RHYTHM 2017

Arrhythmias & Heart Failure

New Insights & Technological Advances

March 2-3

9th Congress Edition

Novotel PARIS Tour Eiffel

Genetic and PVCs

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CHU DIJON

www.rhythmcongress.com

Disclosure

Speaker name:

.Gabriel LAURENT

I do not have any potential conflict of interest regarding this presentation

Cardiac chanelopathies

- Long QTS
- Short QTS
- BRS
- CPVT
- ERS (Early repolarization Sd)
- MEPPC syndrome

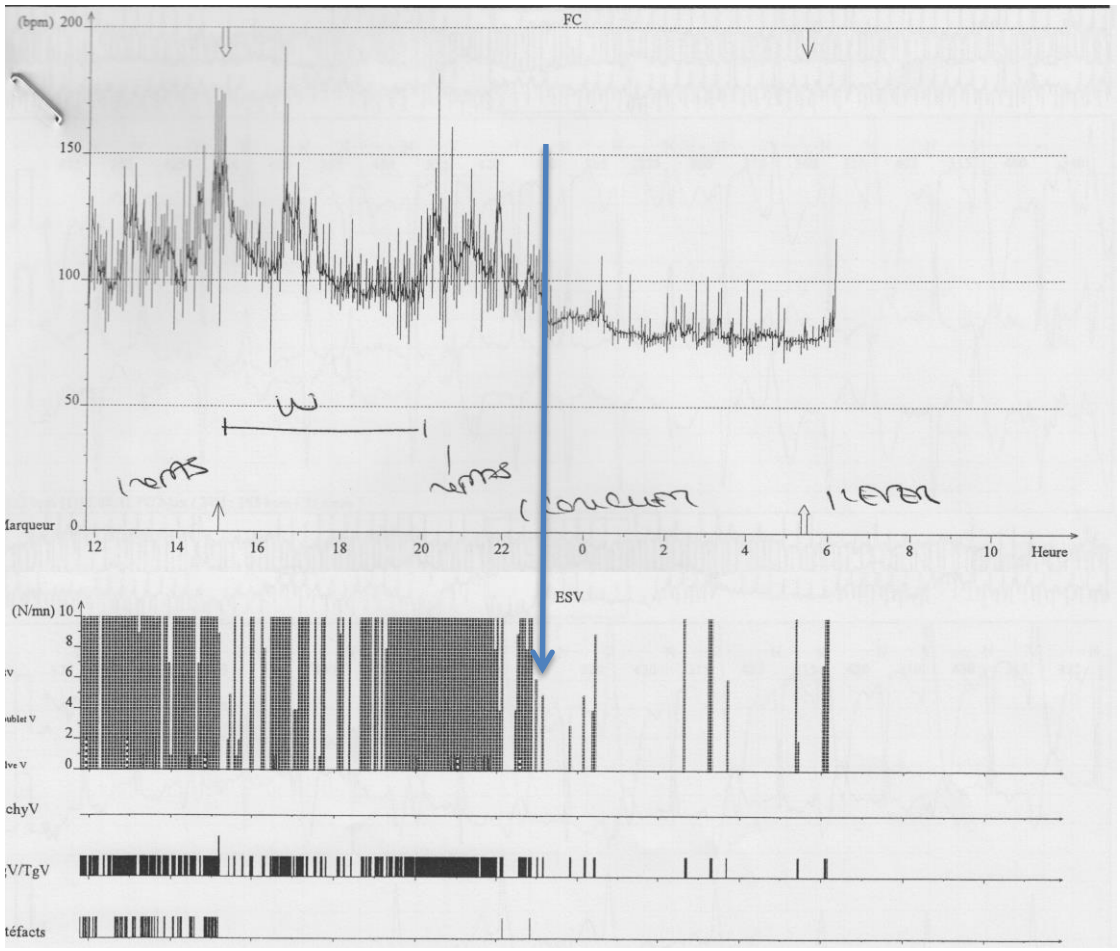
Cardiomyopathies

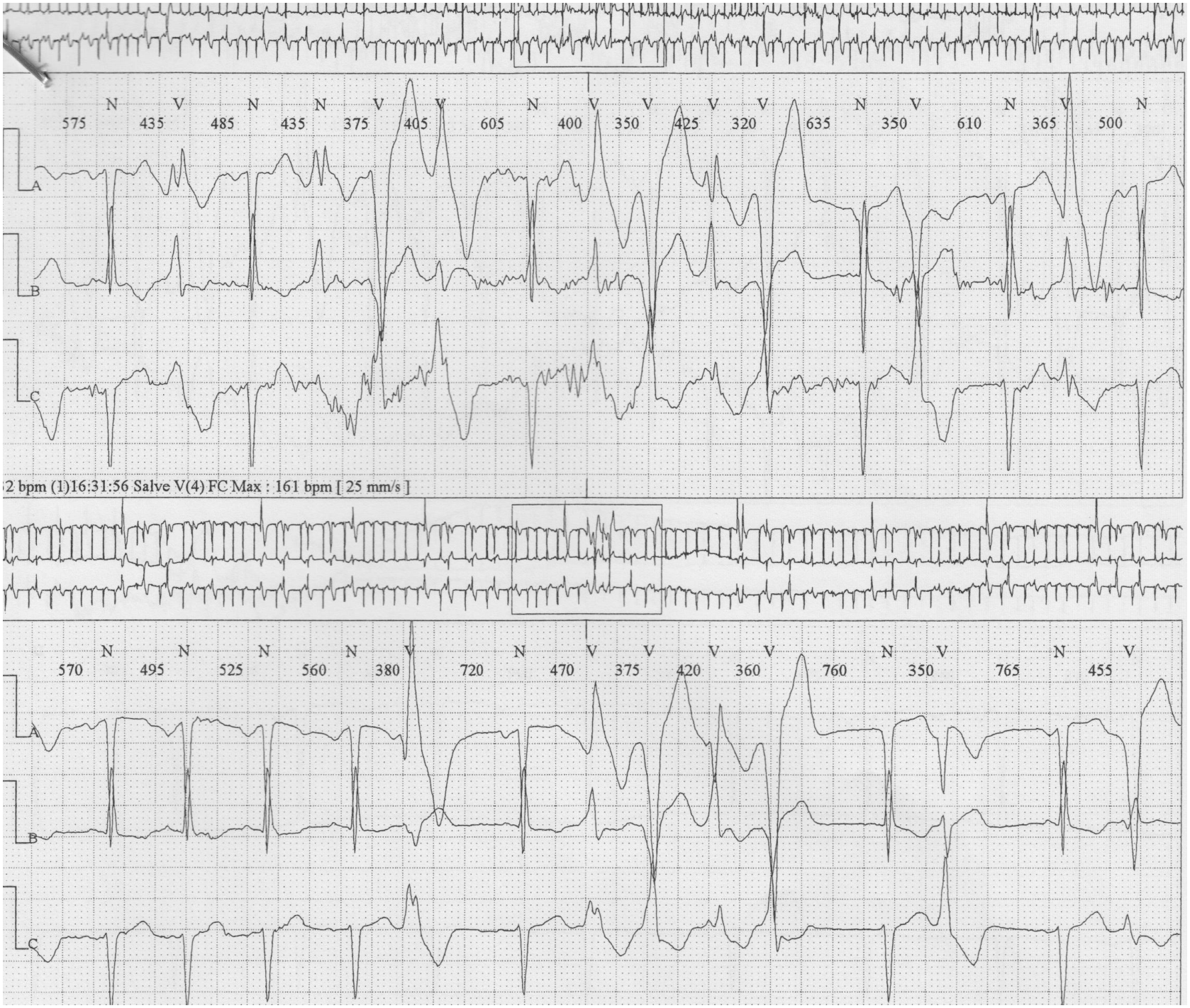
- ARVC
- HCM

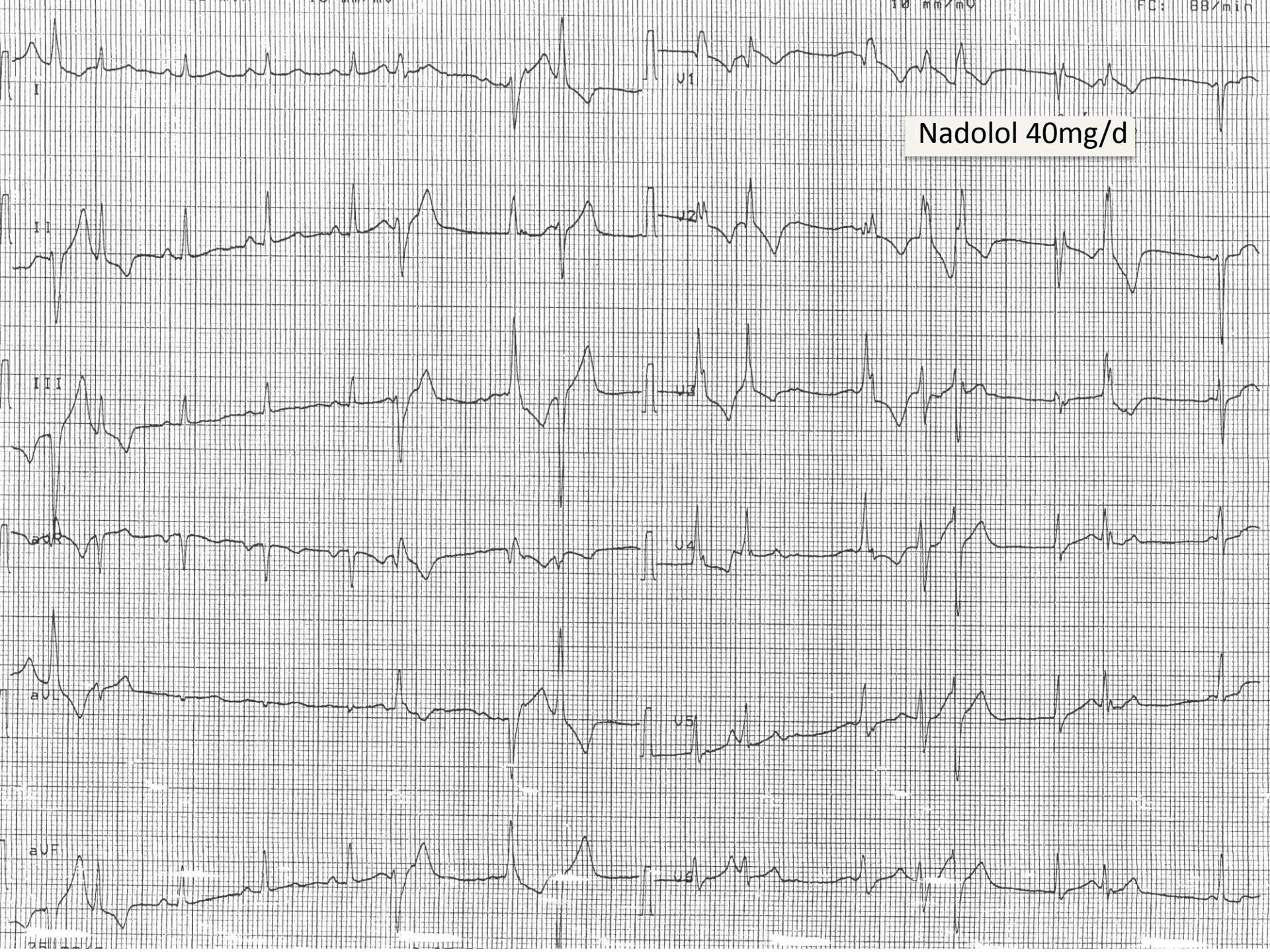
Mélanie 1984

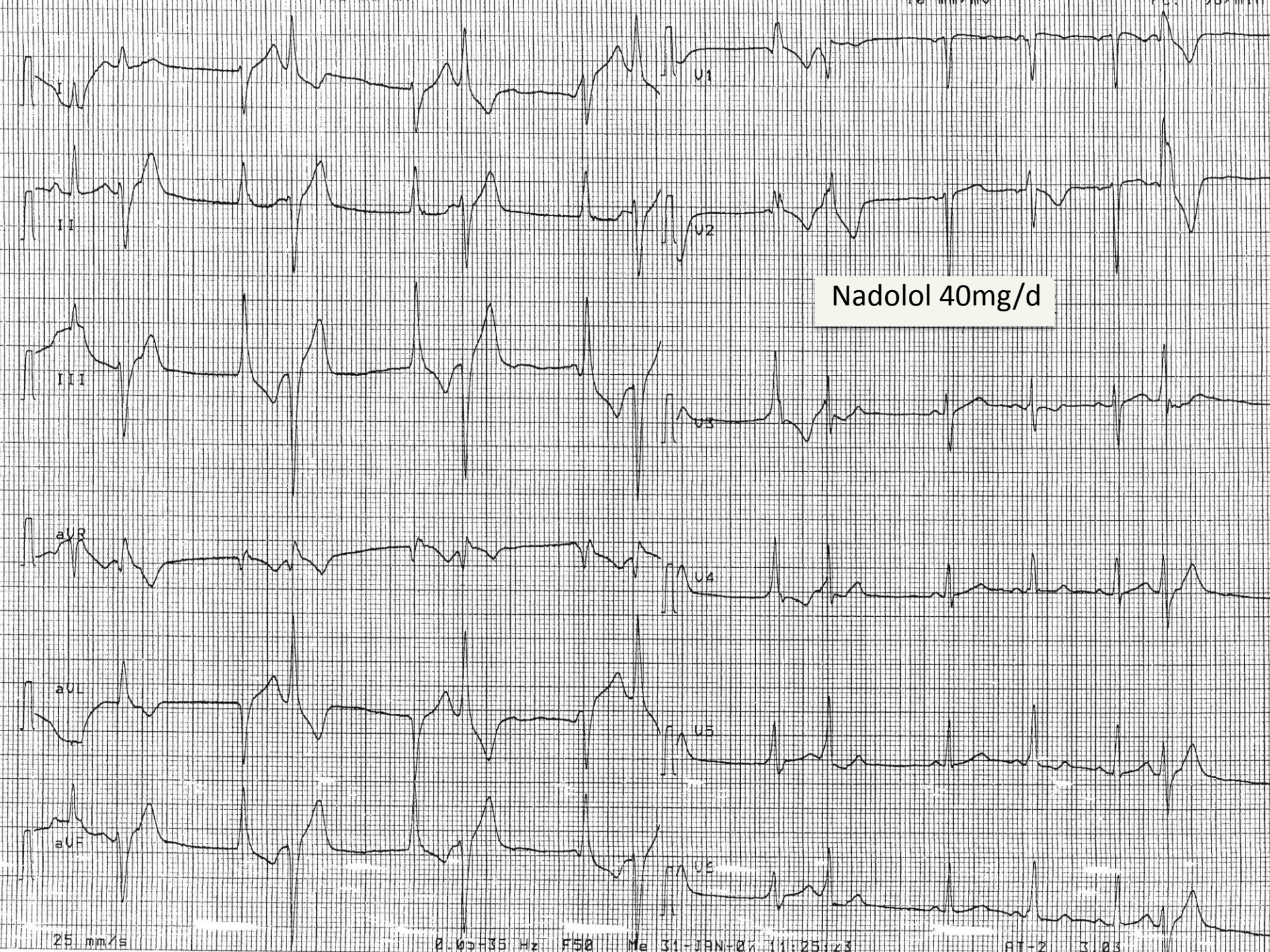
- PVCs since 2002 and syncopes:
  - No structural heart disease
  - Excercice test : « stopped prematurely because of numerous and polymorphic PVCs »
  - Coronaro-angiography: normal
  - Nadolol 40mg per day in 2010 (hypotension)
  - Genetic testing in 2011
- Cousin: SCD at 20 years of age

