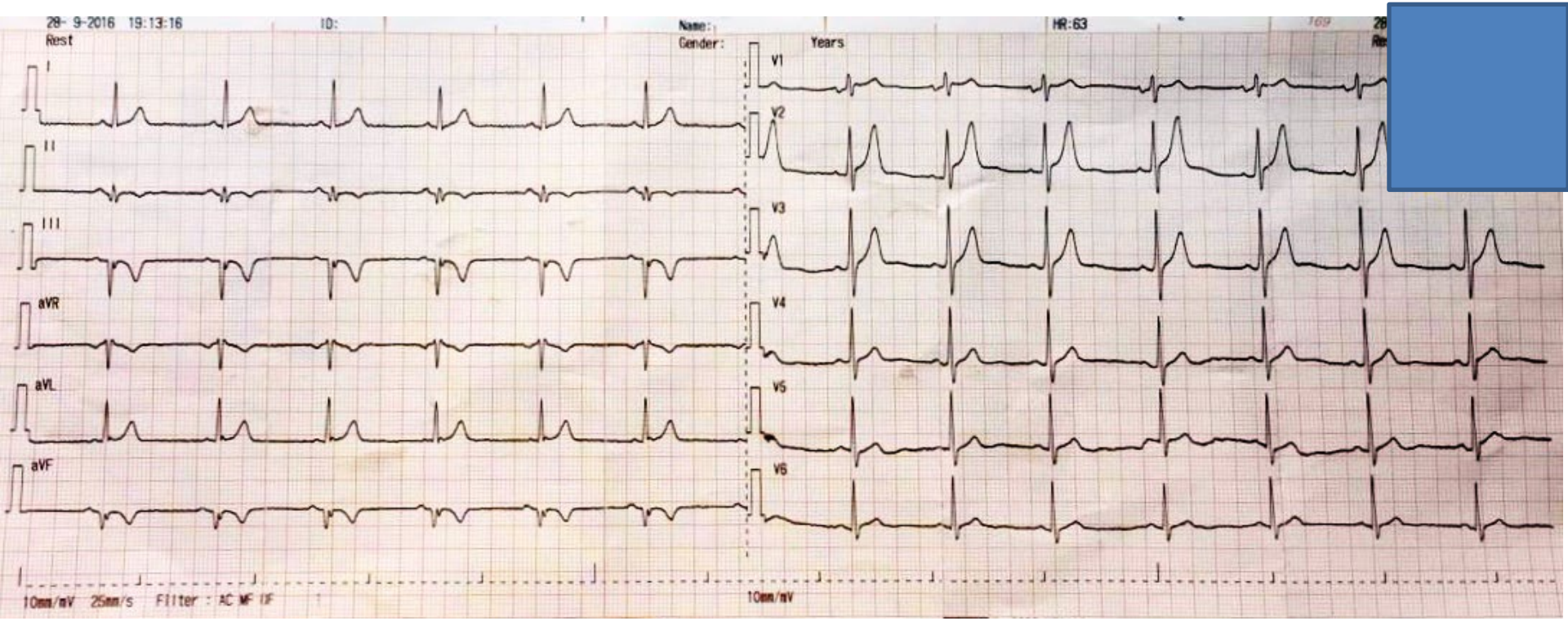
End-diastolic diameter (cm)	5.2
End-systolic diameter (cm)	3.9
Anteroseptal wall thickness (cm)	0.8
Inferolateral wall thickness (cm)	0.8

Right Ventricle:

Size:	Normal
Global Function:	Normal
Wall thickness:	Normal
Segmental function:	Normal
Delayed enhancement:	Absent

1. Normal LV size and global systolic function.
2. Regional WMA, hypokineisis of basal anterior wall
3. No abnormal LGE in LV wall
4. Normal RV size and systolic function. No abnormal LGE
5. Trivial TR


