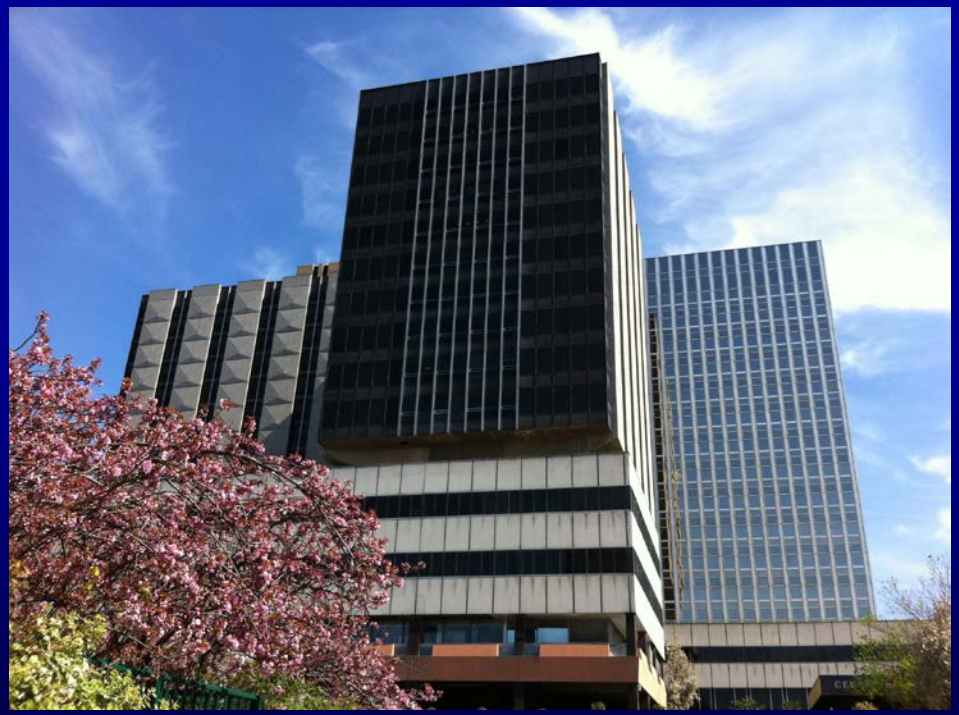
How to manage a patient with catecholaminergic polymorphic ventricular tachycardia ?

Centre de Référence des Maladies Cardiaques Héréditaires



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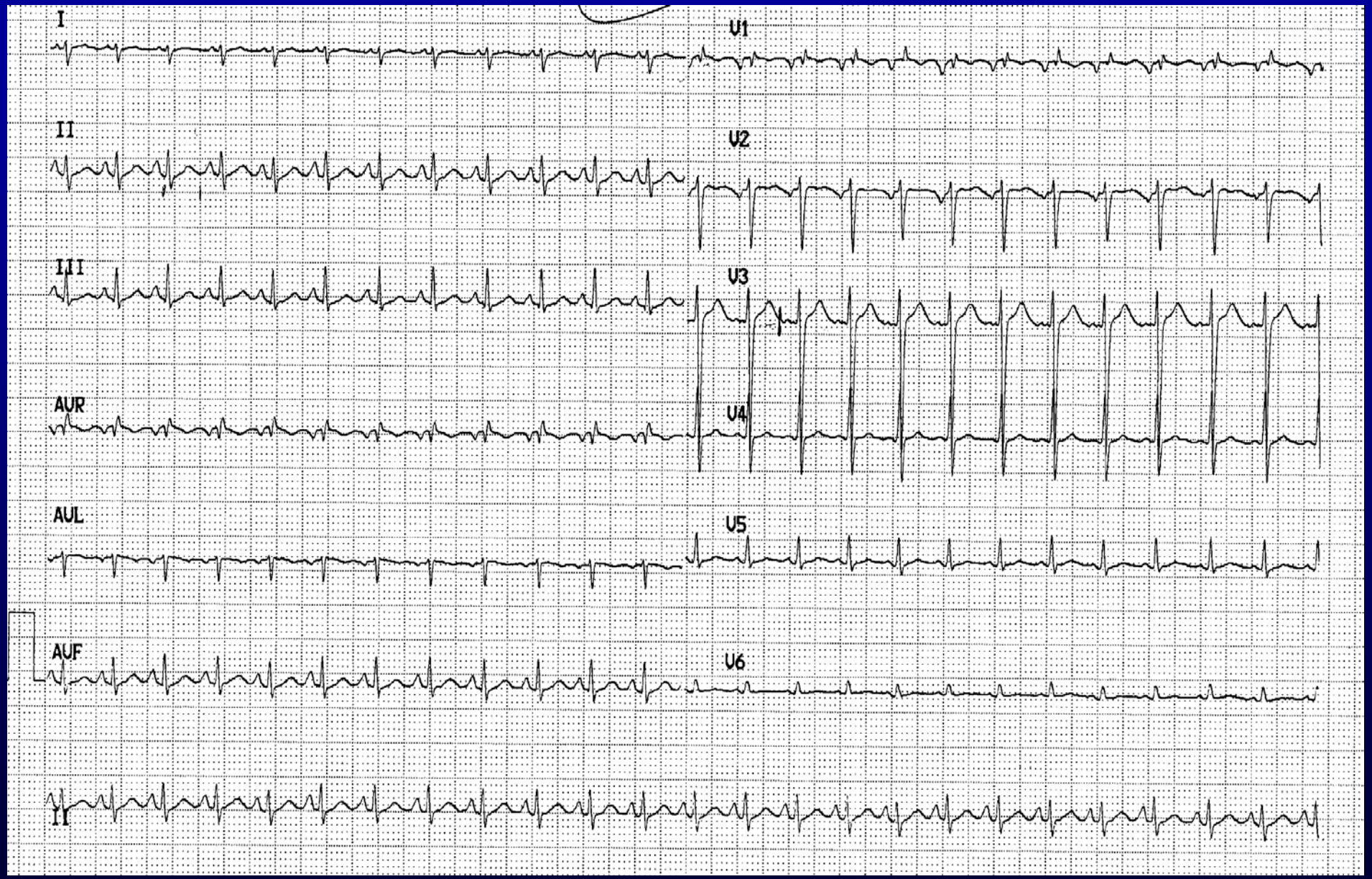
10th Symposium on Advances in Cardiac Diseases. Torino, October 27, 2012