Holter monitoring on medication 2011




N V N N V V N V V V V N V N V N
575 435 485 435 375 405 605 400 350 425 320 635 350 610 365 500
A
B
C
2 bpm (1)16:31:56 Salve V(4) FC Max : 161 bpm [25 mm/s]
N N N N V N V V V V N V N V
570 495 525 560 380 720 470 375 420 360 760 350 765 455
A
B
C


Nadolol 40mg/d


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
Nadolol 40mg/d
25 mm/s

January 2012

- SCD while exercising (jogging)
- Cardioverted 20 times by paramedics
- Mutation: RyR2.

PVCs in CPVT

- The clinical manifestations of CPVT usually occur in the first decade of life and are prompted by physical activity or emotional stress.
- Diagnosis is challenging because patients have a normal ECG and echocardiogram, therefore an exercise stress test that elicits VA (bidirectional PVCs or polymorphic PVCs/VT) is recommended to establish the diagnosis.

Europace (2015) **17**, 1601–1687
doi:10.1093/europace/euv319

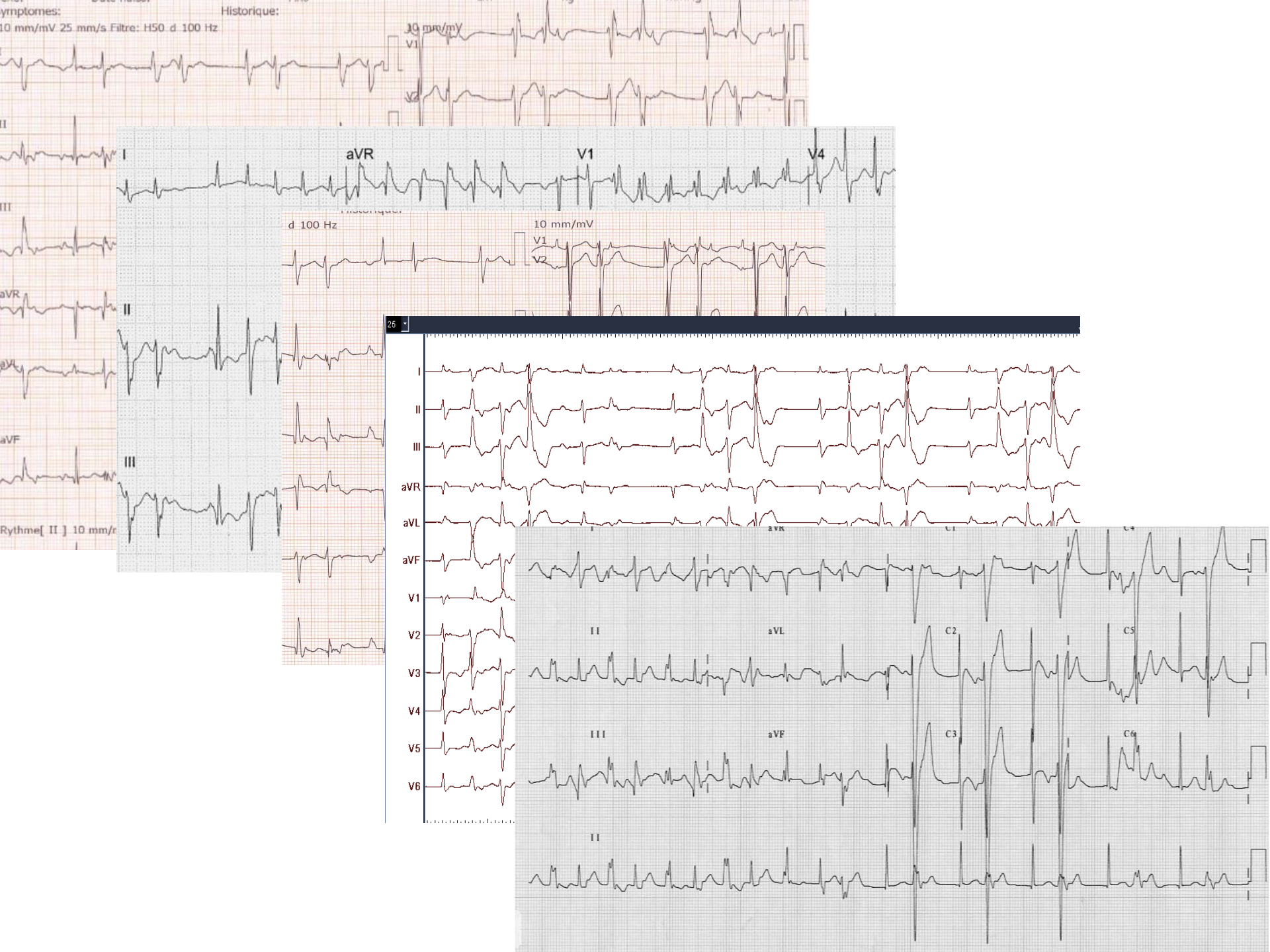
Recommendations	Class[a]	Level[b]
CPVT is diagnosed in the presence of a structurally normal heart, normal ECG and exercise- or emotion-induced bidirectional or polymorphic VT.	I	C
CPVT is diagnosed in patients who are carriers of a pathogenic mutation(s) in the genes *RyR2* or *CASQ2*.	I	C
The following lifestyle changes are recommended in all patients with a diagnosis of CPVT: avoidance of competitive sports, strenuous exercise and stressful environments.	I	C
Beta-blockers are recommended in all patients with a clinical diagnosis of CPVT, based on the presence of documented spontaneous or stress-induced VAs.	I	C
ICD implantation in addition to beta-blockers with or without flecainide is recommended in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal therapy.	I	C
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers, when there are risks/	IIa	C
Left cardiac sympathetic denervation may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT/several appropriate ICD shocks while on beta-blockers or beta-blockers plus flecainide and in patients who are intolerant or have contraindication to beta-blockers.	IIb	C

Multifocal Ectopic Purkinje-Related Premature Contractions

A New *SCN5A*-Related Cardiac Channelopathy

Gabriel Laurent, MD, PHD,* Samuel Saal, MD,† Mohamed Yassine Amarouch, PHD,‡§‖ Delphine M. Béziau, MSC,‡§‖ Roos F. J. Marsman, MSC,¶ Laurence Faivre, MD, PHD,† Julien Barc, PHD,‡‖ Christian Dina, PHD,‡‖ Geraldine Bertaux, MD,* Olivier Barthez, MD,* Christel Thauvin-Robinet, MD, PHD,† Philippe Charron, MD, PHD,# Véronique Fressart, MD, PHD,** Alice Maltret, MD,†† Elisabeth Villain, MD,†† Estelle Baron, BA,‡‖ Jean Mérot, PHD,‡§‖ Rodolphe Turpault, PHD,‡‡‖ Yves Coudière, PHD,‡‡‖ Flavien Charpentier, PHD,‡§‖§§ Jean-Jacques Schott, PHD,‡‖§§ Gildas Loussouarn, PHD,‡§‖ Arthur A. M. Wilde, MD, PHD,¶ Jean-Eric Wolf, MD, PHD,* Isabelle Baró, PHD,‡§‖ Florence Kyndt, PHARMD, PHD,‡‖‖‖ Vincent Probst, MD, PHD‡‖§§

Dijon, Nantes, and Paris, France; and Amsterdam, the Netherlands

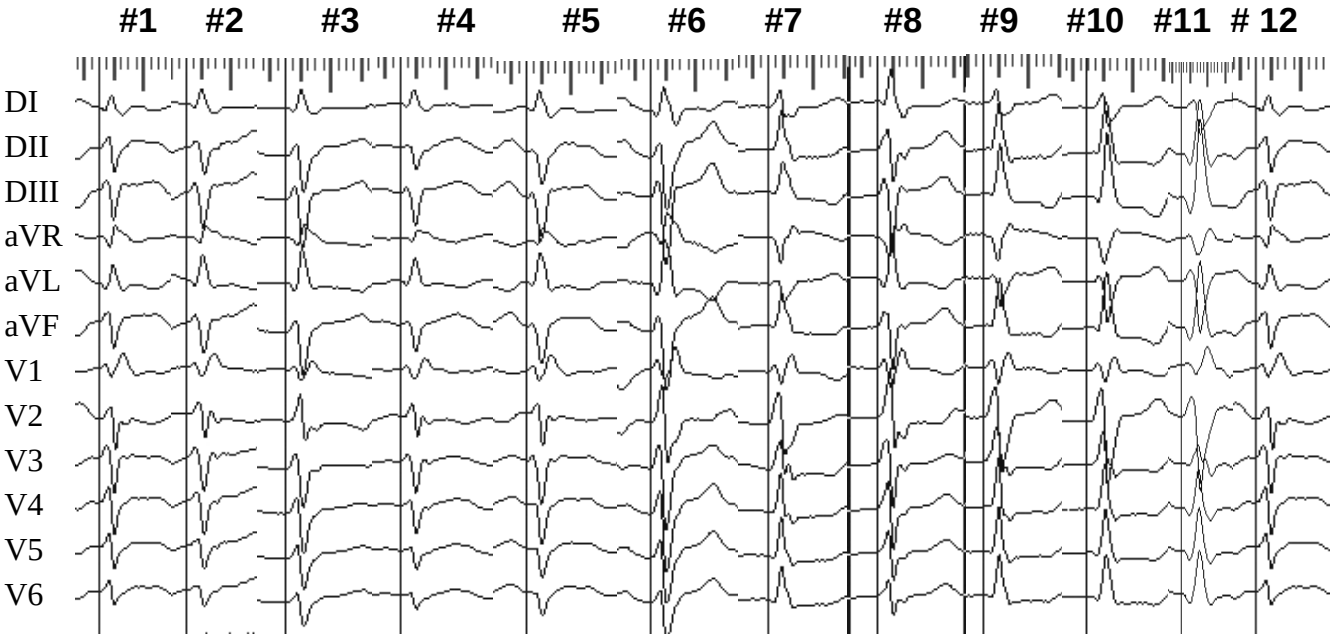

ymptomes:
Historique:
10 mm/mV 25 mm/s Filtre: H50 d 100 Hz
10 mm/mV
V1
V2
I
II
III
aVR
aVL
aVF
Rythme[II] 10 mm/
I
aVR
V1
V4
II
III
d 100 Hz
10 mm/mV
V1
V2
25
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
II
aVL
C2
C5
III
aVF
C3
C6
II