60
SCD during sleep
36
SCD after exercise
70
ECG-ER
40
abnormal ECG
43
ECG-ER
47
ECG-TI
syncope
36
proband
8



IIIA atypical chest pain

Cousin, son of the uncle that died suddenly

דו"ח תוצאה אנליזה גנטית לפאנל
Comprehensive Cardiomyopathy

Cardiomyopathy	HPO

תוצאות הבדיקה – אותרו שינויים גנטיים לדיווח

Pathogenic	**SCN5A**	NM_000335.5 **c.3595dup, p.His1199ProfsTer41** Associated Condition: Long QT syndrome 3, Brugada syndrome 1	Gene Inheritance **AD | AR**	gnomAd **<0.001%**	Zygosity **Heterozygote**

פירוט תוצאות הבדיקה

SCN5A | c.3595dup (p.His1199ProfsTer41)

NM_000335.5 | Frameshift | chr3:38616855 T>TG (hg19)

Zygosity and Depth: Proband: Heterozygote – 61 (41%)

Gene Summary: The protein encoded by this gene is an integral membrane protein and tetrodotoxin-resistant voltage-gated sodium channel subunit. This protein is found primarily in cardiac muscle and is responsible for the initial upstroke of the action potential in an electrocardiogram. Defects in this gene have been associated with long QT syndrome type 3 (LQT3), atrial fibrillation, cardiomyopathy, and Brugada syndrome 1, all autosomal dominant cardiac diseases. Alternative splicing results in several transcript variants encoding different isoforms. [provided by RefSeq, May 2022]
Frequency: The variant is rare, observed in 1 alleles out of 246,108 (0%) in the gnomAD reference population dataset.
Variant type: Null variant in a gene where loss of function is a known mechanism of disease.
Clinical evidence: This variant has previously been described in ClinVar (VCV924057) with the following classifications: P (1).
Gene coverage: 100% of SCN5A is covered with at least 10x.
Summary: Taken together, we interpret this variant to be Pathogenic.

Summary

- Asymptomatic, but with significant family history of SCD
- ECG c/w hypertrophy
- MRI- ? (no hypertrophy, ARVC)
- Stress test revealed an Epsilon wave – sign of advanced arrhythmogenic cardiomyopathy (ARVC)
- Genetic- SCN5A pathogenic mutation

SCN5A mutations

Table 8 Gene implicated in Brugada syndrome

Gene	Locus	Phenotype—syndrome	Protein (functional effect)	Frequency	ClinGen classification
SCN5A	3p22.2	BrS/AD	Loss of $I_{Na1.5}$ channel function	15–30%	Definite

EHRA/HRS consensus statement 2022

- SCN5A gain-of-function mutation in **LQTS type III-** not compatible with the phenotype
- **CPVT**- very rare, not compatible with the phenotype (no exercise induced arrhythmia)
- SCN5A associated phenotype **Multifocal Purkinje-related Premature Contractions** (MEPPC)- usually with high burden PVCs increasing in exercise and can mimic CPVT although
- **Dilated cardiomyopathy**

Case Reports > Herz. 2014 Mar;39(2):271-5. doi: 10.1007/s00059-013-3998-5. Epub 2013 Dec 8.

SCN5A mutation in Chinese patients with arrhythmogenic right ventricular dysplasia

J Yu [1], J Hu, X Dai, Q Cao, Q Xiong, X Liu, X Liu, Y Shen, Q Chen, W Hua, K Hong