Sad case report of CPVT

- Little girl, 8 years old
- No history of personal or familial loss of consciousness nor sudden death.
- Syncope after a sprint race.
- CPR and cardioversion by the paramedics.
- Initial ECG : sinus tachycardia 150 b/min – QTc 440 ms.
- Normal echocardiography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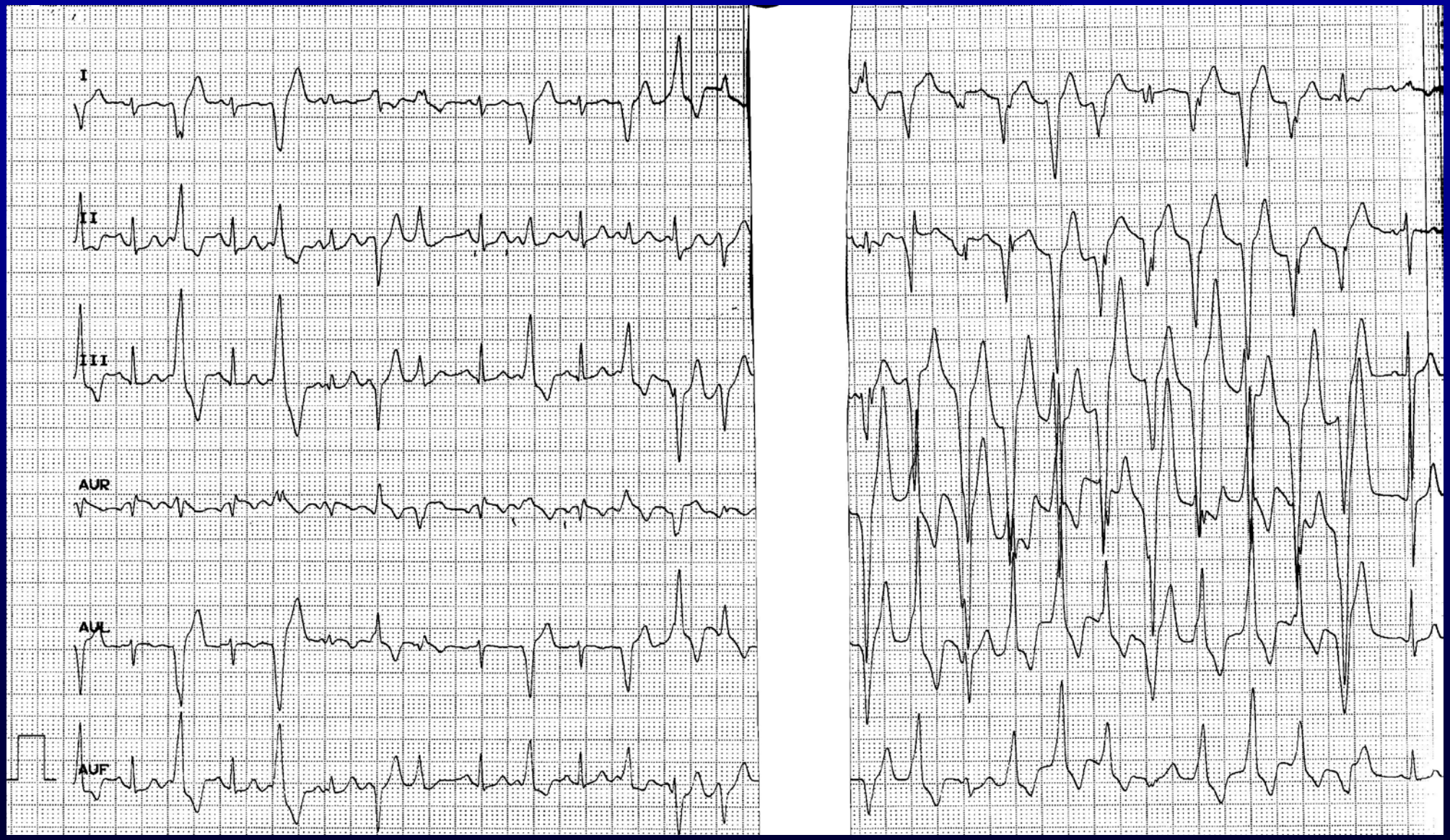
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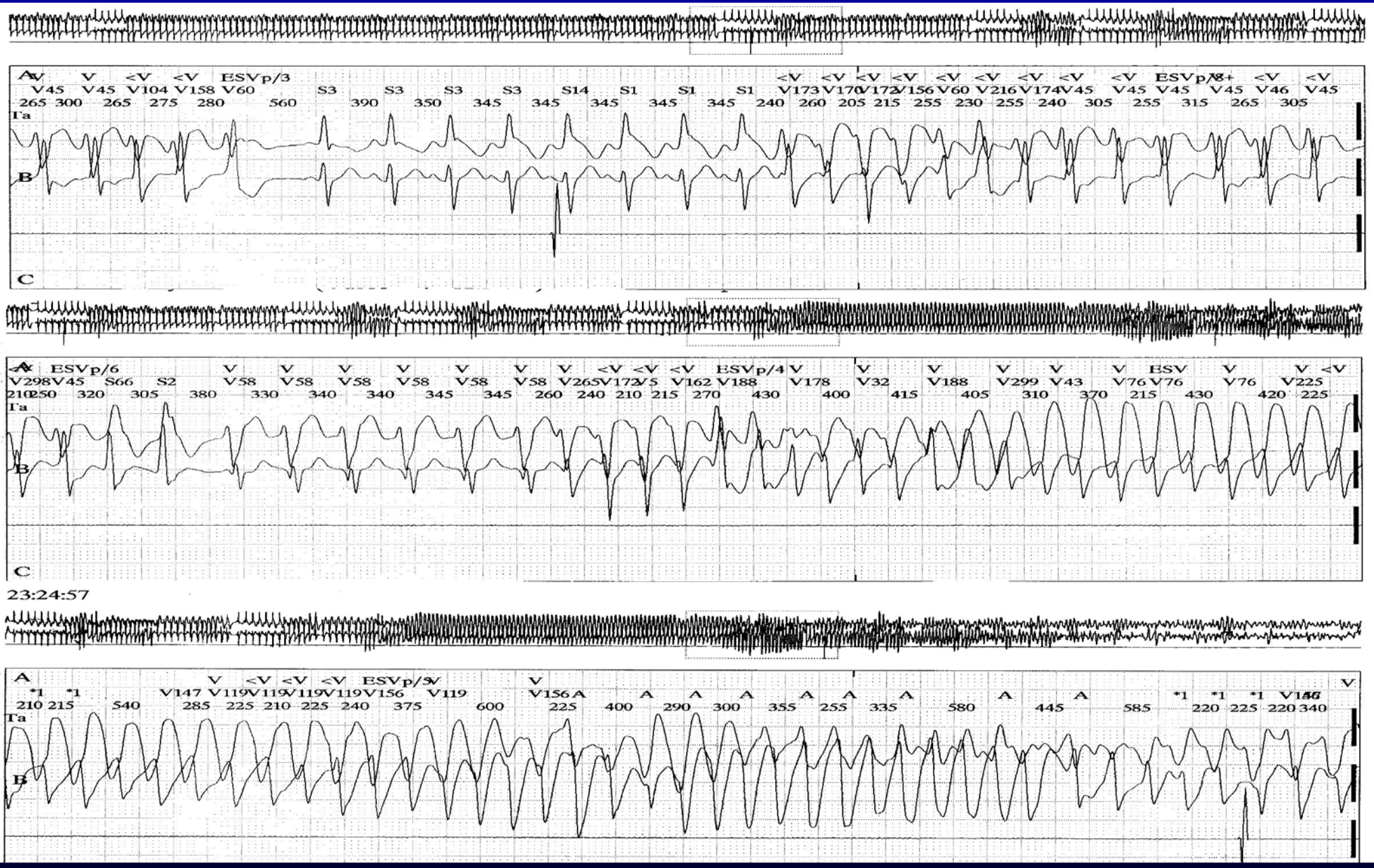
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- Negative autopsy
- Familial screening was negative.
- Genetic study confirms CPVT with a RyR2 mutation Phe 4020 Leu Exon 90 in this little girl.
- This mutation was not found in her family.

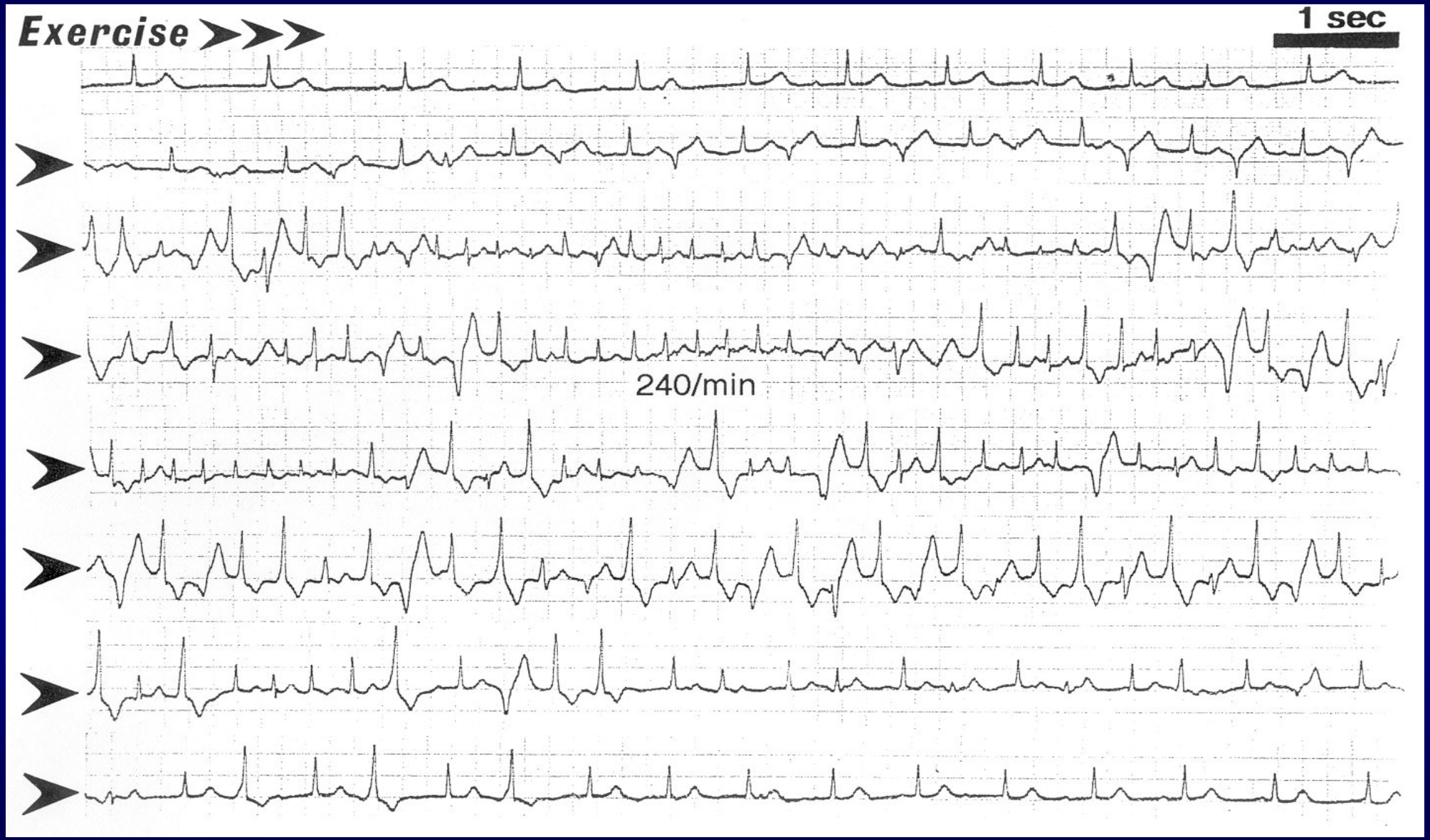
Catecholaminergic Polymorphic VT

- Children (mean age : 10 years at the time of the diagnosis), referred for *stress*- or *emotion-induced syncope* : key element.
- Diagnosis often delayed : in almost half of the cases, these children are initially treated as epileptic for several months and even years.
- Family history often positive (30 %) for sudden cardiac death or syncope in relation to similar triggers.