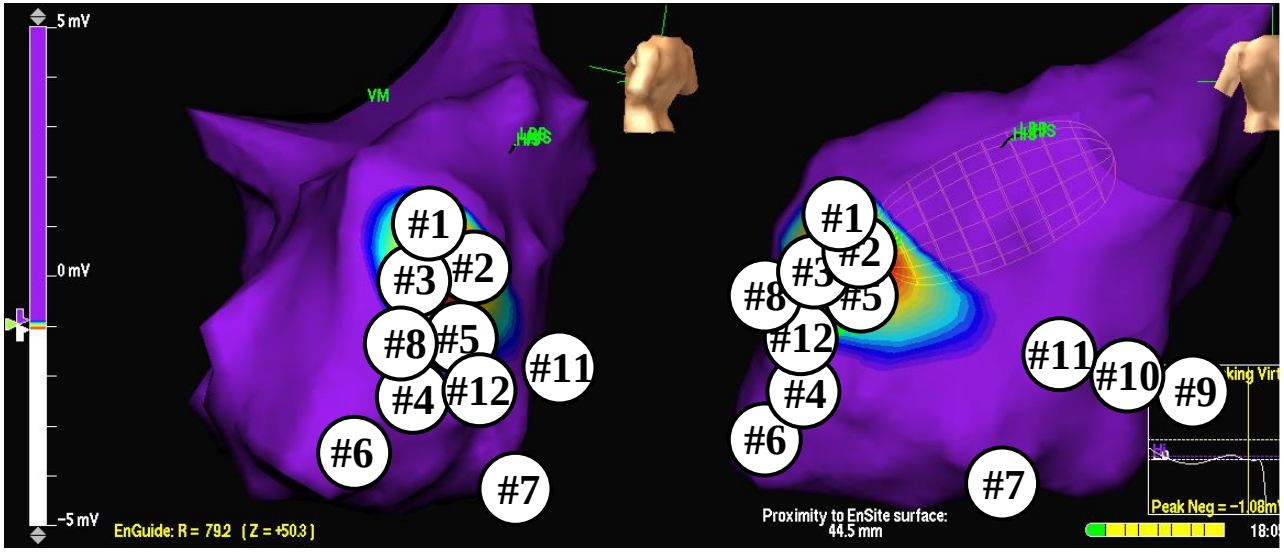
Remarkably constant phenotype

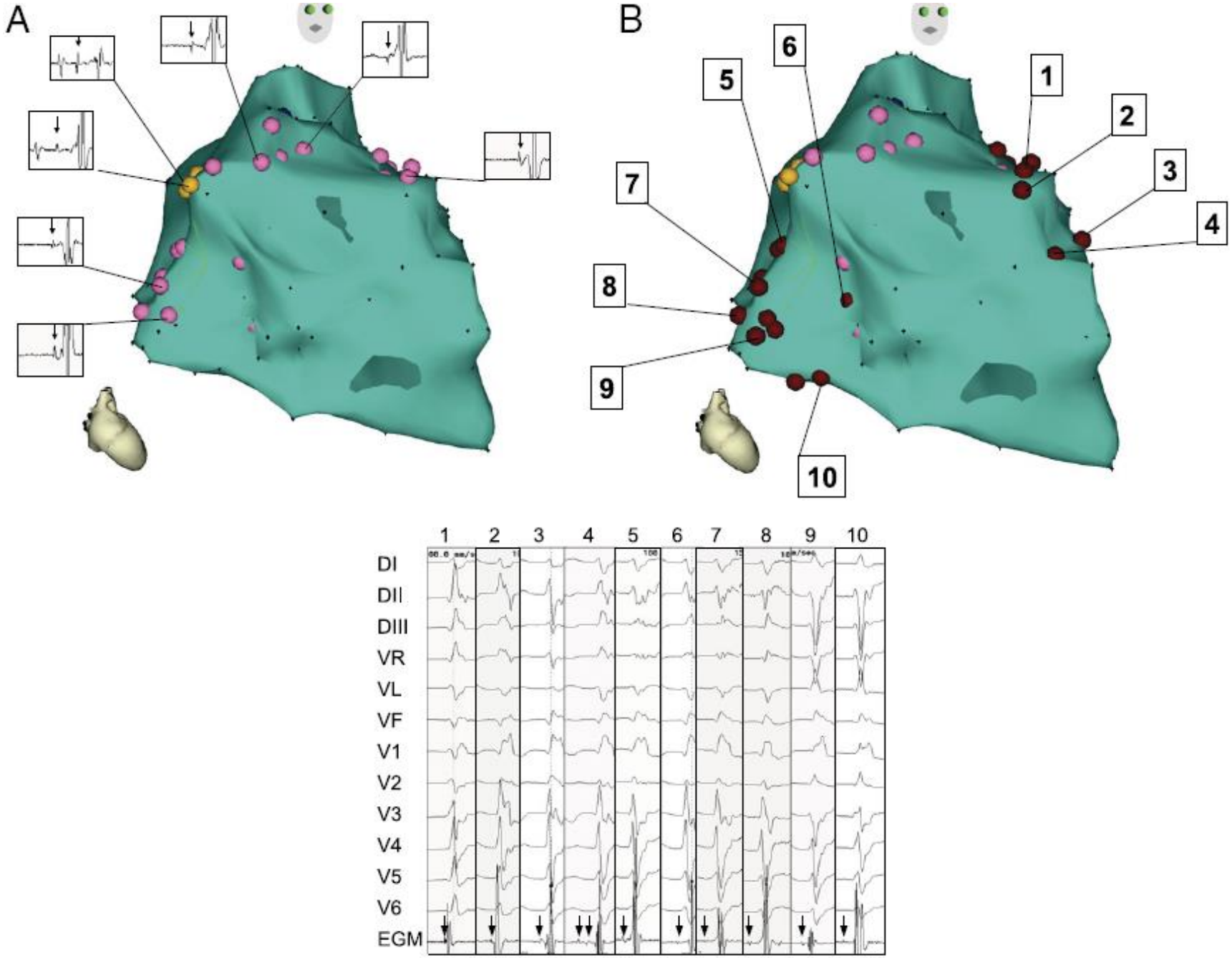
- “Chaotic" ECGs, rare narrow sinus or junctional beats competing with various complexes polymorphic PVCs/NSVT
- Numerous PVCs with various RBBB patterns (right to left axis variations), and /or LBBB patterns.
- **Overdrive suppression of the PVCs during exercise test**
- No QT prolongation or ST-segment elevation.
- Five patients affected by syncope or presyncope,
- SCD reported in 5 :4 month-, 11 year-old and 3 adults (29-71)

Clinical data of the affected family members

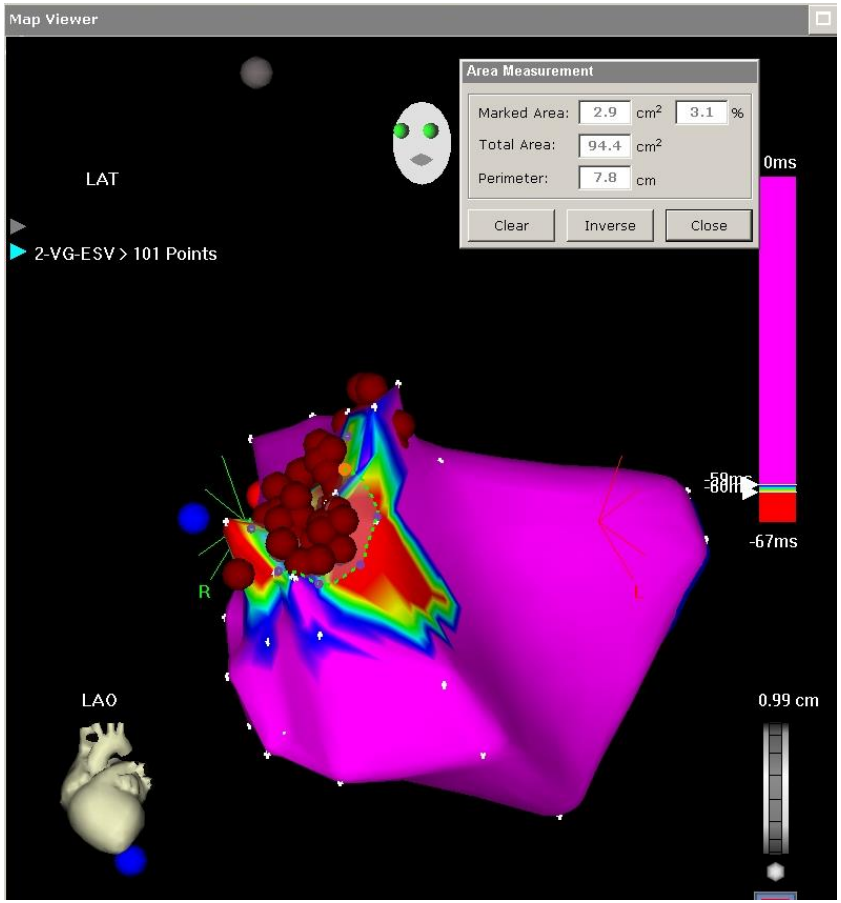
Patient #	QTc (ms)*	Gender	Symptoms	NSVT†	Total PVC/ 24 h	LVEF Before Medication (%)	Atrial Arrhythmia	PVC Morpho†
Family 1								
I.1	—	M	SD	—	—	—	—	—
II.2	423	F	Syncope	No	62,000	73	Paroxysmal atrial arrhythmia	R
II.4	358	F	Dyspnea	Yes	>25,000	35	No	R and L
II.6	426	F	Dyspnea	No	—	59	No	—
II.7	362	M	Dyspnea, SD	No	—	47	No	—
II.8	391	M	Syncope	No	—	60	No	—
III.1	361	F	Syncope	Yes	>50,000	32	Paroxysmal atrial arrhythmia	R and L
III.2	365	F	No	No	—	60	No	—
III.6	380	M	Palpitations	Yes	>25,000	47	No	R and L
III.7	360	M	Dyspnea	No	>25,000	67	No	R and L
III.9	407	F	No	No	200	—	No	no
III.11	413	M	No	No	11	—	No	no
III.12	—	M	SD	—	—	—	No	—
Family 2								
I.2	—	F	—	—	—	—	—	—
II.1	410	M	Palpitations	—	—	—	No	—
II.3	420	M	SD	—	—	—	Atrial flutter	—
III.1	405	M	No	No	18,000	60	No	L
III.2	408	M	Presyncope	No	86,000	60	No	L
Family 3								
I.1	—	M	SD	Yes	—	—	Atrial bigeminy	R and L
II.2	414	F	Palpitations	Yes	60,000	58	Paroxysmal atrial arrhythmia	R and L
II.3	431	F	Palpitations	Yes	7,134	>50	Atrial fibrillation	R and L
III.1	399	F	Dyspnea	Yes	35,650	35	Paroxysmal atrial arrhythmia	R and L
III.2	415	M	Near collapse	No	17,706	>50	Atrial flutter	R and L
III.4	430	M	Palpitations	Yes	3,516	>50	Paroxysmal atrial arrhythmia	—

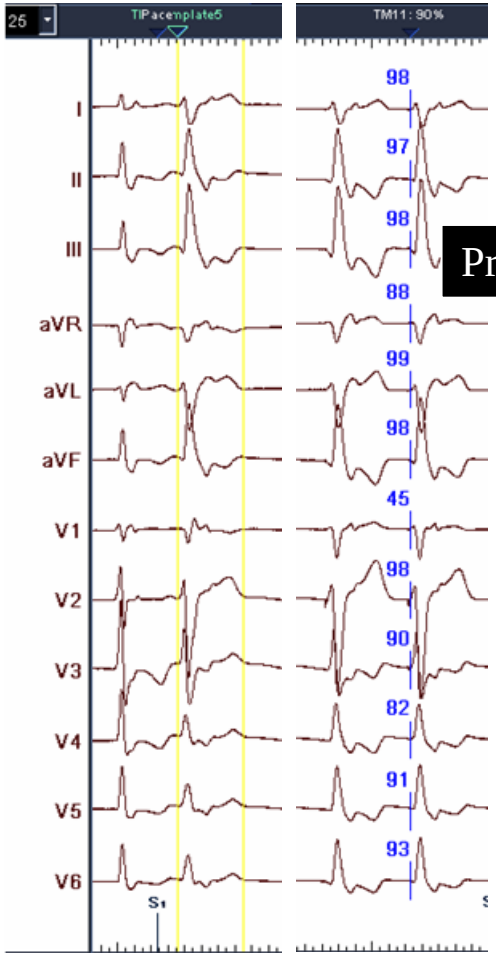

#1
#2
#3
#4
#5
#6
#7
#8
#9
#10
#11
12
DI
DII
DIII
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

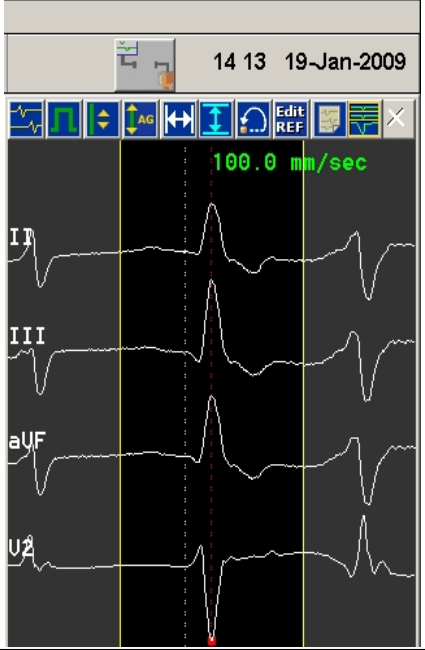

5 mV
0 mV
-5 mV
VM
#1
#2
#3
#4
#5
#6
#7
#8
#9
#10
#11
#12
EnGuide: R = 79.2 [Z = +50.3]
Proximity to EnSite surface:
44.5 mm
Peak Neg = -1.08m


A
B
1
2
3
4
5
6
7
8
9
10
DI
DII
DIII
VR
VL
VF
V1
V2
V3
V4
V5
V6
EGM

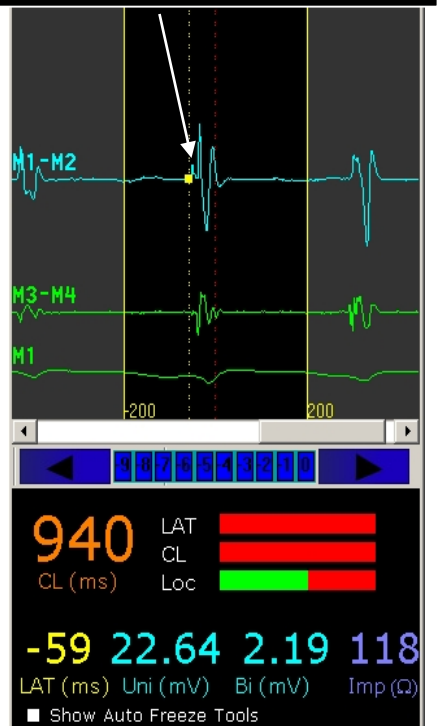
Ablation?