Missense mutation; recurrent VT, negative family Hx

LETTERS TO THE EDITOR

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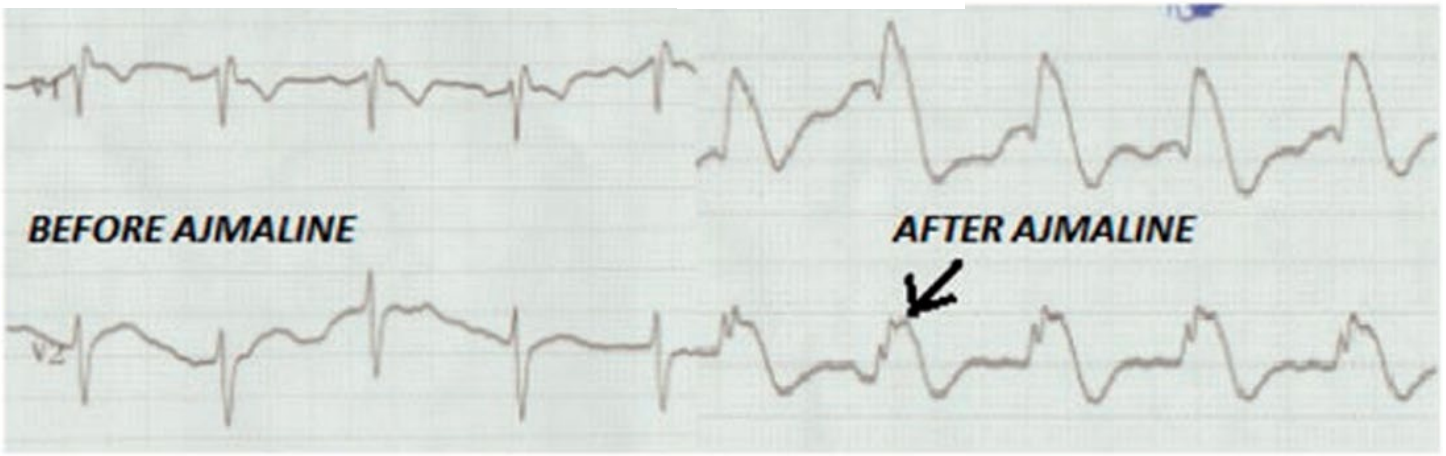
Ajmaline-induced epsilon wave: as a potential interim risk factor between the spontaneous- and drug-induced type 1 Brugada electrogram?



Europace 2018

Recommendation Table 43 — Recommendations for management of patients with Brugada syndrome

Recommendations	Class[a]	Level[b]
Diagnosis		
It is recommended that BrS is diagnosed in patients with no other heart disease and a spontaneous type 1 Brugada ECG pattern.[974–976]	I	C
It is recommended that BrS is diagnosed in patients with no other heart disease who have survived a CA due to VF or PVT and exhibit a type 1 Brugada ECG induced by sodium channel blocker challenge or during fever.[135,136,975,981,982]	I	C
Genetic testing for *SCN5A* gene is recommended for probands with BrS.[164,1016]	I	C
BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of: • Arrhythmic syncope or nocturnal agonal respiration • A family history of BrS • A family history of SD (<45 years old) with a negative autopsy and circumstance suspicious for BrS.	IIa	C
Risk stratification, prevention of SCD and treatment of VA		
ICD implantation is recommended in patients with BrS who: (a) Are survivors of an aborted CA and/or (b) Have documented spontaneous sustained VT.[980,990–992]	I	C
ICD implantation should be considered in patients with type 1 Brugada pattern and an arrhythmic syncope.[990,992,996]	IIa	C
Implantation of a loop recorder should be considered in BrS patients with an unexplained syncope.[997,999]	IIa	C
Quinidine should be considered in patients with BrS who qualify for an ICD but have a contraindication, decline, or have recurrent ICD shocks.[922,1006,1007]	IIa	C
Isoproterenol infusion should be considered in BrS patients suffering electrical storm.[1008]	IIa	C
Catheter ablation of triggering PVCs and/or RVOT epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy.[1010–1015]	IIa	C
PES may be considered in asymptomatic patients with a spontaneous type I BrS ECG.[155]	IIb	B
ICD implantation may be considered in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extra stimuli.[155]	IIb	C
Catheter ablation in asymptomatic BrS patients is not recommended.	III	C