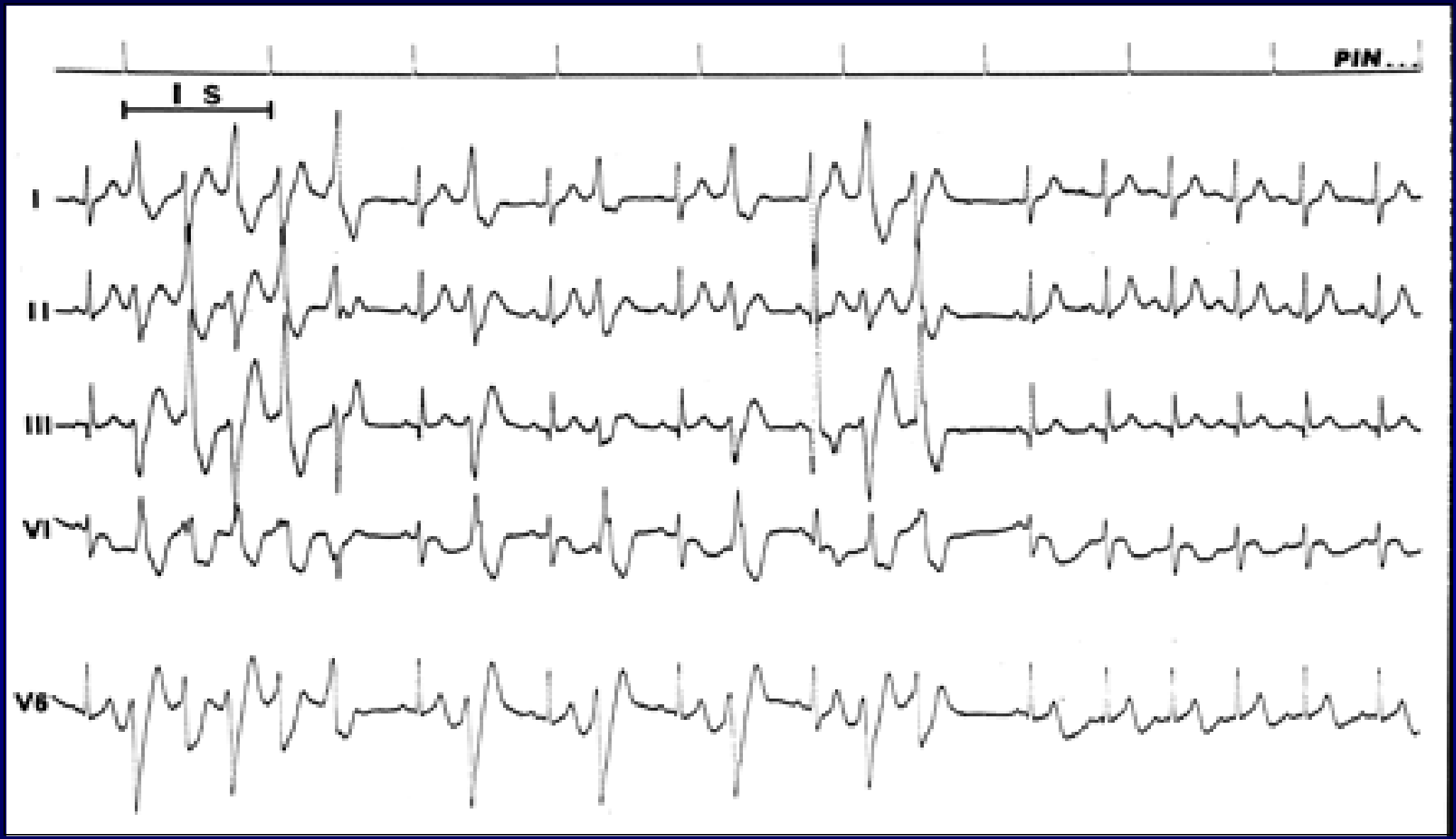
✓ *Leenhardt A et al. Catecholaminergic Polymorphic Ventricular Tachycardia in Children Circulation. 1995;91:1512-1519*

✓ *Coumel P et al. Catecholamine-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. Br Heart J. 1978;40:28-37*

Catecholaminergic Polymorphic Ventricular Tachycardia



A Leenhardt et al. Circulation 1995; 91: 1512-9.



A Leenhardt et al. Circulation 1995; 91: 1512-9.

Prevalence of CPVT in SCD Cohort

Among 49 cases of SCD with unknown origin, molecular autopsy disclosed *RYR2* and LQTS related mutation in 7 (14%) and 10 patients (20%), respectively.

Tester DJ, et al. J Am Coll Cardiol 2007;49:240

Among 173 ca[illegible] negative[illegible] y.o.), *RYR2* and LQTS relate[illegible] was see[illegible] 25 patients (14%), respective[illegible]

Clin Proc 2012; 87: 524-39

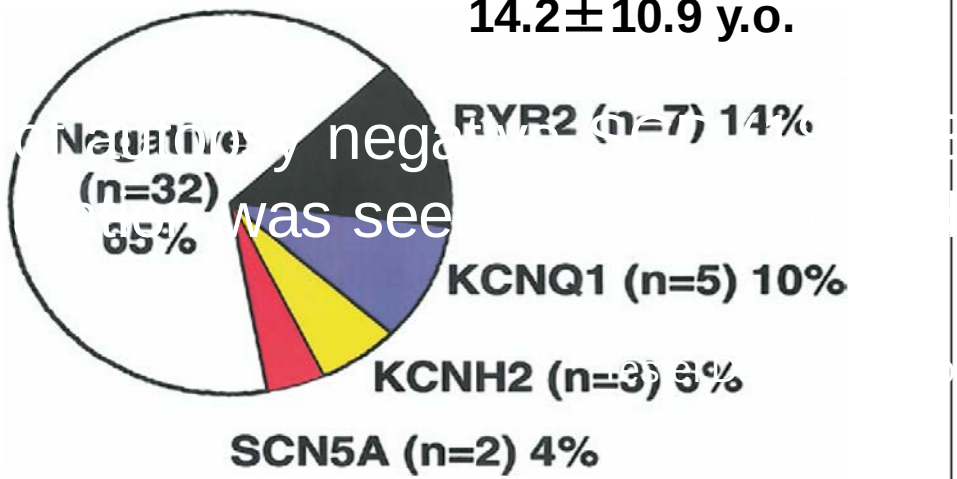


Figure 2 **Summary of the Yield of Postmortem Cardiac Channel Genetic Testing in Cases of Autopsy-Negative SUD**

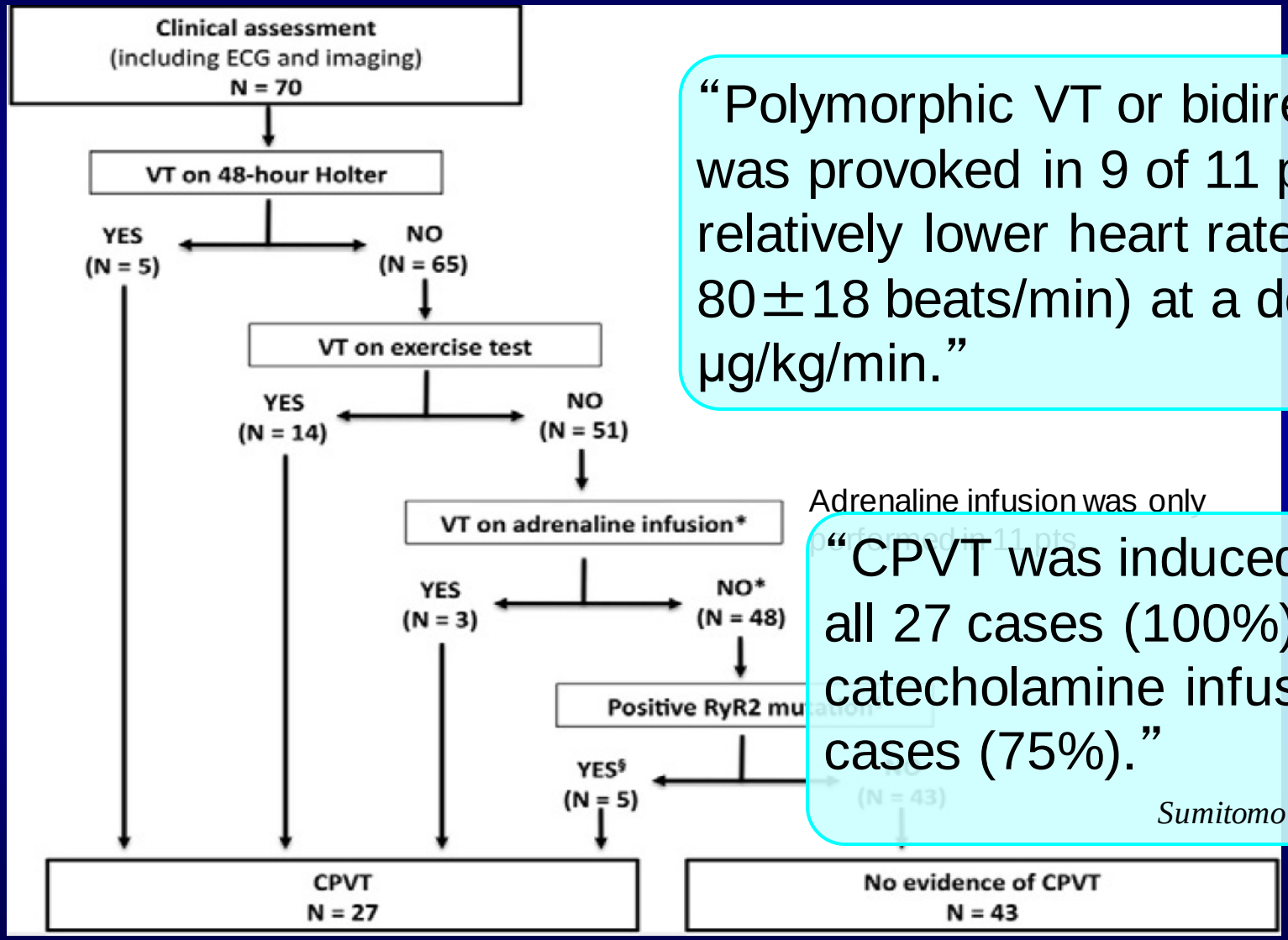
Depicted is a pie chart summarizing the frequency and distribution of cardiac channel genotypes detected after a molecular autopsy of 49 medical examiner/coroner-referred cases of sudden unexplained death (SUD).

Diagnosis of CPVT

CPVT is diagnosed in the presence of :

- Unexplained exercise or catecholamine induced bidirectional or polymorphic VTs
- In a patient with a structurally normal heart (and normal coronary artery if > 40 years)
- Normal ECG (low heart rate at rest)
- When evaluating relatives of a CPVT index case, the diagnosis of CPVT should be considered among family members who manifest exercise induced PVCs in the absence of heart disease.

Catecholamine stress for the diagnosis



"Polymorphic VT or bidirectional VT was provoked in 9 of 11 patients at relatively lower heart rates (mean 80±18 beats/min) at a dose of 0.20 μg/kg/min."

Adrenaline infusion was only performed in 11 pts

"CPVT was induced by exercise in all 27 cases (100%) and by catecholamine infusion in 12 of 16 cases (75%)."

Sumitomo N, et al. Heart 2003; 89: 66

Sy RW, et al. Heart Rhythm 2011;8:864–71

Catecholamine stress for the diagnosis

TABLE 3

Results of the Intravenous Epinephrine Infusion Test

	All	*RYR2* Mutation Carriers	Genetically Undefined CPVT Patients	Family Members	*P*
n	81	25	11	45	
Baseline heart rate (bpm)	81 ± 14	79 ± 13	83 ± 12	82 ± 14	NS
Baseline RRs (mmHg)	127 ± 19	125 ± 17	129 ± 18	127 ± 20	NS
Maximal heart rate (bpm)	101 ± 16	101 ± 14	104 ± 29	101 ± 13	NS
Maximal RRs (mmHg)	156 ± 20	153 ± 21	149 ± 16	159 ± 20	NS
Number of PVCs (n)	0 (0–118)	0 (0–118)	0 (0–79)	0 (0–41)	NS
Maximal PVCs per minute (n)	0 (0–35)	0 (0–24)	0 (0–35)	0 (0–12)	NS
Consecutive PVCs (n)	0 (0–24)	0 (0–24)	0 (0–11)	0 (0–1)	NS
Discontinued test (n)	13 (16%)	4 (16%)	3 (27%)	6 (13%)	NS
Positive epinephrine test (n)	8 (10%)	3 (12%)	4 (36%)	1 (2%)	NS

Values are presented as mean ± SD continuous normally distributed variables, as median (range) for non-normally distributed variables, and as number of subjects (%) for categorical variables. PVC = premature ventricular complex.