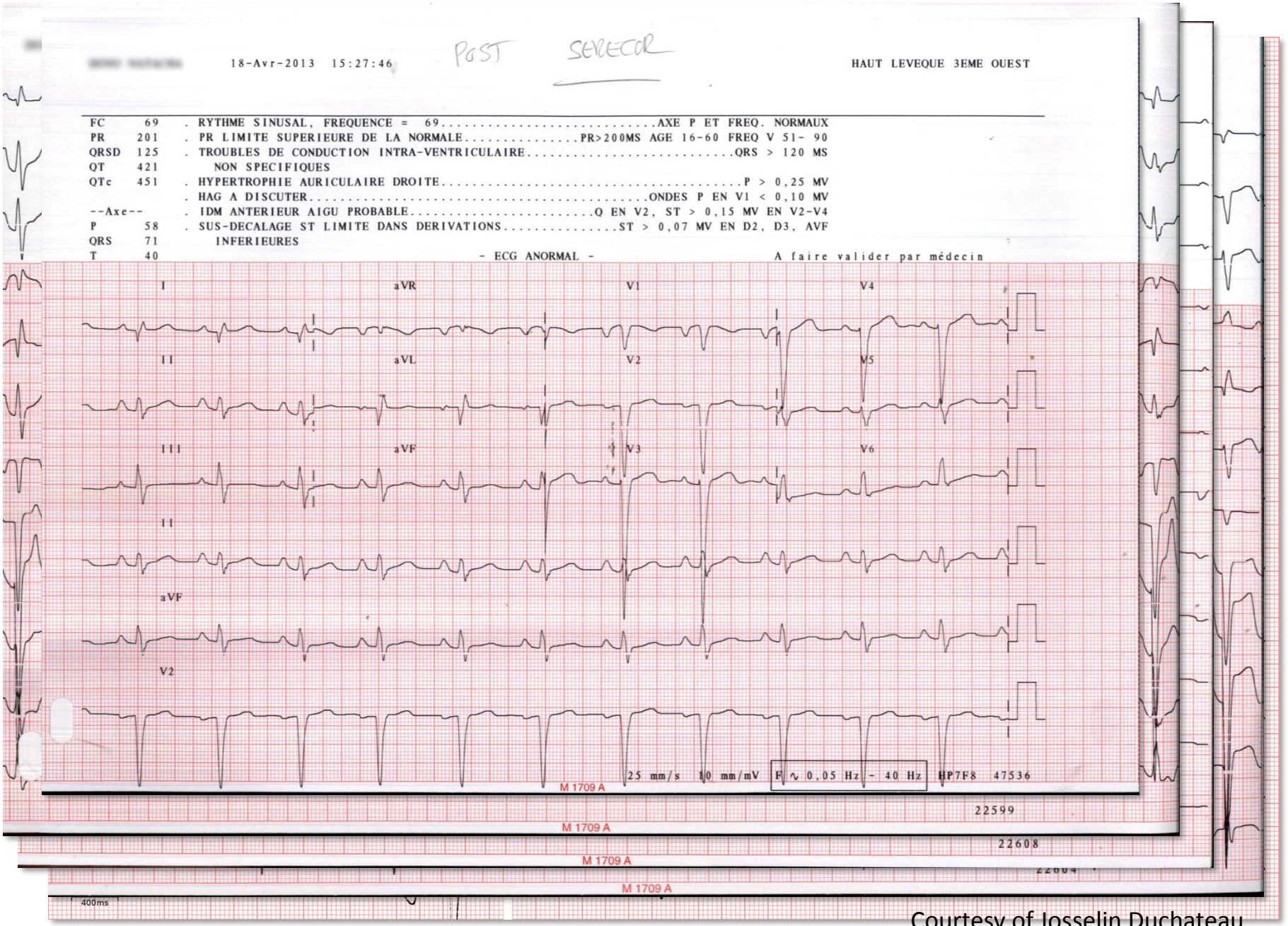






Presystolic Purkinje potential

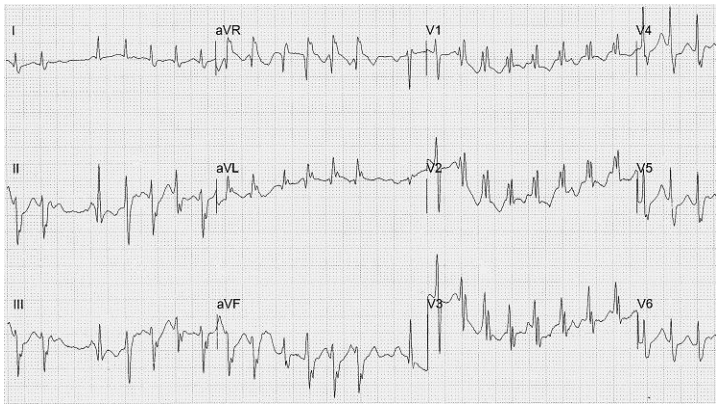


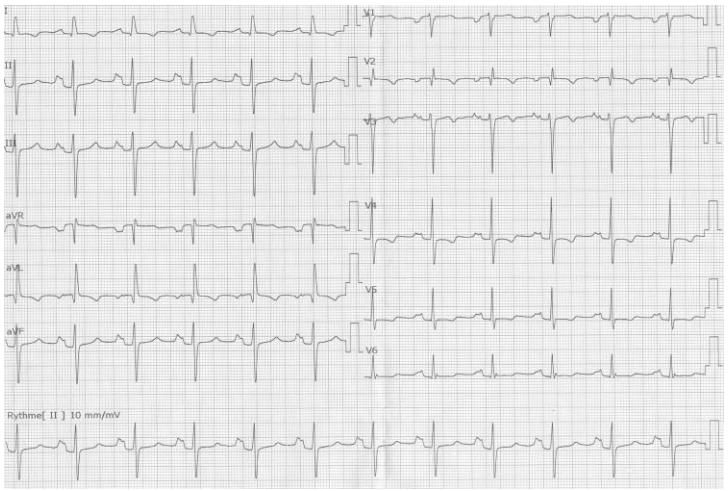


Courtesy of Josselin Duchateau
IHU LIRYC – Equipe Signal

Follow-Up and Treatment of the Family Members

Patient #	Treatment	PVC/24 h on Medication	LVEF on (Before) Medication (%)
Family 1			
I.1	—	—	—
II.2	Hydroquinidine	<5,000	60 (73)
II.4	Hydroquinidine	<5,000	50 (35)
II.6	Amiodarone	4	—
II.7	None	—	—
II.8	None	—	—
III.1	Hydroquinidine	<5,000	56 (32)
III.2	None	—	—
III.6	*	—	—
III.7	None	—	—
III.9	None	—	—
III.11	None	—	—
III.12	—	—	—
Family 2			
I.2	None	—	—
II.1	Amiodarone	—	45 (20)
II.3	—	—	—
III.1	Hydroquinidine	2,500	60 (60)
III.2	Hydroquinidine	7,700	60 (60)
Family 3			
I.1	—	—	—
II.2	Flecainide	125	58
II.3	Flecainide	5,791	>50 (>50)
III.1	PropafeNon†	31,894	50 (35)
III.2	Flecainide	486	52 (>50)
III.4	Flecainide	21	>50 (>50)





Conclusion

- PVC phenotypes
- Bidirectional PVCs or polymorphic PVCs/VT
  - CPVT (BB, Flecainide, ICD, LCSD)
  - MEPPC syndrome
    - Rate dependant PVCs from the fascicular-Purkinje system
    - Sensitive to Hydroquinidine
    - Transient tachycardia DCM-induced, syncope, SCD
    - Ablation is not the solution!

Thank you for your attention

PVCs in HCM

- NSVT occurs in 25% of patients during ambulatory ECG monitor
- Its prevalence increases with age and correlates with LV wall thickness and late gadolinium enhancement on CMR.
- NSVT during ambulatory monitoring is associated with an increased risk of SCD.
- Documented NSVT during or immediately following exercise is very rare, but may be associated with a higher risk of SCD.

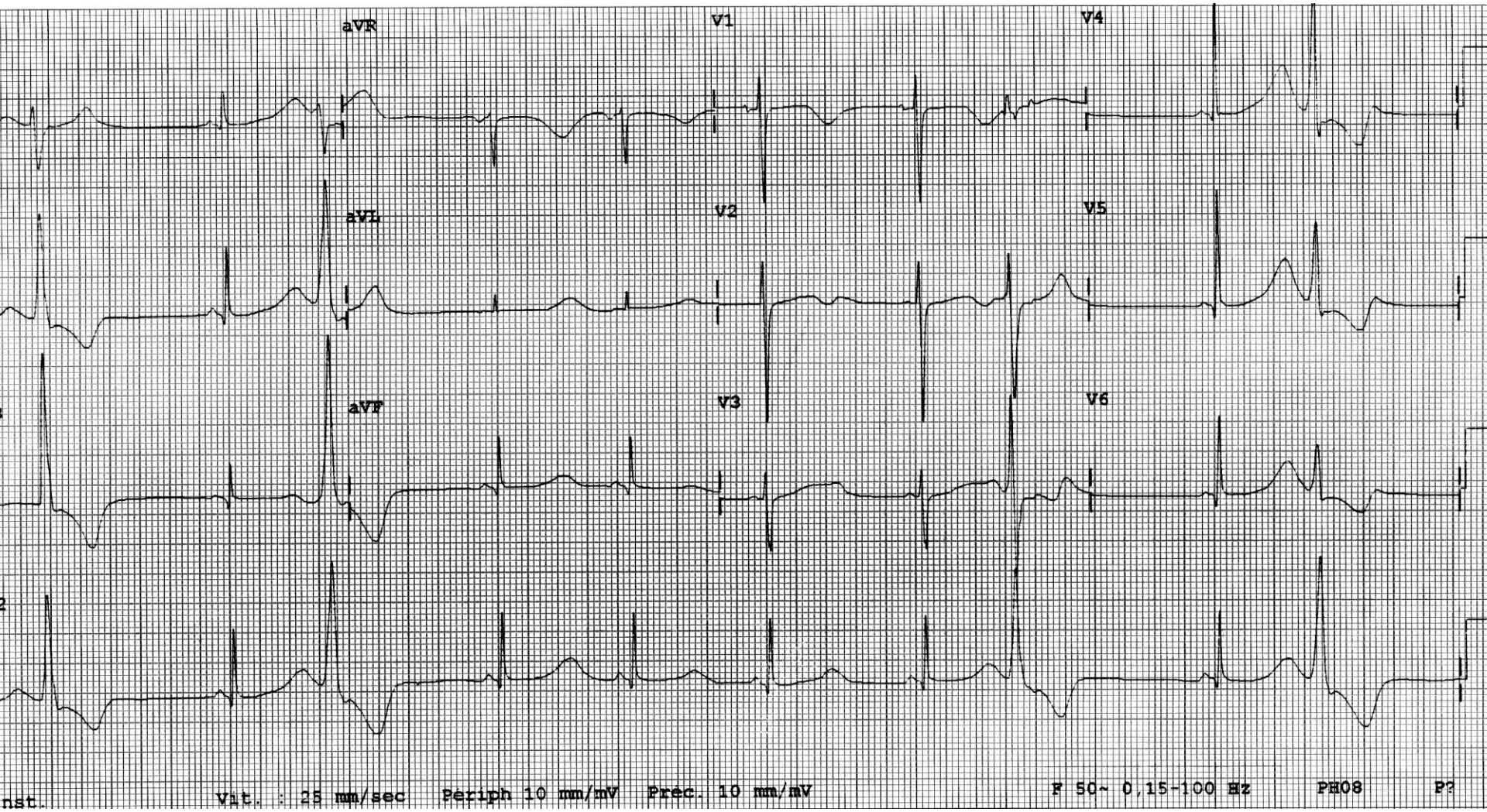
PVCs in ARVC

Up to two-thirds of patients have VAs on resting or ambulatory ECG monitoring and exercise testing.