TABLE 5

Comparison of the Maximal Exercise Stress Test and Intravenous Epinephrine Infusion (n = 81)

	Exercise Stress Test	
Epinephrine Test	**Positive**	**Negative**
Positive	7	1
Negative	18	55
All	25	56

"Intravenous epinephrine infusion test cannot replace the maximal exercise stress test in facilitating diagnosis of CPVT due to its low sensitivity."

Marjamaa A, et al. J Cardiovasc Electrophysiol 2012; 23: 194-9

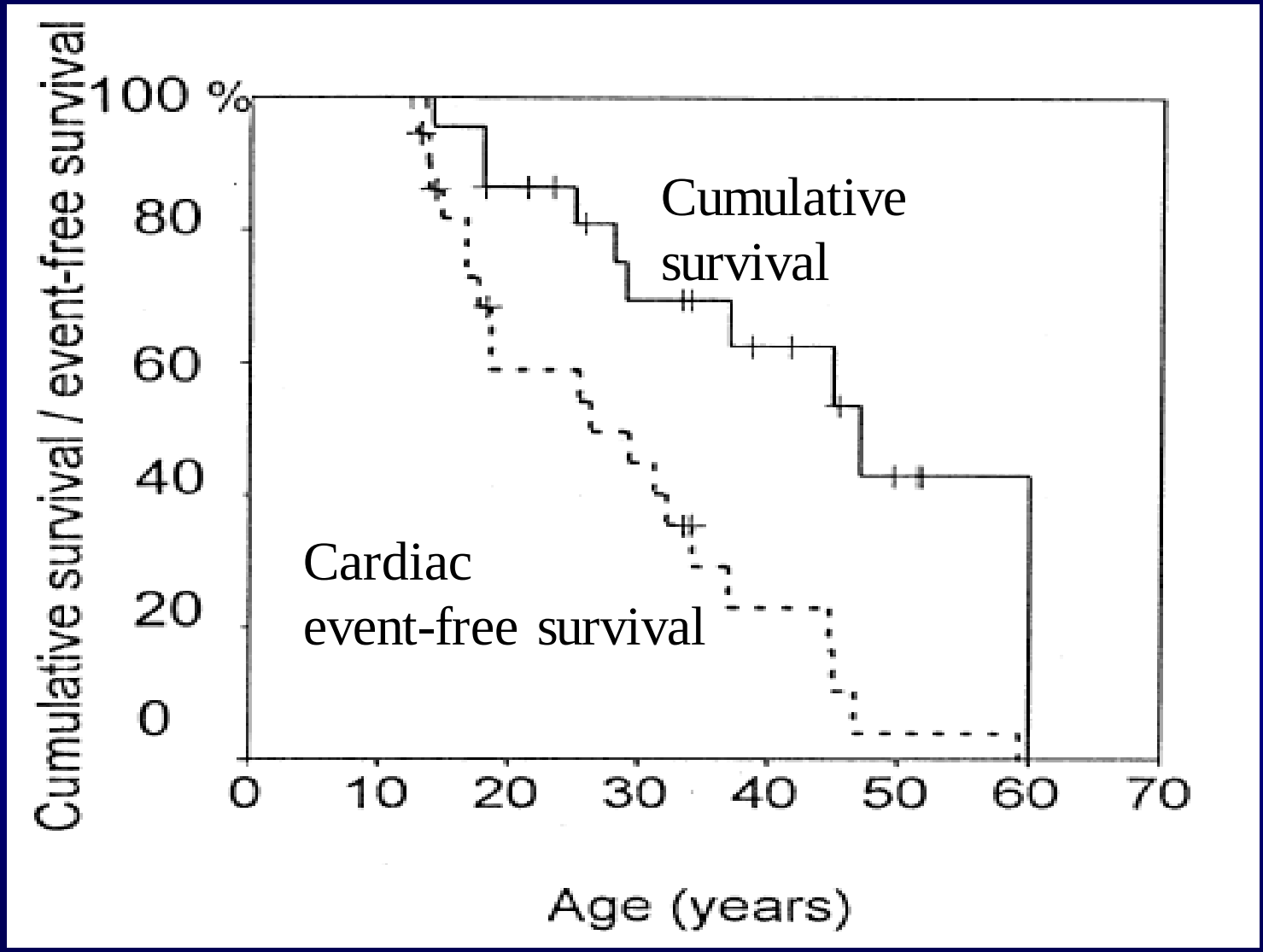
Genetic of catecholaminergic polymorphic VT

Gene	Locus	Protein	Frequency
*RYR2** (CPVT1)	1q42.1-q43	Ryanodine receptor 2	50–60%
*KCNJ2** (CPVT3)	17q23	Kir2.1	10%
*CASQ2** (CPVT2)	1p13.3-p11	Calsequestrin 2	1–2%
TRDN		Triadin	?

Mutations identified in 60% of patients meeting the definition of CPVT

From DJ Tester and MJ Ackerman Circulation. 2011;123:1021-37.
and Roux-Buisson N, et al. Hum Mol Genet 2012; 21: 2759

Prognosis of untreated CPVT patients



Cumulative cardiac mortality by the age of 30 years : 31%

Swan H, et al. J Am Coll Cardiol 1999;34:2035

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

Meiso Hayashi, MD; Isabelle Denjoy, MD; Fabrice Extramiana, MD, PhD; Alice Maltret, MD; Nathalie Roux Buisson, MD; Jean-Marc Lupoglazoff, MD, PhD; Didier Klug, MD; Miyuki Hayashi, MD; Seiji Takatsuki, MD; Elisabeth Villain, MD; Joël Kamblock, MD; Anne Messali, MD; Pascale Guicheney, PhD; Joël Lunardi, MD, PhD; Antoine Leenhardt, MD

Background—The pathophysiological background of catecholaminergic polymorphic ventricular tachycardia is well understood, but the clinical features of this stress-induced arrhythmic disorder, especially the incidence and risk factors of arrhythmic events, have not been fully ascertained.

Methods and Results—The outcome in 101 catecholaminergic polymorphic ventricular tachycardia patients, including 50 probands, was analyzed. During a mean follow-up of 7.9 years, cardiac events defined as syncope, aborted cardiac arrest, including appropriate discharges from implantable defibrillators, or sudden cardiac death occurred in 27 patients, including 2 mutation carriers with normal exercise tests. The estimated 8-year event rate was 32% in the total population and 27% and 58% in the patients with and without β-blockers, respectively. Absence of β-blockers (hazard ratio [HR], 5.48; 95% CI, 1.80 to 16.68) and younger age at diagnosis (HR, 0.54 per decade; 95% CI, 0.33 to 0.89) were independent predictors. Fatal or near-fatal events defined as aborted cardiac arrest or sudden cardiac death occurred in 13 patients, resulting in an estimated 8-year event rate of 13%. Absence of β-blockers (HR, 5.54; 95% CI, 1.17 to 26.15) and history of aborted cardiac arrest (HR, 13.01; 95% CI, 2.48 to 68.21) were independent predictors. No difference was observed in cardiac and fatal or near-fatal event rates between probands and family members.

Conclusions—Cardiac and fatal or near-fatal events were not rare in both catecholaminergic polymorphic ventricular tachycardia probands and affected family members during the long-term follow-up, even while taking β-blockers, which was associated with a lower event rate. Further studies evaluating concomitant therapies are necessary to improve outcome in these patients. (***Circulation***. **2009;119:2426-2434.**)

CPVT patients

Table 1. Baseline Characteristics of the 101 Patients

Proband, n	50
Family member, n	51
Male gender, n	54
Age at first symptom, y	12±8
Age at diagnosis, y	15±10
≤10, n	39
11–20, n	42
≥21, n	20
Severest symptom before the diagnosis, n	
Syncope	45
Aborted cardiac arrest	11
Palpitations or near syncope	5
Asymptomatic before diagnosis, n	40
Corrected QT interval, ms	403±21

M. Hayashi et al. Circulation. 2009;119:2426-34.

CPVT patients

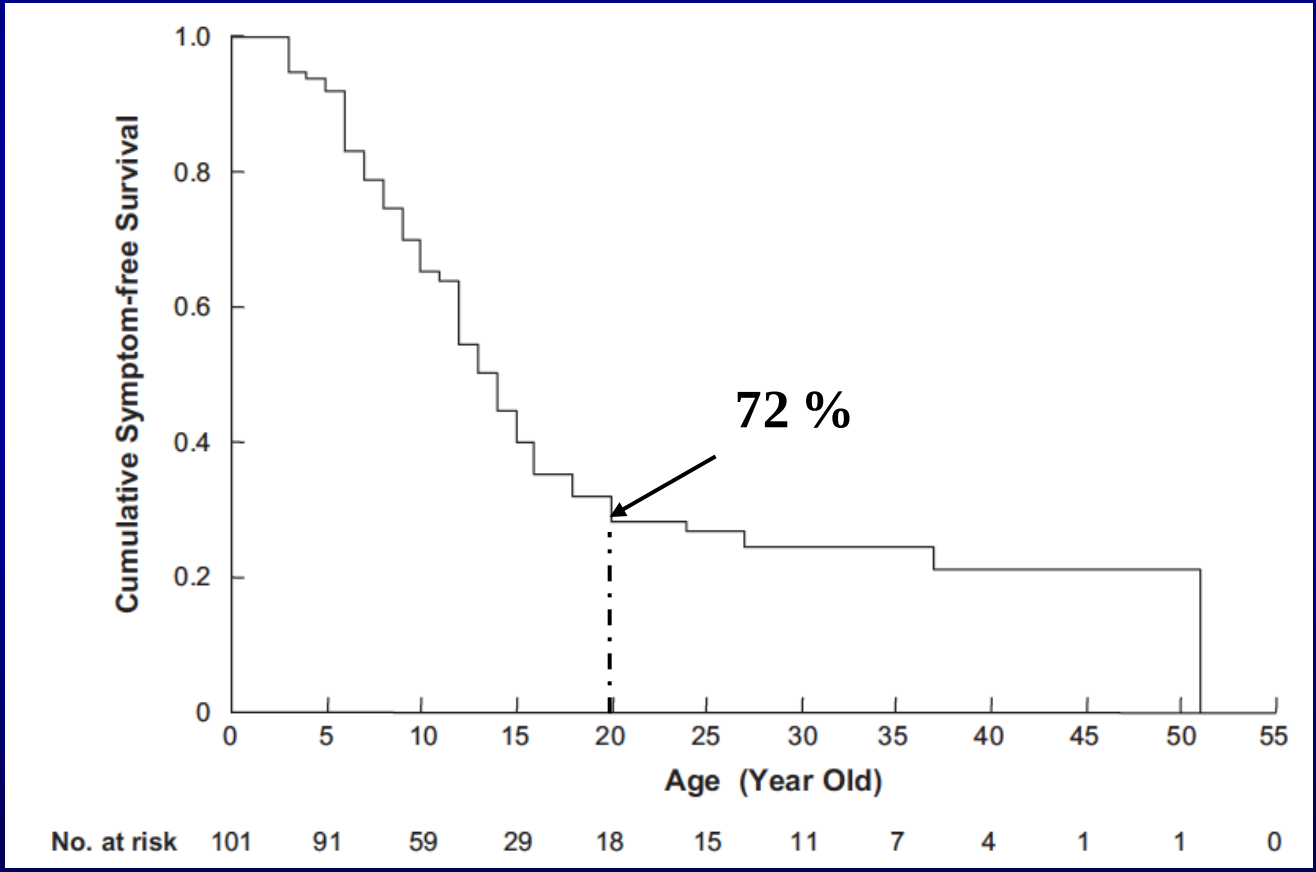
Table 1. Baseline Characteristics of the 101 Patients

Mutation, n	
RYR2	72
CASQ2	7
Not identified, n	16
Not analyzed, n	6
Silent genetic mutation carrier, n	17

M. Hayashi et al. Circulation. 2009;119:2426-34.

CPVT : natural history before the diagnosis

- Cardiac symptoms before the diagnosis were reported in 61 patients (60%): all probands and 11 family members.



Symptom-free survival curve before the diagnosis of CPVT.

M. Hayashi et al. Circulation. 2009;119:2426-34.

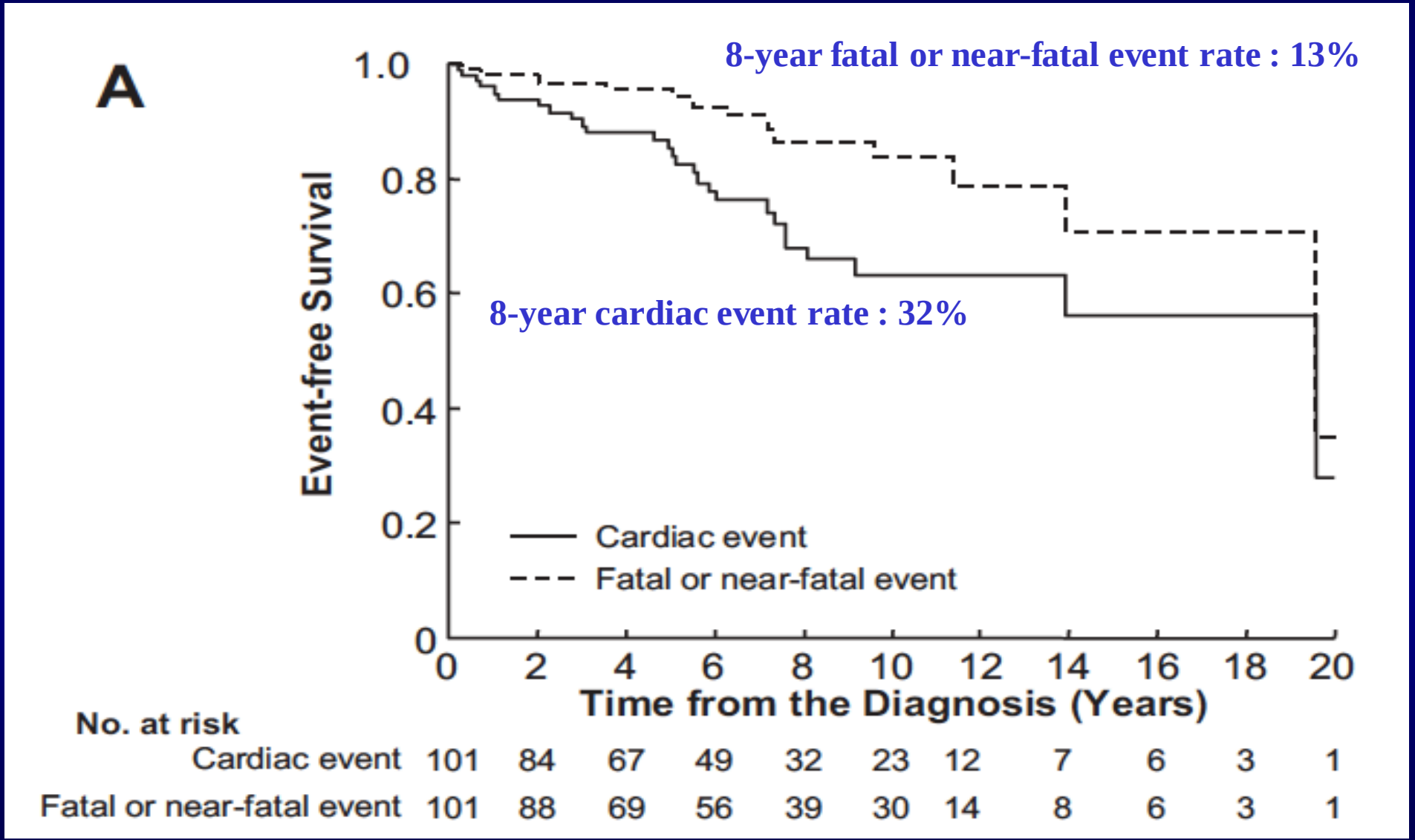
CPVT : follow-up

- Mean F-up : 7.9 ± 4.9 years
- Events :
  - Cardiac events (syncope under physical or emotional stress, ACA, including appropriate ICD discharges, or SCD) : **32%**
  - Fatal or near-fatal events (4 ACA and 5 SCD as first evt) : **13%**

- No difference in the cardiac or fatal or near-fatal event rate between the probands and family members (both in the total study population and in the subgroup of patients treated with beta-blockers).
- No difference between asymptomatic patients with a positive genotype vs symptomatic.

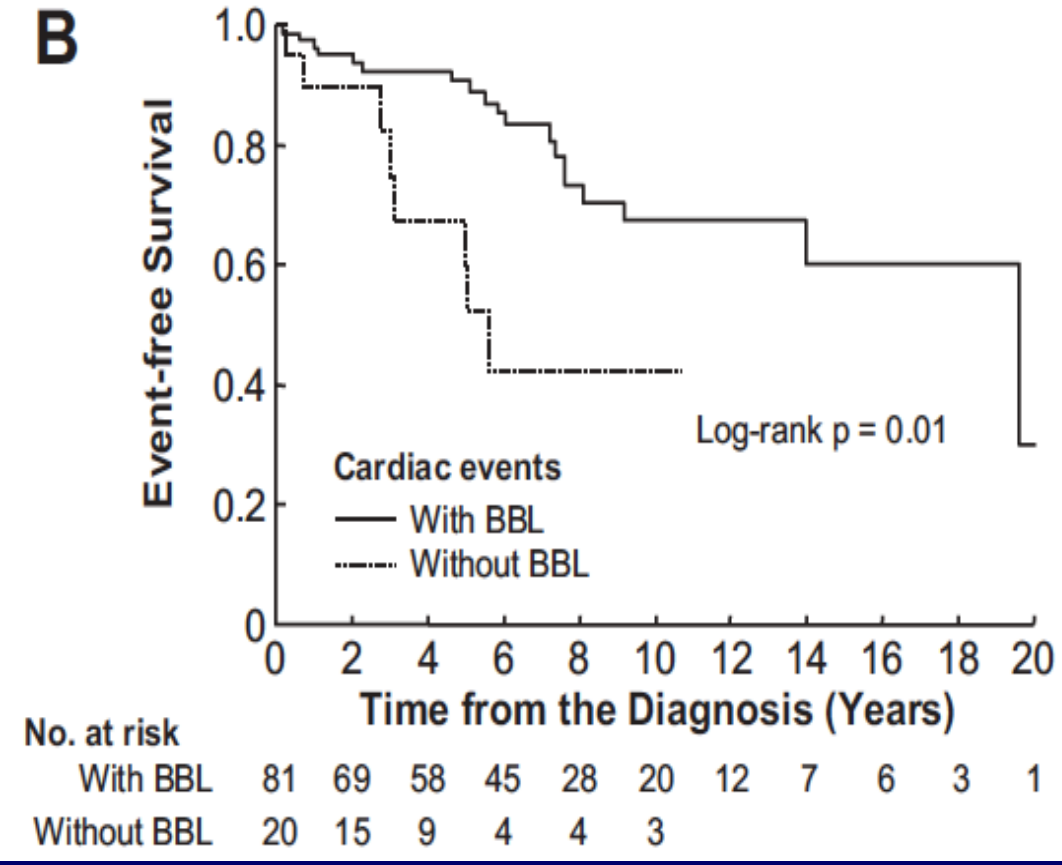
M. Hayashi et al. Circulation. 2009;119:2426-34.