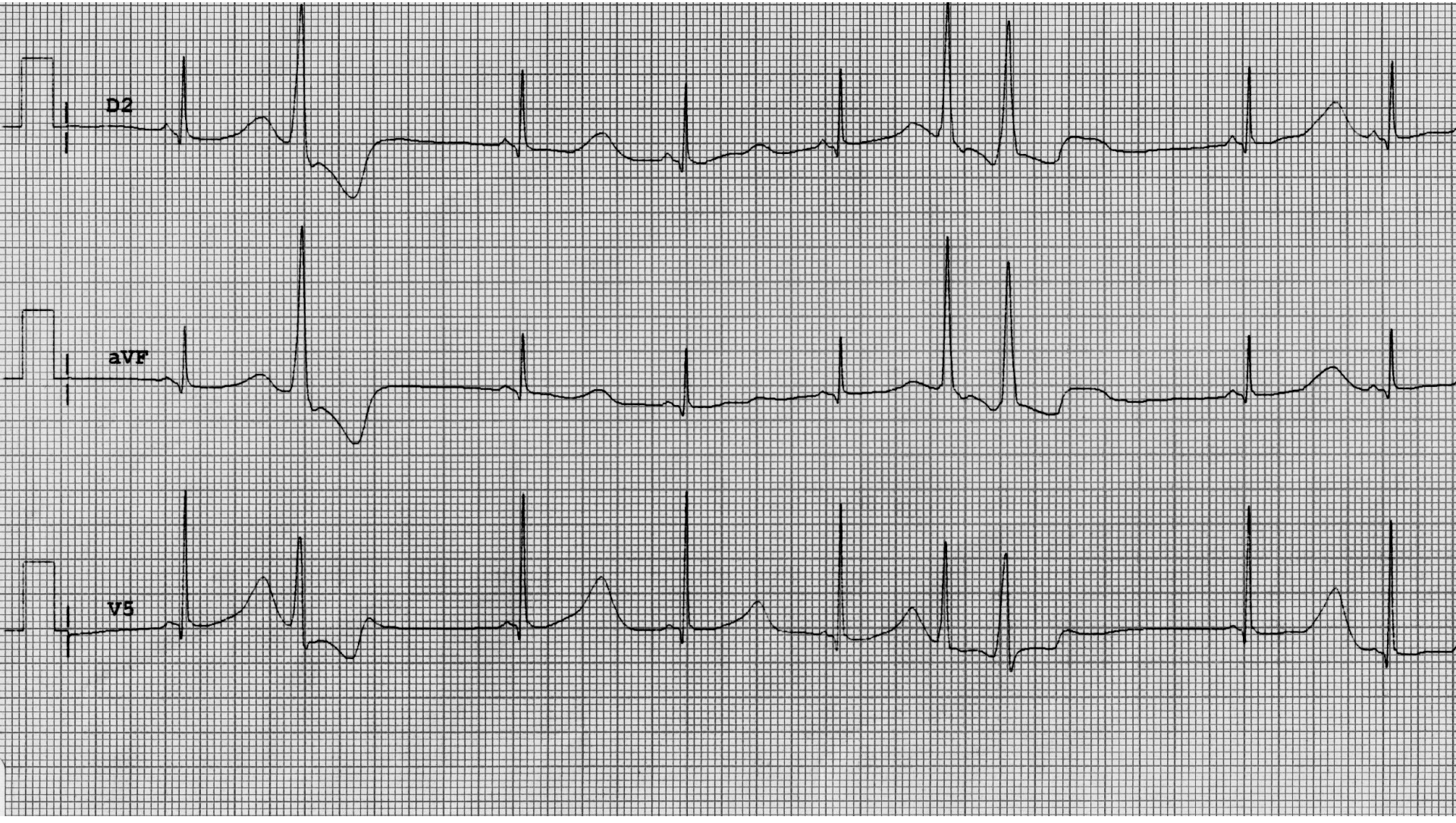
These VAs are usually of RV origin (i.e. show a left bundle branch morphology), but the QRS axis during VT usually differs from the QRS axis in RVOT, and many patients have multiple QRS morphologies.

PVCs in LQTs

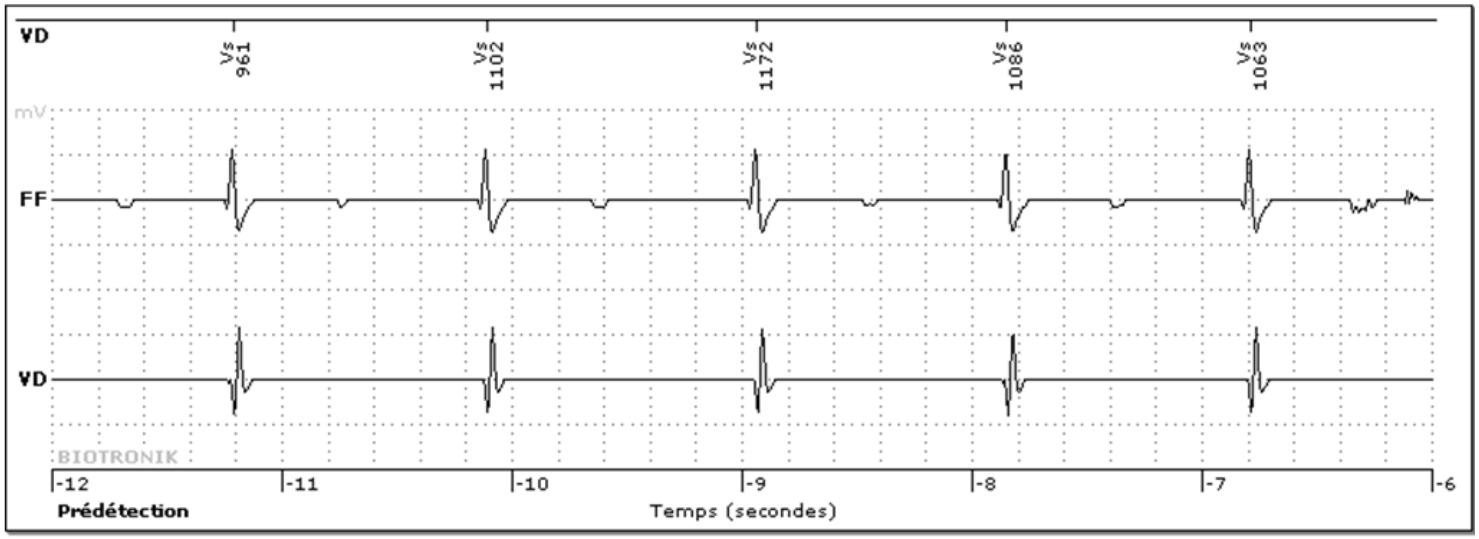
Olivia 11

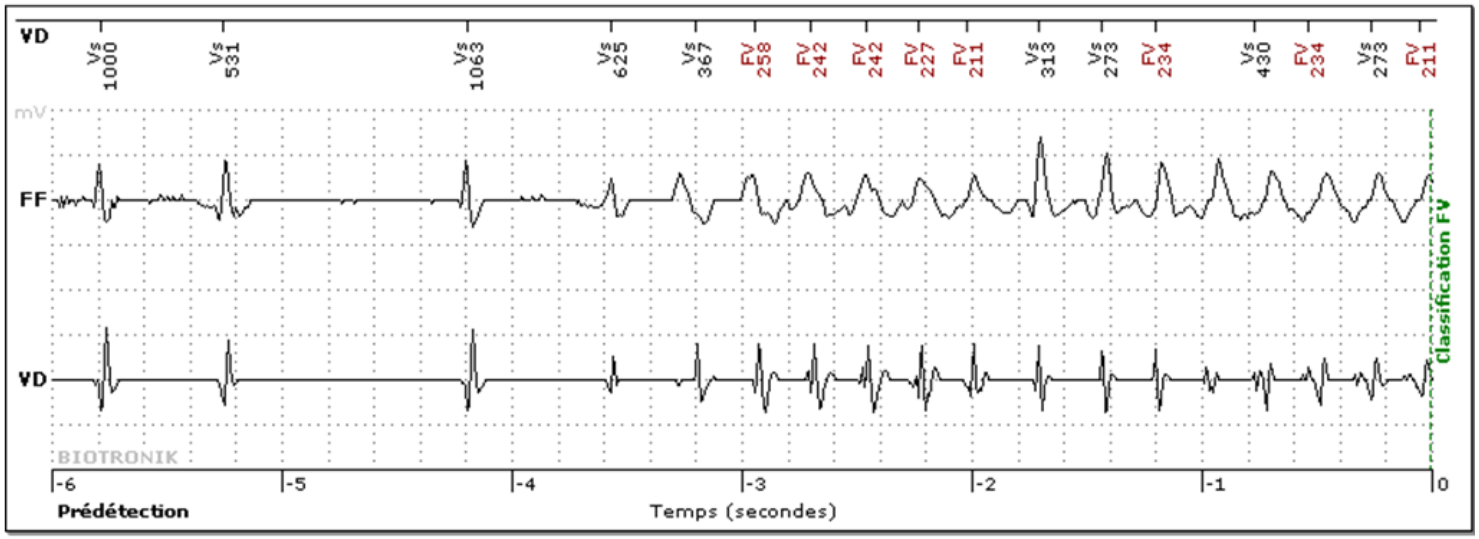

aVR
V1
V4
aVL
V2
V5
aVF
V3
V6
Vit. : 25 mm/sec
Périph 10 mm/mV
Préc. 10 mm/mV
F 50~ 0,15-100 Hz
PH08

LQT1

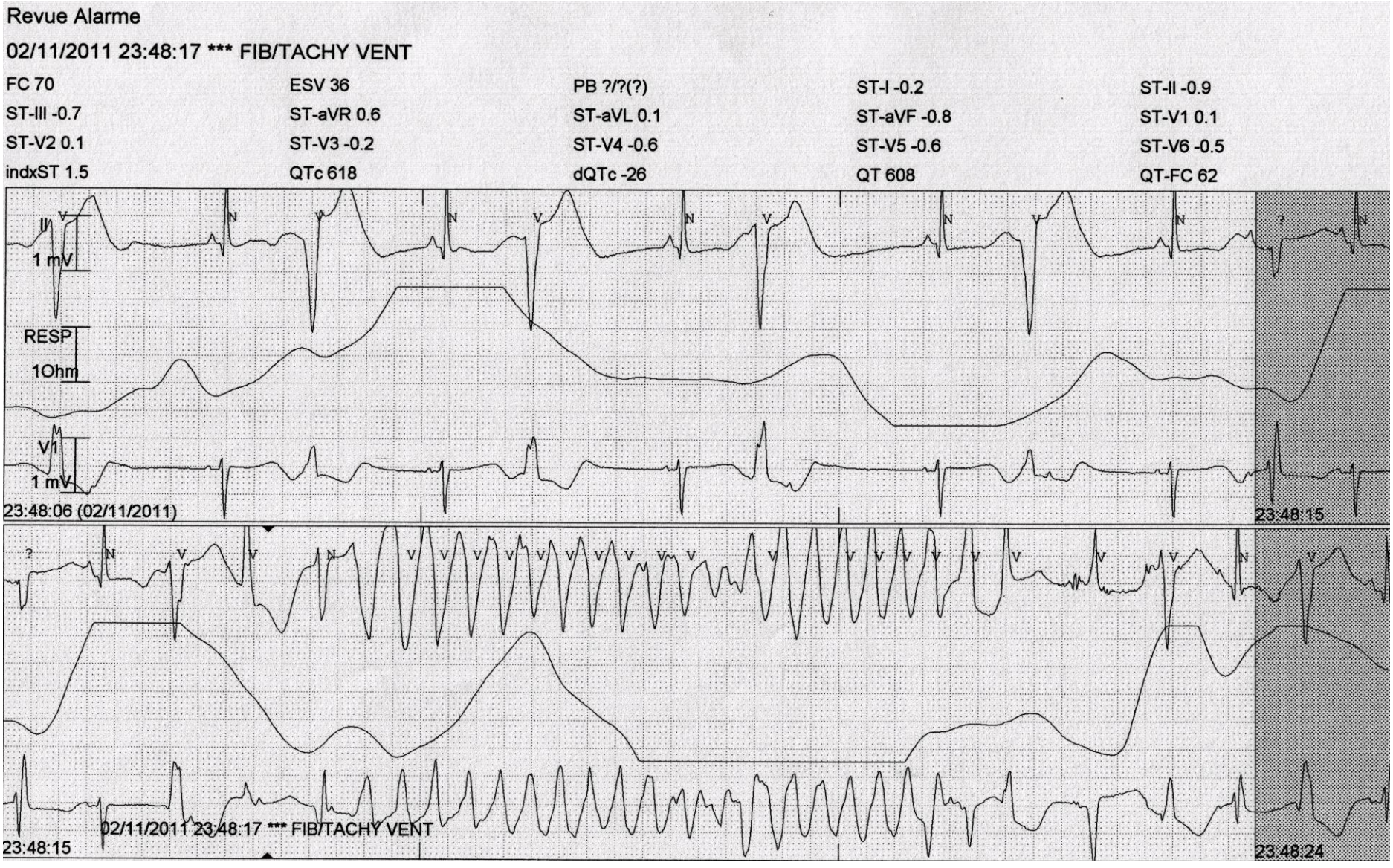


HM


VD
Vs 961
Vs 1102
Vs 1172
Vs 1086
Vs 1063
mV
FF
VD
BIOTRONIK
-12
-11
-10
-9
-8
-7
-6
Prédétection
Temps (secondes)


VD
Vs 1000
Vs 531
Vs 1063
Vs 625
Vs 367
FV 258
FV 242
FV 242
FV 227
FV 211
Vs 313
Vs 273
FV 234
Vs 430
FV 234
Vs 273
FV 211
mV
FF
VD
Classification FV
BIOTRONIK
-6
-5
-4
-3
-2
-1
0
Prédétection
Temps (secondes)

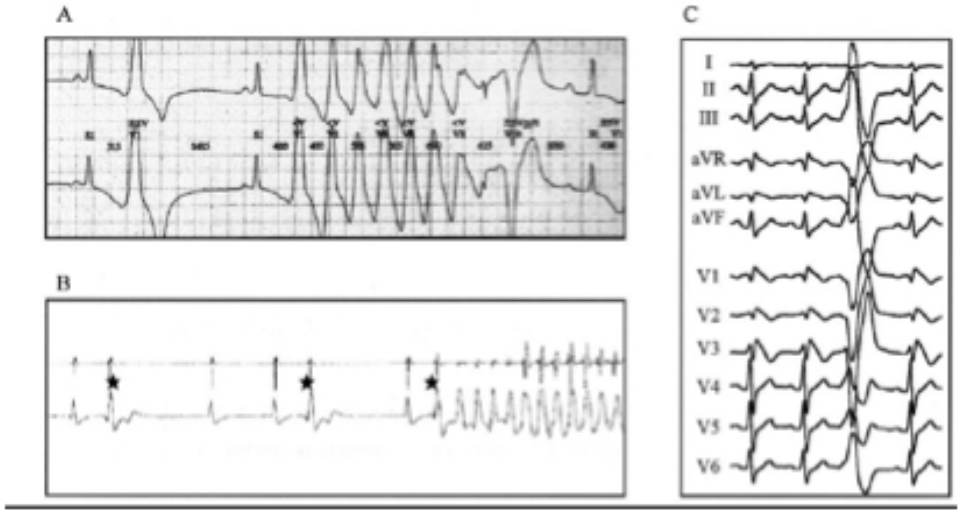
LQT2

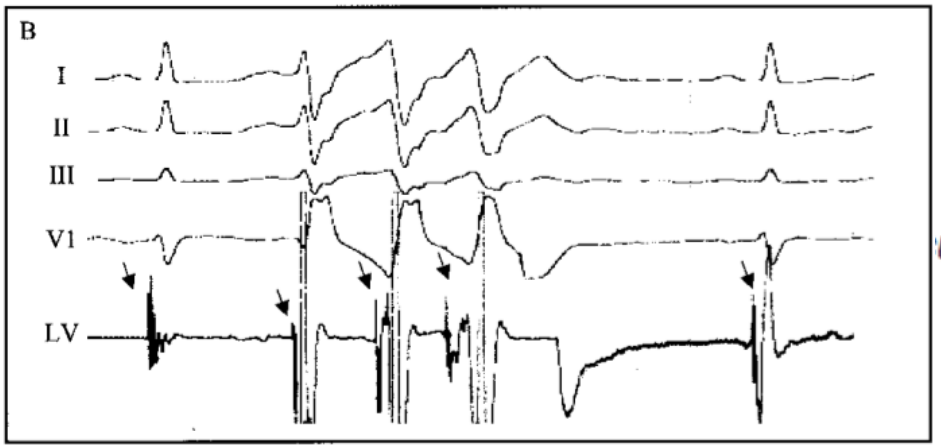

Revue Alarme
02/11/2011 23:48:17 *** FIB/TACHY VENT
FC 70
ESV 36
PB ?/?(?)
ST-I -0.2
ST-II -0.9
ST-III -0.7
ST-aVR 0.6
ST-aVL 0.1
ST-aVF -0.8
ST-V1 0.1
ST-V2 0.1
ST-V3 -0.2
ST-V4 -0.6
ST-V5 -0.6
ST-V6 -0.5
indxST 1.5
QTc 618
dQTc -26
QT 608
QT-FC 62
II
1 mV
RESP
1Ohm
V1
1 mV
23:48:06 (02/11/2011)
23:48:15
02/11/2011 23:48:17 *** FIB/TACHY VENT
23:48:15
23:48:24

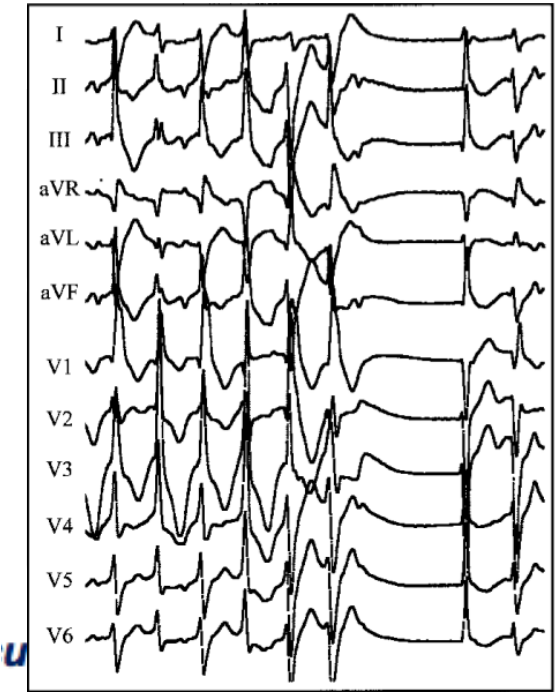
Mapping and Ablation of Ventricular Fibrillation Associated With Long-QT and Brugada Syndromes

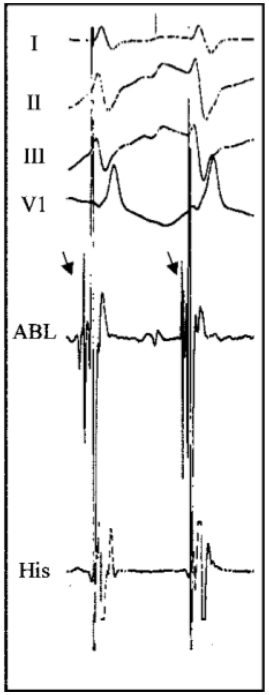
Michel Haïssaguerre, MD; Fabrice Extramiana, MD; Mélèze Hocini, MD; Bruno Cauchemez, MD; Pierre Jaïs, MD; Jose Angel Cabrera, MD; Geronimo Farre, MD; Antoine Leenhardt, MD; Prashanthan Sanders, MBBS; Christophe Scavée, MD; Li-Fern Hsu, MBBS; Rukshen Weerasooriya, MBBS; Dipen C. Shah, MD; Robert Frank, MD; Philippe Maury, MD; Marc Delay, MD; Stéphane Garrigue, MD; Jacques Clémenty, MD