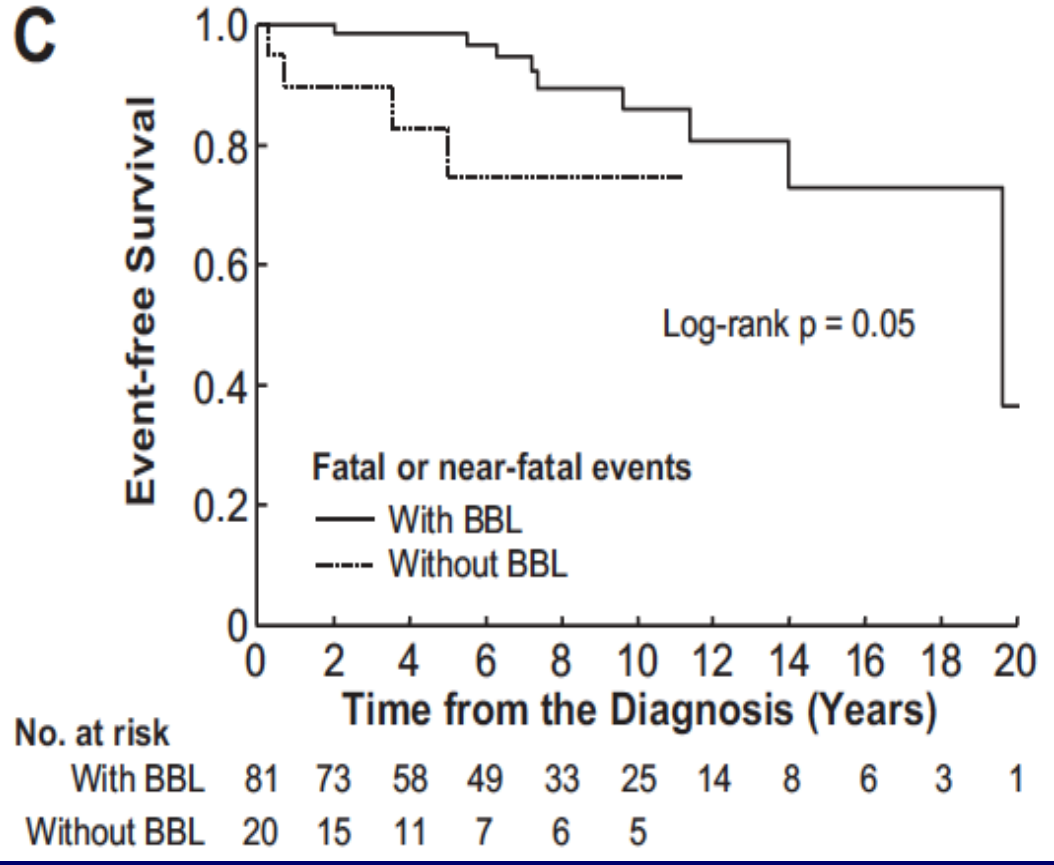
CPVT : follow-up



M. Hayashi et al. Circulation. 2009;119:2426-34.

CPVT : effect of beta-blockers





8-year cardiac event rates : 27 vs 58 %

8-year fatal or near-fatal event rates : 11 vs 25 %

M.Hayashi et al. Circulation. 2009;119:2426-34.

CPVT : effect of beta-blockers

- 27 % of the patients experienced cardiac events « under beta-blocker » :
  - 32 % of them did not take the drug on the day of the event.
  - 5 sudden deaths, 1 without treatment
  - 13 syncope, 4 without any treatment

M.Hayashi et al. Circulation. 2009;119:2426-34.

CPVT : Predictors for developing events

- Fatal or near-fatal events were observed between 13 and 26 years of age in 12 of the 13 patients (92%)
- Independent predictor of future cardiac events (multivariable analysis) :
  - absence of therapy with any beta-blockers
  - younger age at the time of the diagnosis.
- Independent predictor for fatal or near-fatal events (multivariable analysis) :
  - absence of therapy with any beta-blockers
  - history of ACA.

M. Hayashi et al. Circulation. 2009;119:2426-34.

CPVT : effectiveness of beta-blockers

- Significantly lower cardiac and fatal or near-fatal event rates in the patients with beta-blockers. Nonetheless, insufficient effect of beta-blockers.

- Why incomplete effect ?
  - Poor drug compliance ?
  - Type of beta-blocker ? Our non randomized data suggest that taking beta-blockers other than nadolol or too low dosages of nadolol could be associated with higher event rates.
  - Absence of reliable tests to ascertain the treatment's efficacy ?

M. Hayashi et al. Circulation. 2009;119:2426-34.

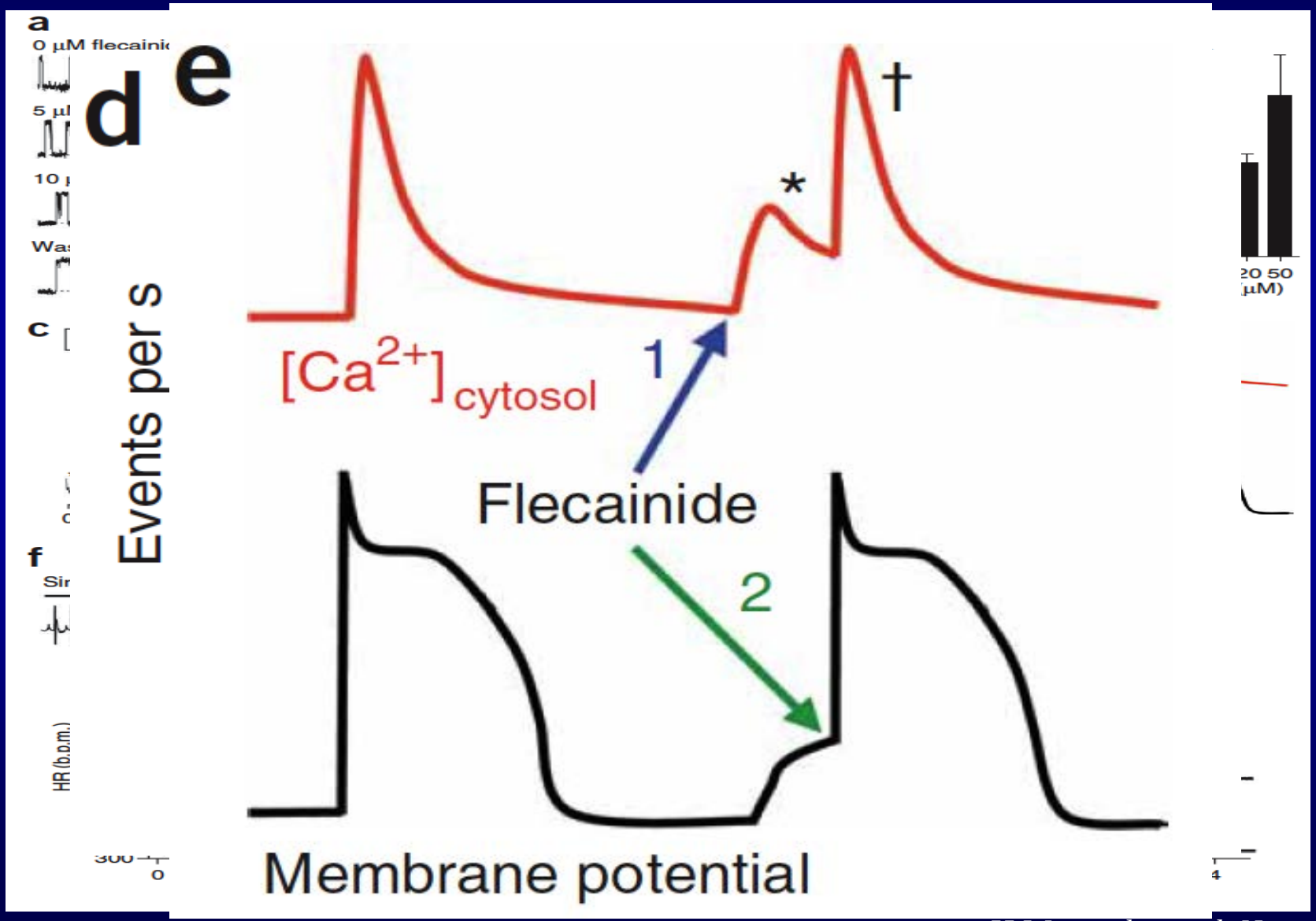
CPVT and beta-blockers : Summary

- Beta-blockers without sympathomimetic activity are recommended in all symptomatic patients with a diagnosis of CPVT.
- Beta-blockers without sympathomimetic activity are useful in asymptomatic CPVT patients with or without pathogenetic mutation.
- Recommended lifestyle changes in all CPVT patients : Avoiding competitive sports, avoiding strenuous exercise and limiting exposure to excessive emotional stress