Circulation 2003

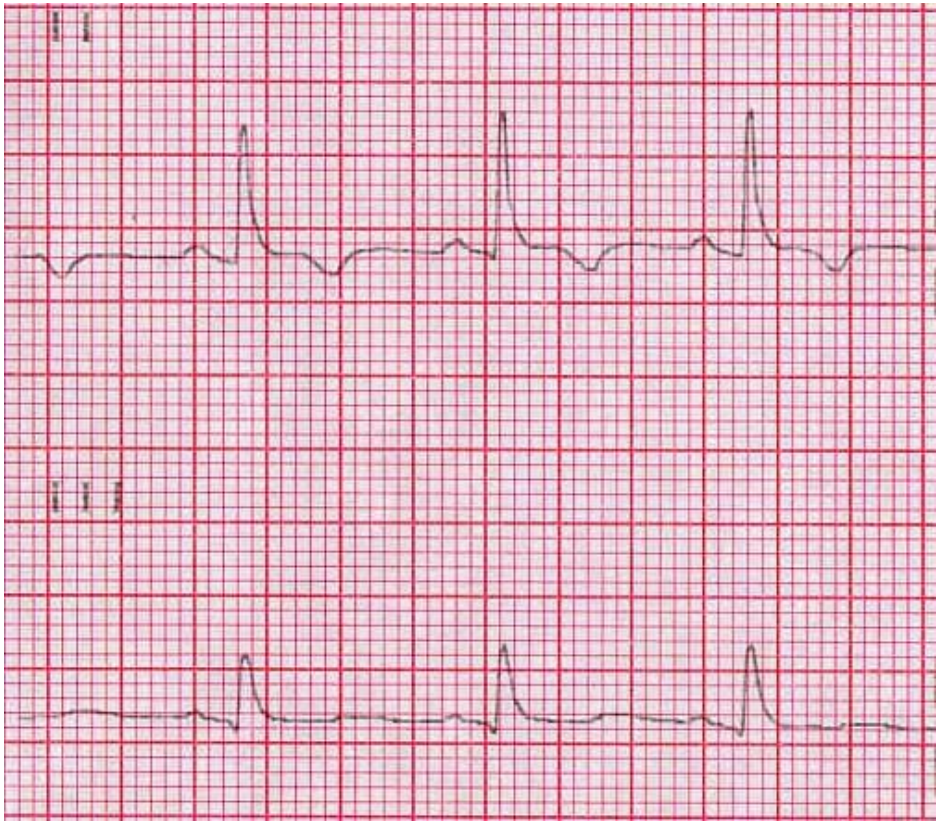


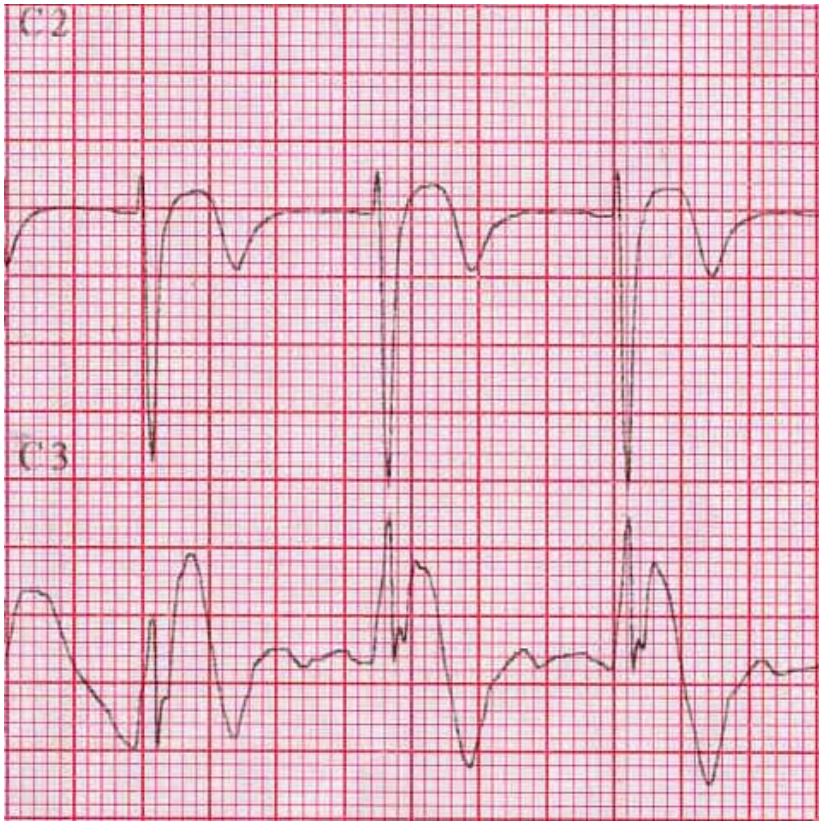




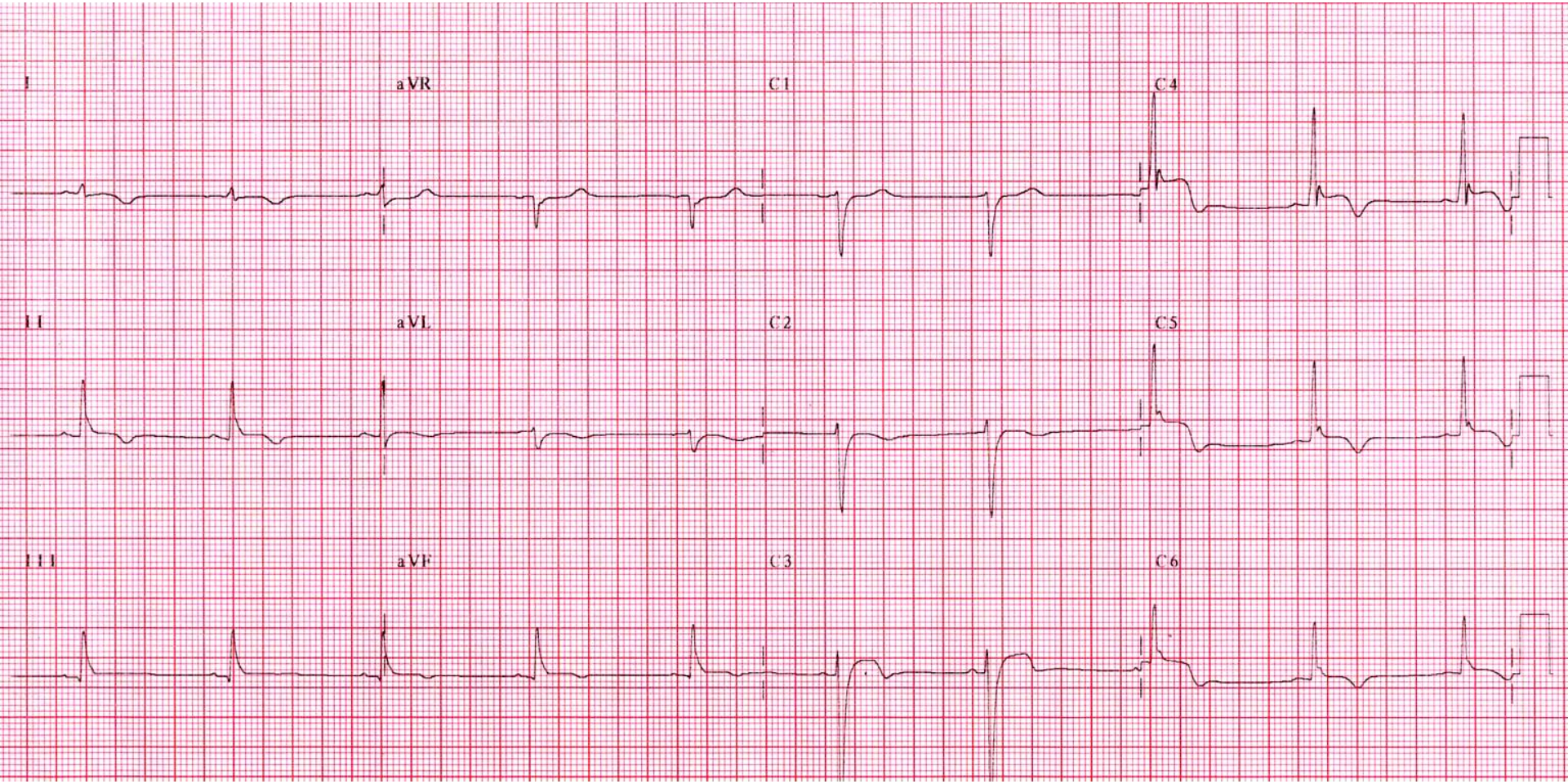


Devrim 1er ECG après ACC

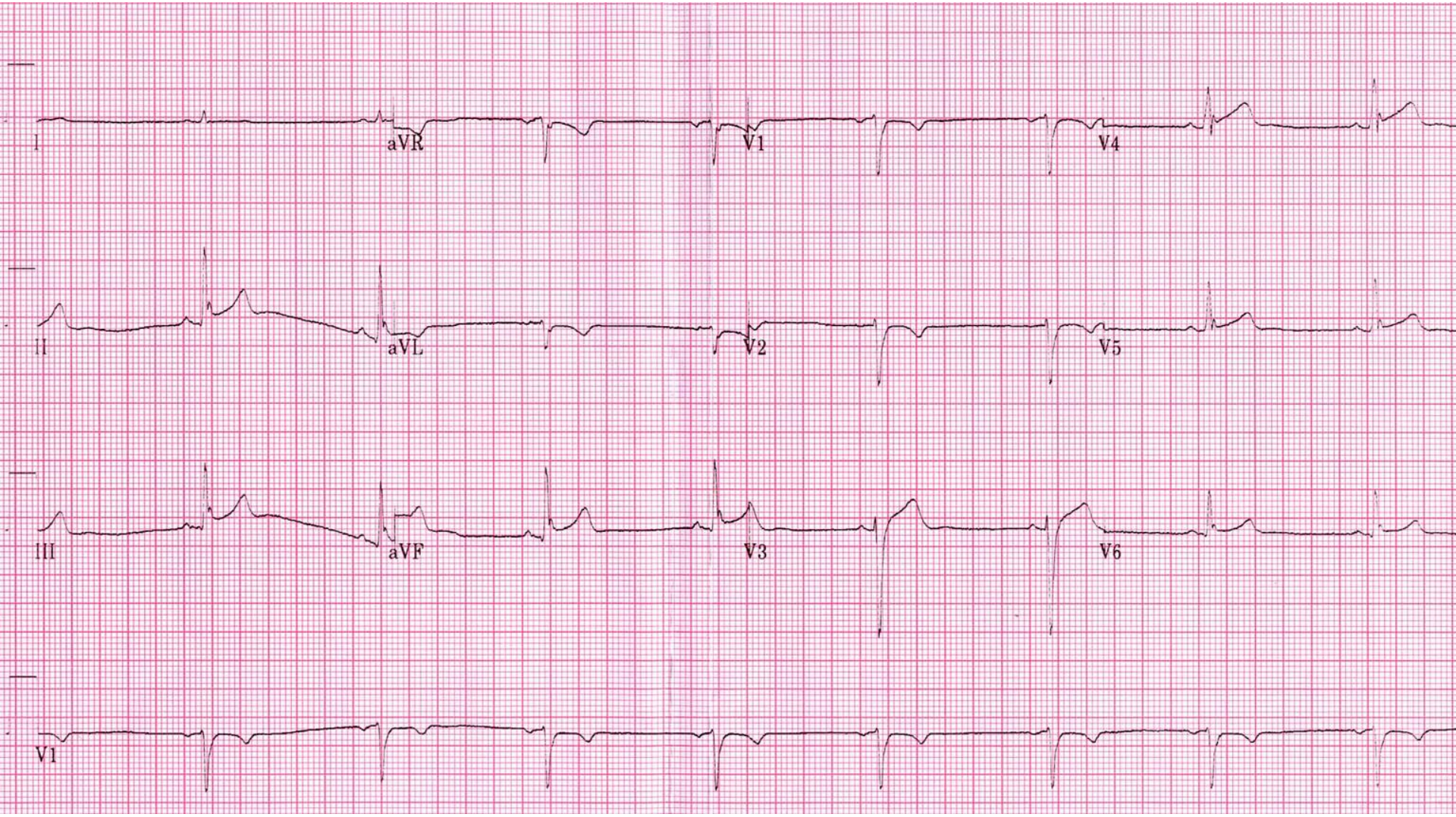




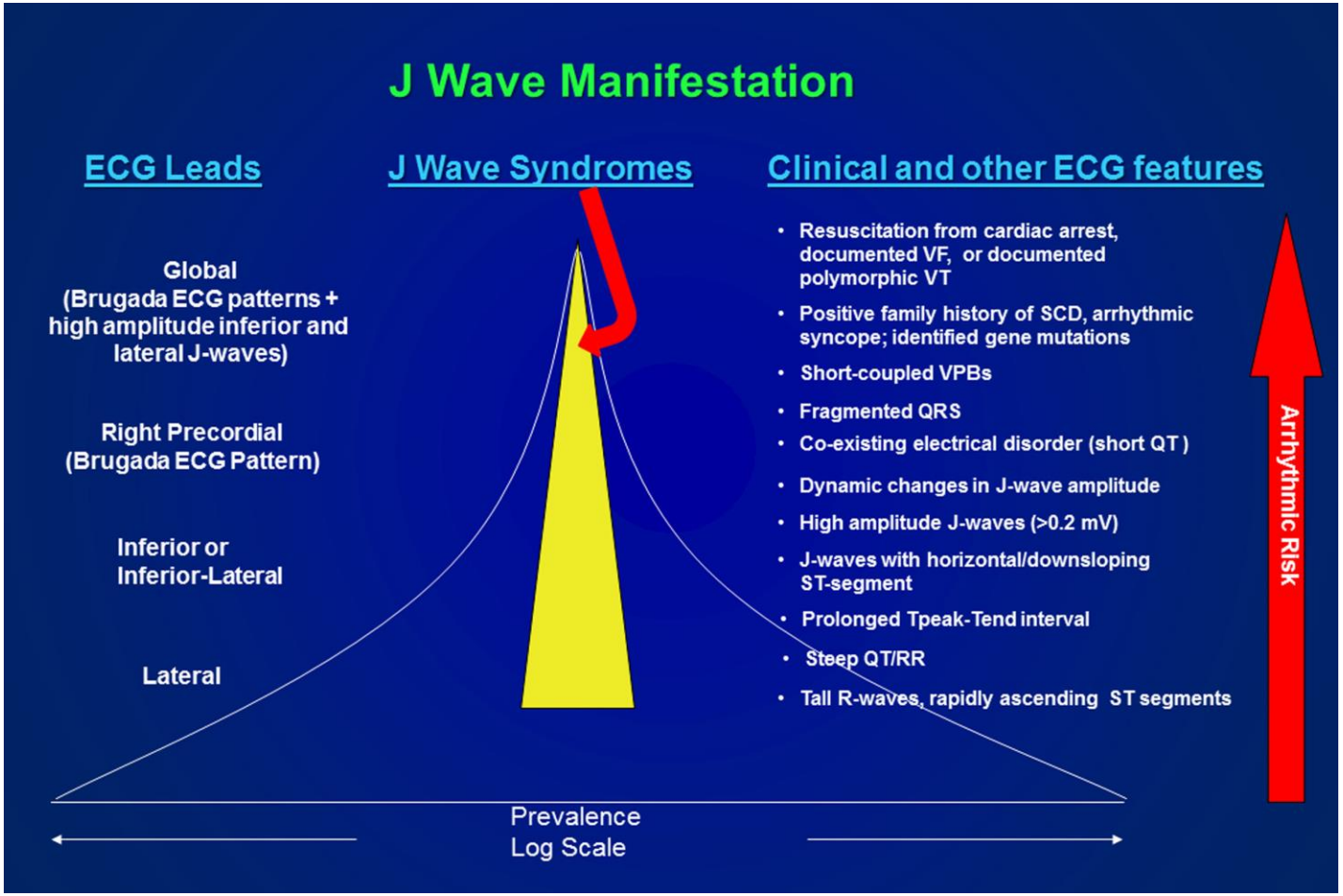
Devrim J10



Devrim aujourd’hui

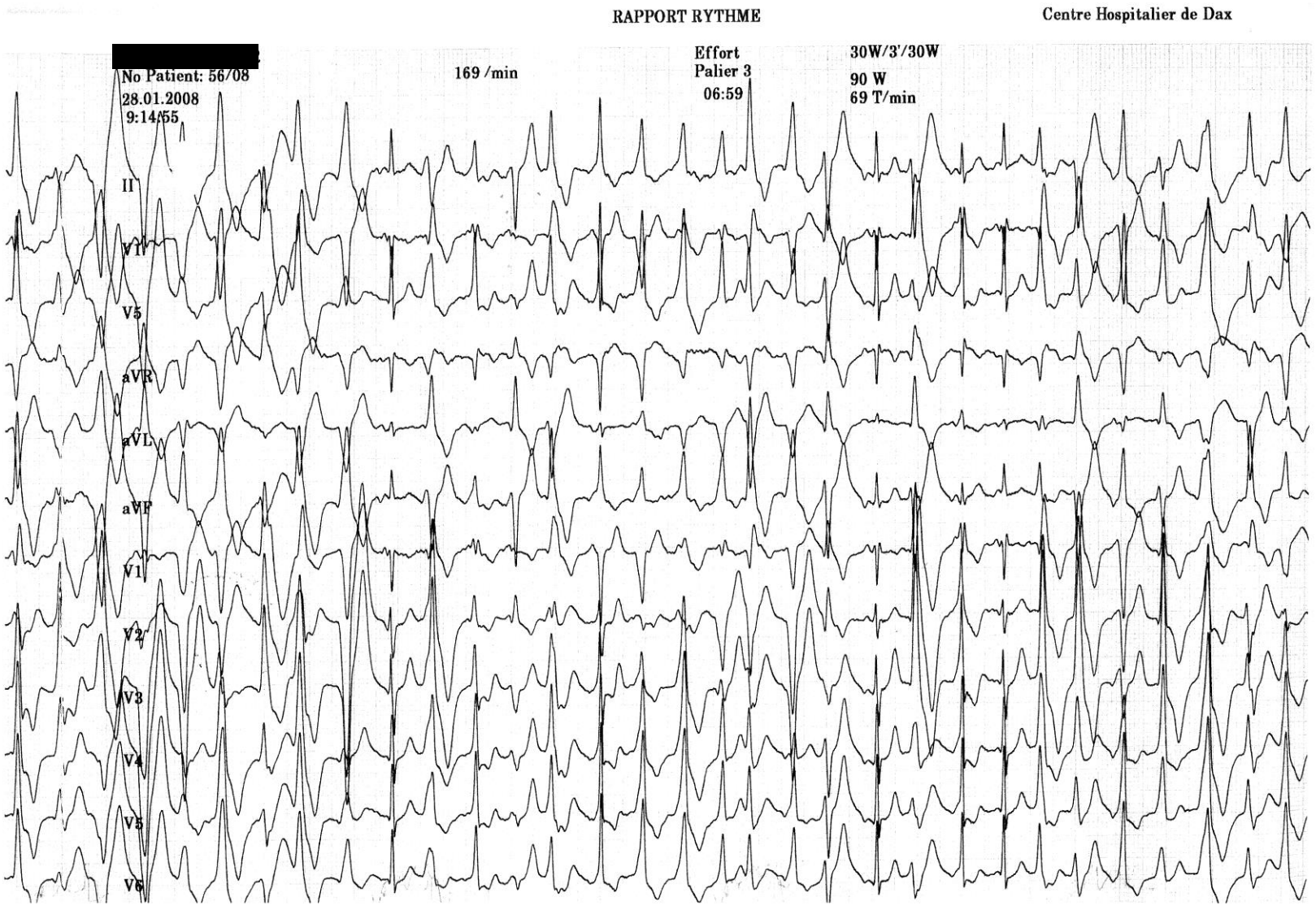


Prevalence and arrhythmic risk associated with the appearance of ECG J waves

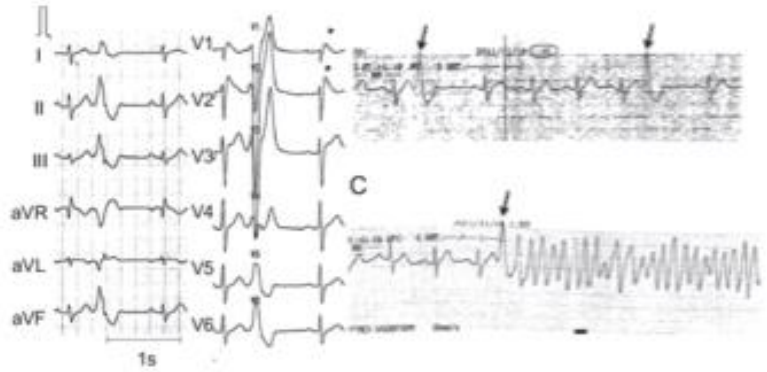


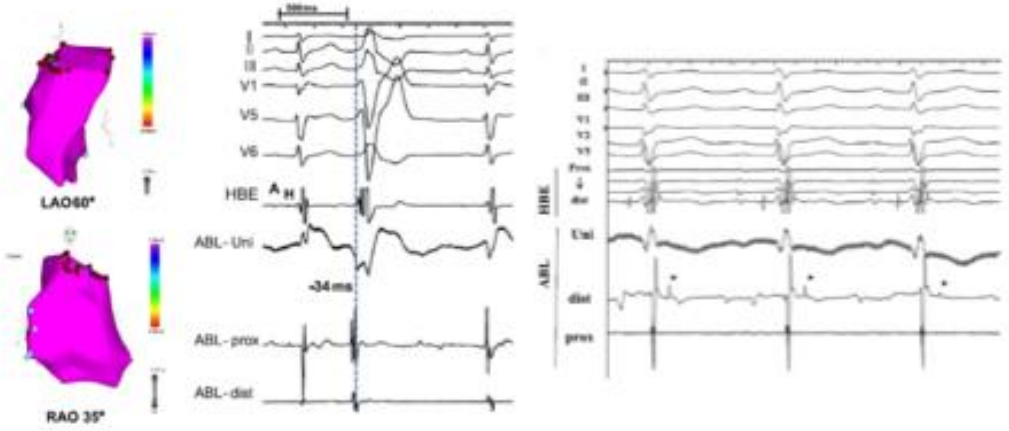
Heart Rhythm 2016 13, e295-e324DOI: (10.1016/j.hrthm.2016.05.024)
J wave expert consensus October 2016

CPVT


RAPPORT RYTHME
Centre Hospitalier de Dax
[redacted]
No Patient: 56/08
28.01.2008
9:14:55
169 /min
Effort
Palier 3
06:59
30W/3'/30W
90 W
69 T/min
II
VI
V5
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

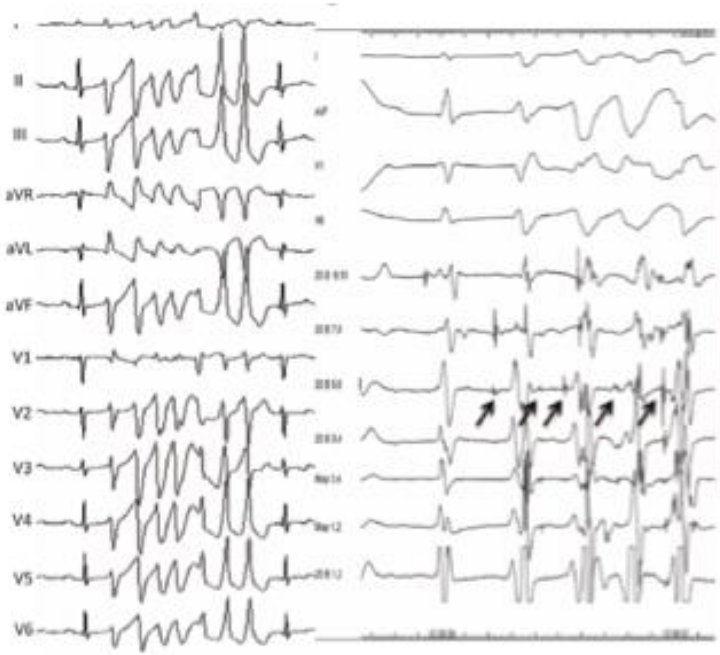
PVC ablation at the time of VF inCPVT

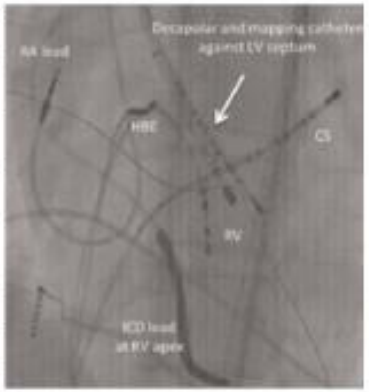




Adapted from AK Talib, Journal of arrhythmia, 2016

PVC triggering CPVT





LV posterior septum

Adapted from Chan KH, Heart, Lung and Circulation 2016

Methods-EP

Standard EP studies (6pts) + 3D navigation systems (3pts)

Precise location of the PVC firing:

- Pre-systolic Purkinje potentials (PP) corresponding to PP during normal SR
- Early endocardial activation mapping with a QS unipolar pattern of the EGM
- Concordant pace mapping.

Methods-Genetic

Candidate gene approach:

Direct sequencing of Lamin A/C, ABCC9, SCN5A

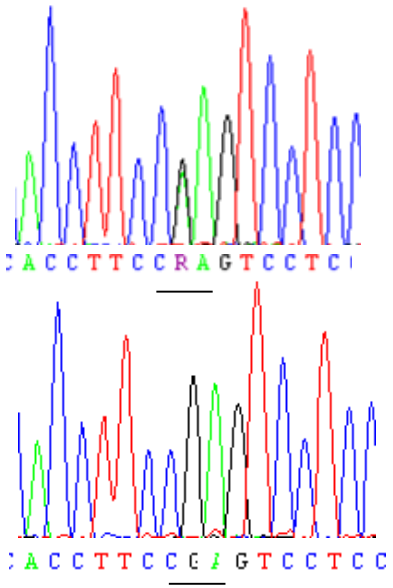
Functionnal studies:

- Patch-clamp experiments: DNA transfected african green monkey kidney fibroblast-like cells (COS-7).
- Computational models of human left-ventricular myocytes and Purkinje cells.

Results-Genetic

Affected

Wild-type

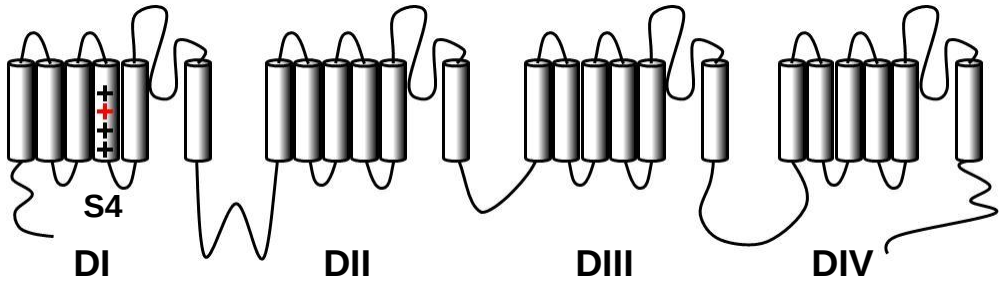


Mutation analysis of SCN5A c.665G>A missense mutation

222

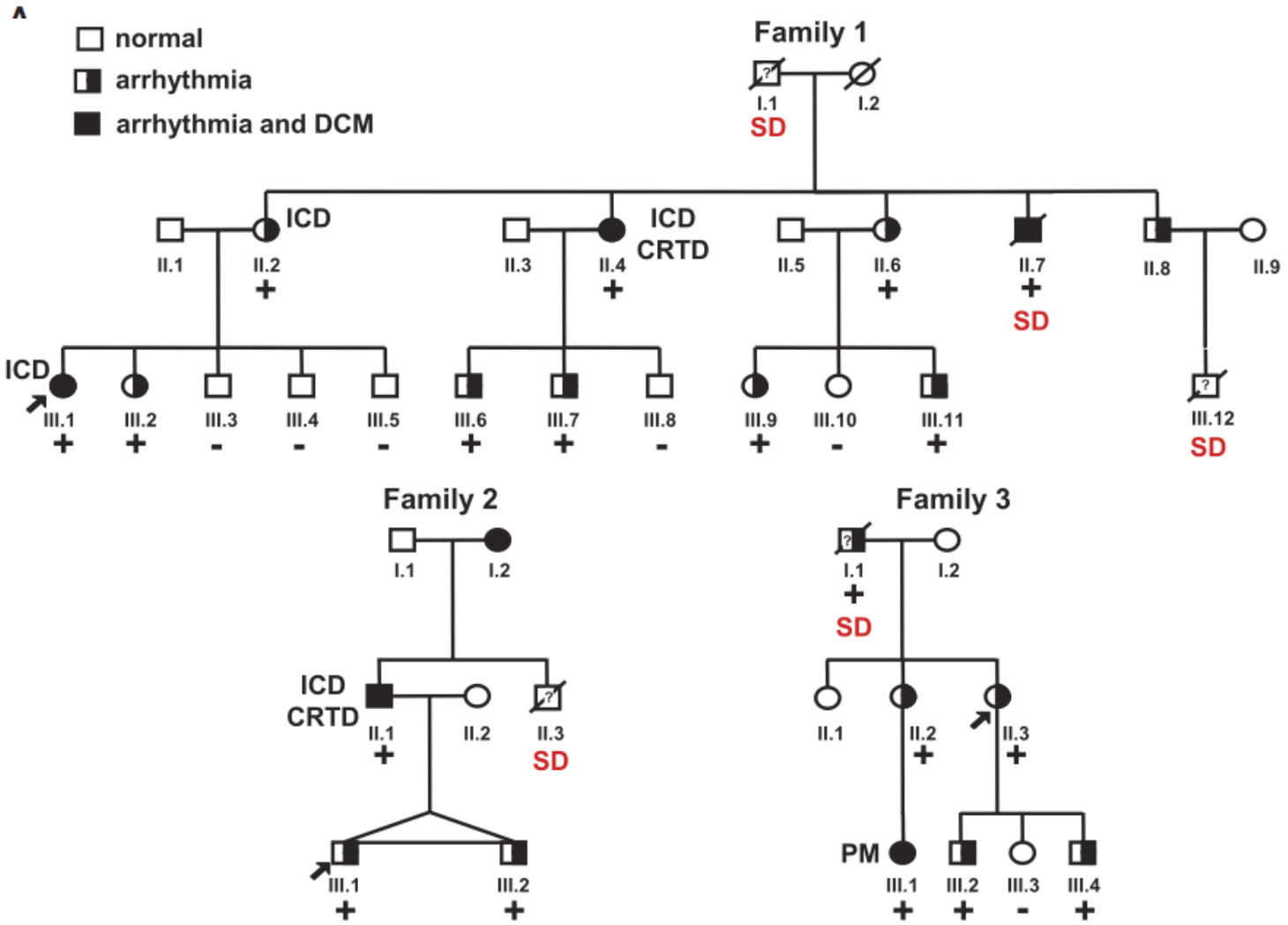
Human	**AYTTEFVDLGNVSALRTFRVLRALKTISVISG**
Rat	**AYVSENI KLGNLSALRTFRVLRALKTISVIPG**
Mouse	**AYVSENI KLGNLSALRTFRVLRALKTISVIPG**
Dog	**AYTTEFVDLGNVSALRTFRVLRALKTISVISG**
Zebrafish	**AYVTEFVDLGNVSALRTFRVLRALKTISVIPG**

Arg222

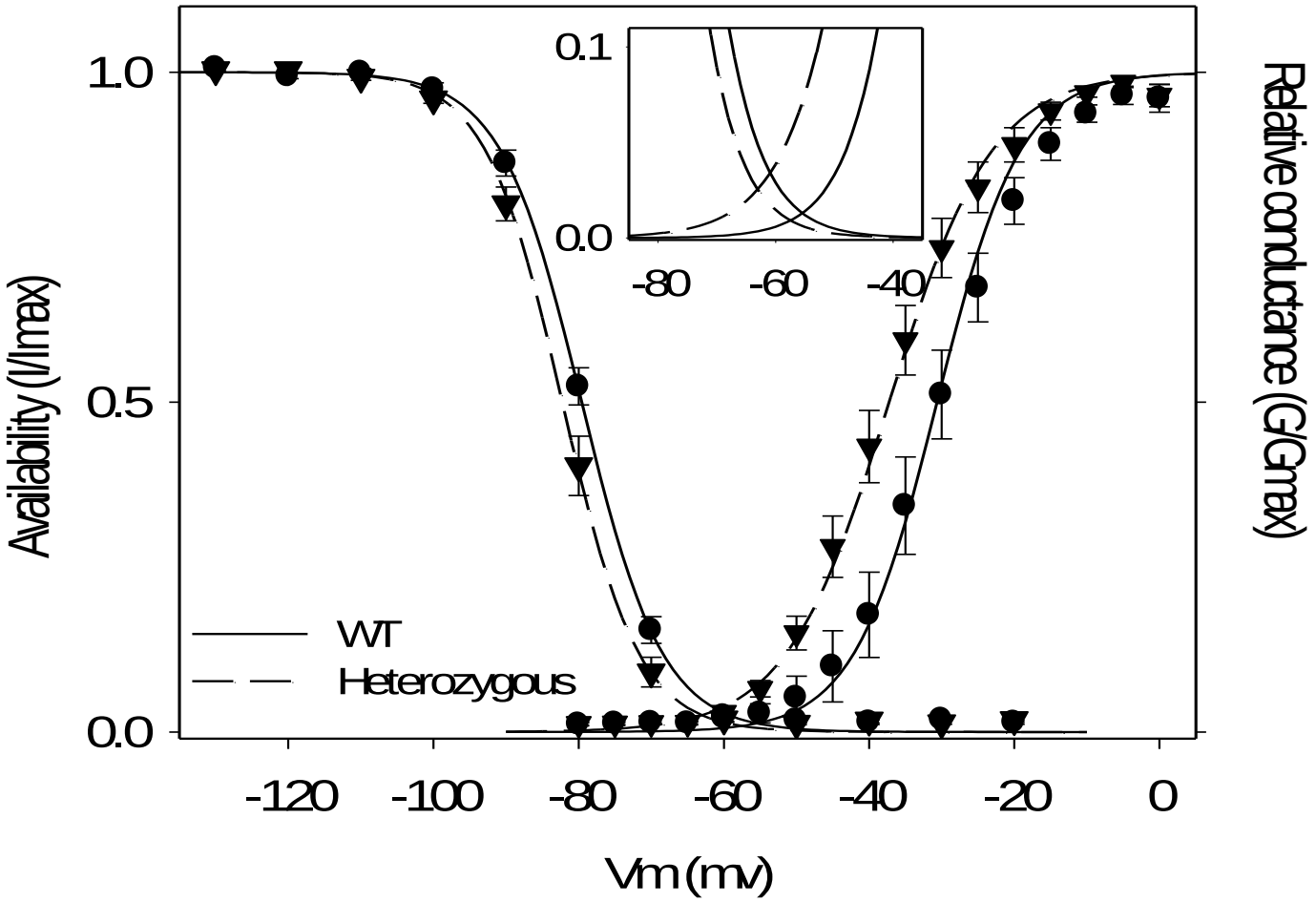


Structure of the cardiac sodium channel Nav1.5

Pedigree and phenotype of the 3 families



Experimental Effects of R222Q Mutation on Nav1.5 Channel in COS-7 Cells



Effects of the R222Q Mutation on a Ventricular CM-AP in the Purkinje/Ventricle Model