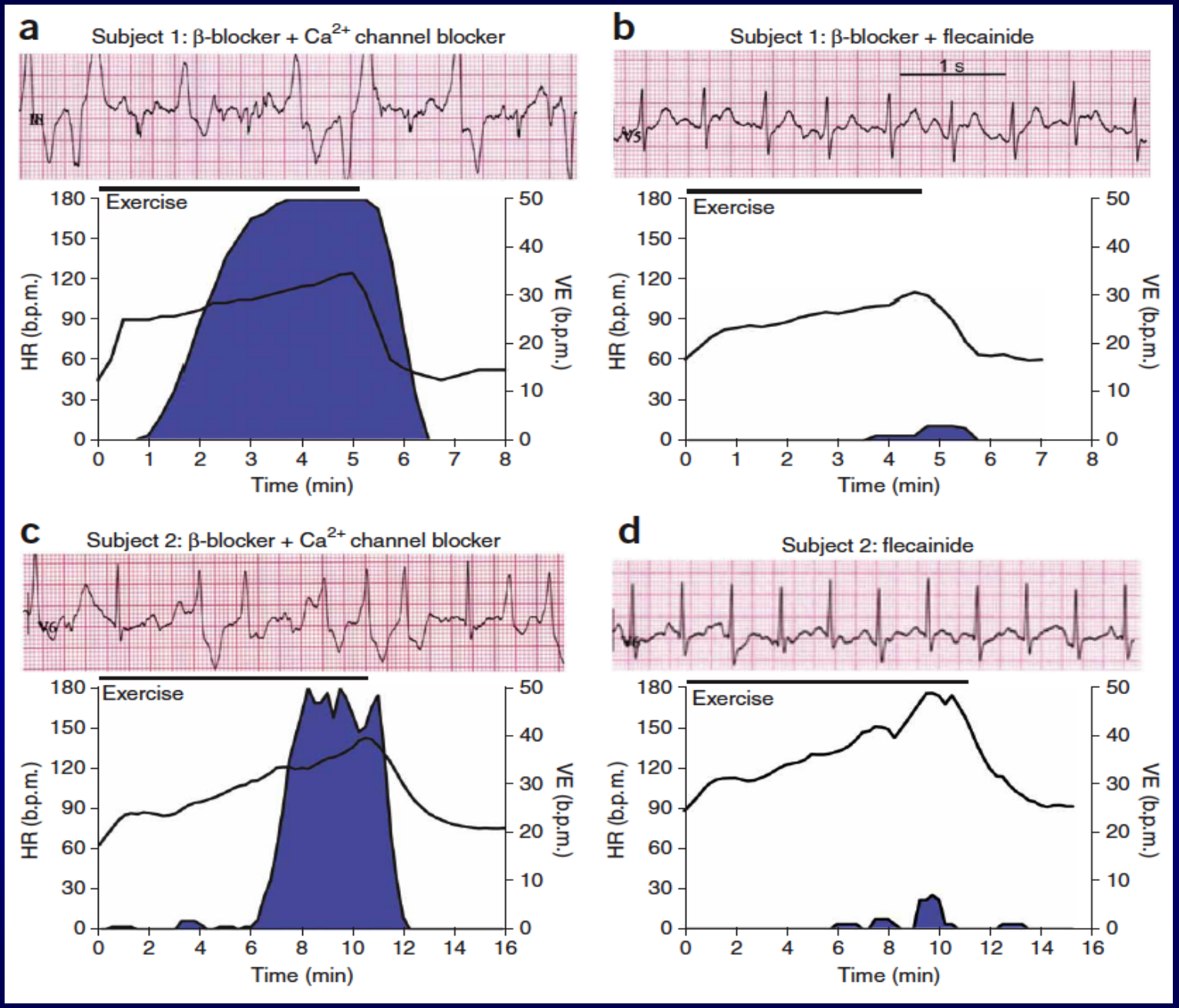
Other therapeutic options in CPVT

- Other drugs :
  - verapamil
  - flecainide
  - inhibitors of RyR2
- Surgical option : Left cardiac sympathetic denervation
  ICD

Flecainide inhibits RyR2 Ca2+ release channels, reduces spontaneous Ca2+ release events, triggered beats and prevents VT in a CPVT mouse model



H Watanabe et al. Nature Science 2009



Flecainide treatment prevents exercise induced ventricular arrhythmia in two subjects with CPVT refractory to conventional drug therapy

H Watanabe et al. Nature Science 2009

Flecainide Therapy Reduces Exercise-Induced Ventricular Arrhythmias in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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Andrew D. Krahn, MD,¶ Sami Viskin, MD,# Antoine Leenhardt, MD,**
Wataru Shimizu, MD, PHD,†† Naokata Sumitomo, MD,‡‡ Frank A. Fish, MD,‡
Zahurul A. Bhuiyan, MD, PHD,† Albert R. Willems, MD, PHD,*

Thirty-three patients received flecainide because of exercise-induced ventricular arrhythmias despite conventional (for different reasons, not always optimal) therapy (median age 25 years; range 7 to 68 years; 73% female). Exercise tests comparing flecainide in addition to conventional therapy with conventional therapy alone were available for 29 patients. Twenty-two patients (76%) had either partial (n = 8) or complete (n = 14) suppression of exercise-induced ventricular arrhythmias with flecainide ($p < 0.001$). No patient experienced worsening of exercise-induced ventricular arrhythmias. The median daily flecainide dose in responders was 150 mg (range 100 to 300 mg). During a median follow-up of 20 months (range 12 to 40 months), 1 patient experienced implantable cardioverter-defibrillator shocks for polymorphic ventricular arrhythmias, which were associated with a low serum flecainide level. In 1 patient, flecainide successfully suppressed exercise-induced ventricular arrhythmias for 29 years.

Results Thirty-three patients received flecainide because of exercise-induced ventricular arrhythmias despite conventional (for different reasons, not always optimal) therapy (median age 25 years; range 7 to 68 years; 73% female). Exercise tests comparing flecainide in addition to conventional therapy with conventional therapy alone were available for 29 patients. Twenty-two patients (76%) had either partial (n = 8) or complete (n = 14) suppression of exercise-induced ventricular arrhythmias with flecainide ($p < 0.001$). No patient experienced worsening of exercise-induced ventricular arrhythmias. The median daily flecainide dose in responders was 150 mg (range 100 to 300 mg). During a median follow-up of 20 months (range 12 to 40 months), 1 patient experienced implantable cardioverter-defibrillator shocks for polymorphic ventricular arrhythmias, which were associated with a low serum flecainide level. In 1 patient, flecainide successfully suppressed exercise-induced ventricular arrhythmias for 29 years.

Conclusions Flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy. (J Am Coll Cardiol 2011;57:2244–54)

Inhibition of Cardiac Ca^{2+} Release Channels (RyR2) Determines Efficacy of Class I Antiarrhythmic Drugs in Catecholaminergic Polymorphic Ventricular Tachycardia

Hyun Seok Hwang, PhD; Can Hasdemir, MD; Derek Laver, PhD; Divya Mehra, BPharm; Kutsal Turhan, MD; Michela Faggioni, MD; Huiyong Yin, PhD; Björn C. Knollmann, MD, PhD

Conclusions—RyR2 cardiac Ca^{2+} release channel inhibition appears to determine efficacy of class I drugs for the prevention of CPVT in $Casq2^{-/-}$ mice. Propafenone may be an alternative to flecainide for CPVT patients symptomatic on β-blockers. (***Circ Arrhythm Electrophysiol.*** **2011;4:128-135.**)

CPVT : Guidelines 2006

- Class I
  - 1. Beta blockers are indicated for patients who are clinically diagnosed with CPVT on the basis of the presence of spontaneous or documented stress induced ventricular arrhythmias. *(Level of Evidence: C)*
  - 2. Implantation of an ICD with use of beta blockers is indicated for patients with CPVT who are survivors of cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: C)*
- Class IIa
  - 1. Beta blockers can be effective in patients without clinical manifestations when the diagnosis of CPVT is established during childhood based on genetic analysis. *(Level of Evidence: C)*
  - 2. Implantation of an ICD with the use of beta blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: C)*
- Class IIb
  - Beta blockers may be considered for patients with CPVT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. *(Level of Evidence: C)*

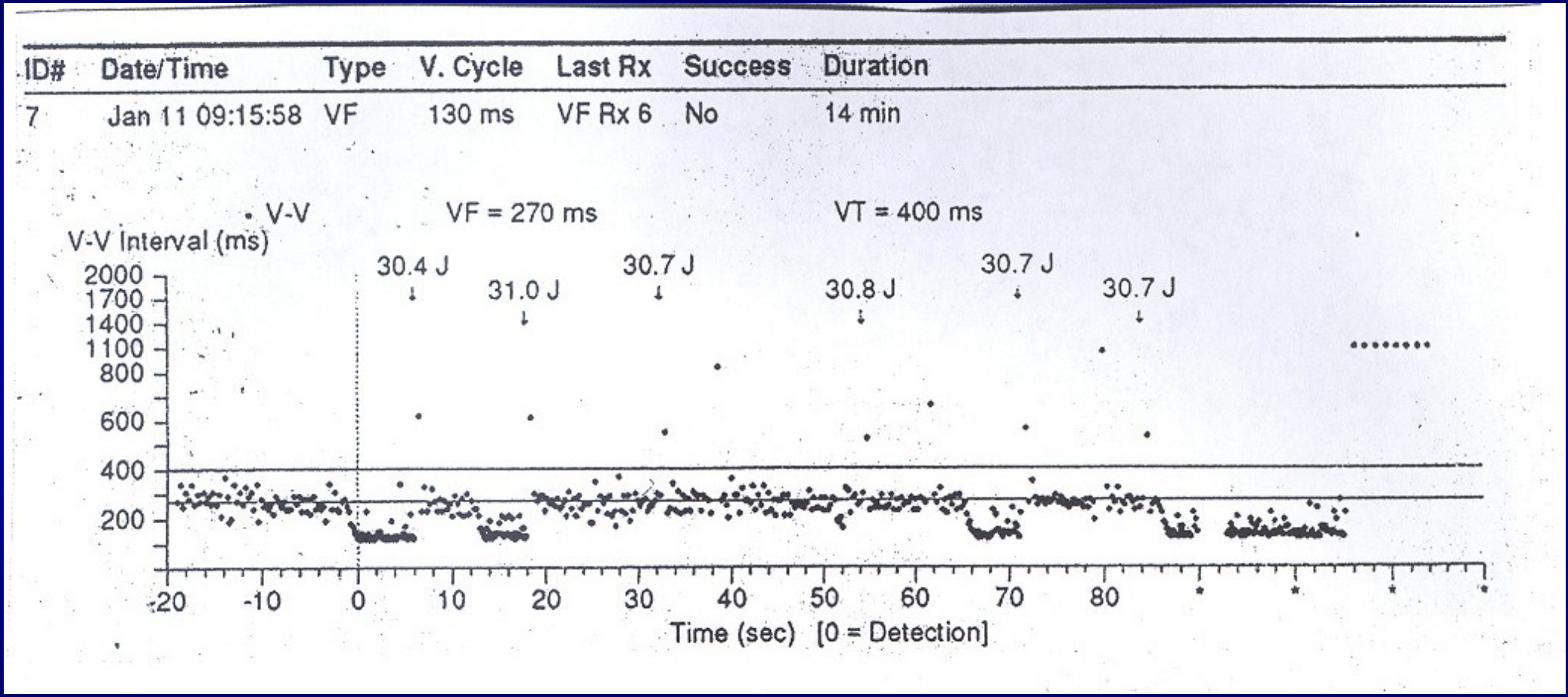
ACC/AHA/ESC 2006 Guidelines JACC 2006;48:e247–e346

CPVT : Guidelines for device-based therapy

- Risk stratification for SCD in catecholaminergic polymorphic VT is not possible given the relatively small number of patients reported
- Beta blockers appear to be an effective treatment
- Patients who have had an episode of VF are considered at higher risk and are usually treated with an ICD in addition to beta-blocker therapy
- The recurrence of sustained VT, hemodynamically untolerated VT, or syncope for which causes other than VT are excluded while the patient is receiving a beta blocker are similarly considered markers of higher risk

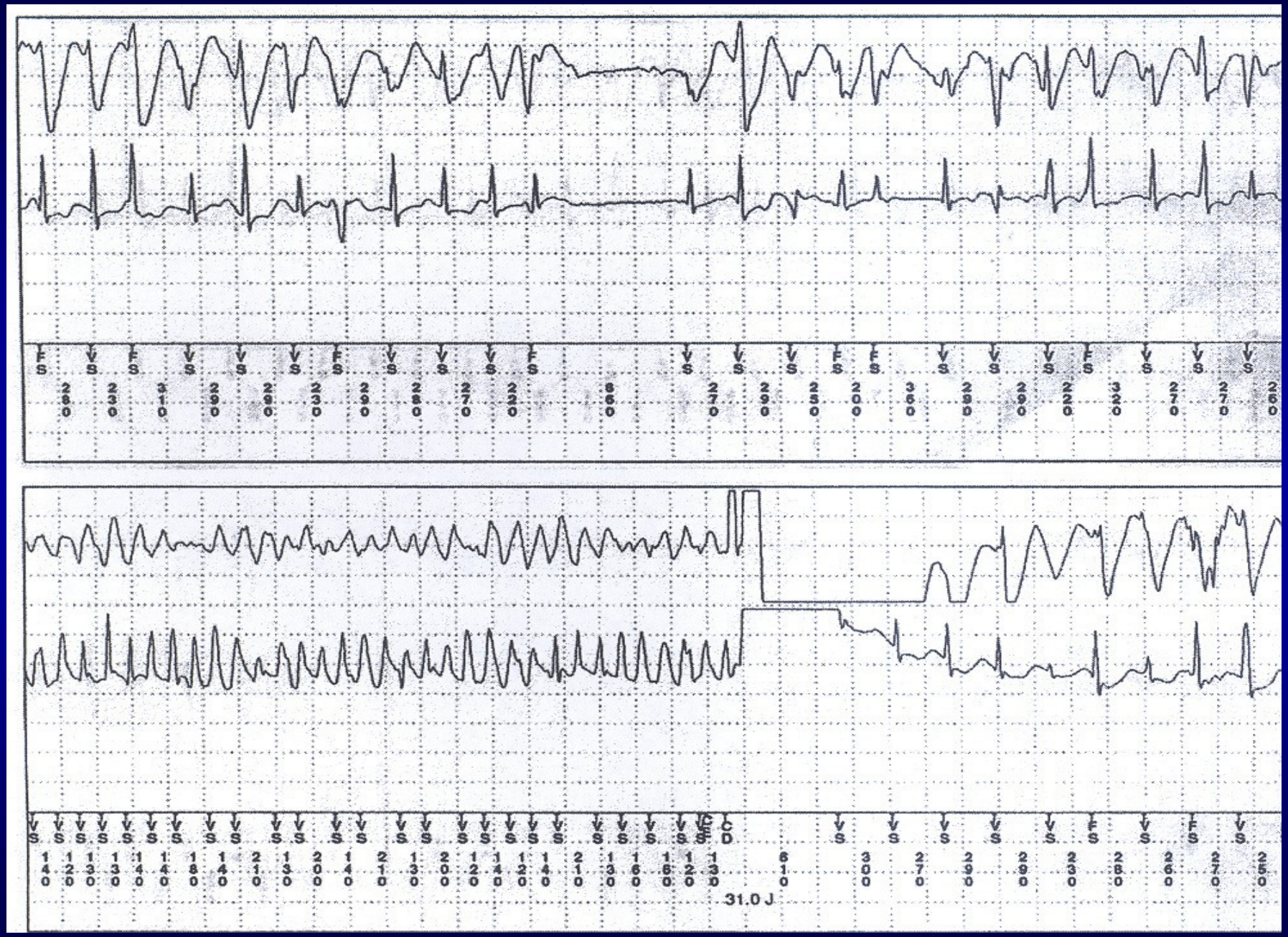
ACC/AHA/HRS Guidelines for Device-Based Therapy. Circulation. 2008;117:e350-e408.)

ICD in Catecholaminergic Polymorphic VT



Painful appropriate shocks trigger further adrenergic stress and arrhythmias.

U. Mohamed et al Heart Rhythm 2006; 12: 1486-9.



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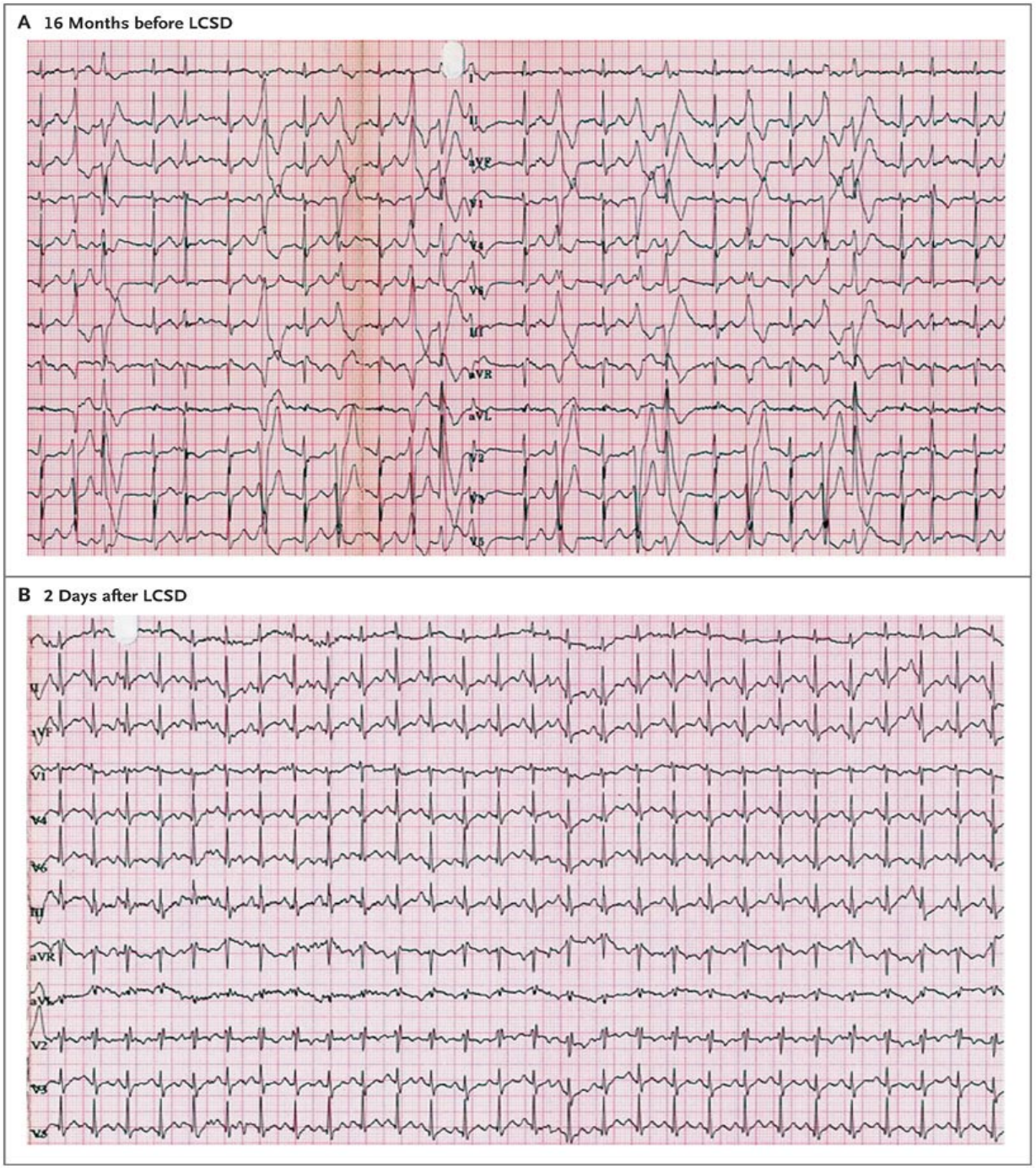

Left cardiac sympathetic denervation in CPVT patient

Surgical technique not universally available, and only been tested in small cohorts.

May be useful in CPVT patients with recurrent syncope or polymorphic VTs while on beta blockers.

From Wilde AAM et al. N Engl J Med 2008;358:2024-9

Unusual features of the case report

- Inaugural sudden death in CPVT : rare
- Mean age of SD in CPVT : 15-20 years, often preceded by syncope
- De novo mutation : rare
- What to do with her brother and sister if the mutation is present in these two children ?
- Molecular autopsy of RyR2 should be considered as a part of the comprehensive medicolegal autopsy investigation of a SUD case and CPVT should be scrutinized carefully in family members of those who experience SUD.

How to manage a CPVT patient in practice

- Treat all phenotypically and/or genotypically diagnosed CPVT patients (questionnable in newly diagnosed asymptomatic elderly adults).
- No competitive sports and importance of drug compliance.
- Use of sympathomimetic agents contraindicated.
- β-blocker as the first line therapy, at the highest tolerable dose, preferably nadolol.
- Flecainide (verapamil ?) may be added, when failure of β-
- In resistent patients discuss LCSD or an ICD on top of the medical therapy.
- Careful monitoring by exercise testing, Holter monitoring.

Conclusion

- Beta -blockers should be prescribed in every CPVT patient regardless of symptoms.
- Further clinical studies should more precisely define the risks and benefits of verapamil, flecainide, other RyR2 inhibitors, and of LCSD.
- The indications of ICD are probably to large in the last recommendations. They should be carefully discussed, on a case by case basis, in the light of other therapeutical alternatives.

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Connie R. Bezzina, Arthur A.M. Wilde

Publications

	Year published	Study subjects		Mean Follow-up period (yrs)	Patients treated with BBLs	Patients with	
		Proband	Family Member			cardiac events	SCD
Leenhardt et al [1]	1995	20	1	7.0	21 (100%)	3 (14%)	2 (10%)
Swan et al [2]	1999	14 (in 2 families)		8	14 (100%)	1 (7%)	0
Lahat et al [3]	2001	13 (in 7 families)		1.7	13 (100%)	2 (15%)	0
Bauce et al [4]	2002	43 (in 8 families)		6.5	26 (60%)	1 (2%)	1 (2%)
Priori et al [5]	2002	30	9	3.3, 4.3 *	39 (100%)	18 (46%)	
Sumitomo et al [6]	2003	25	4	6.8	28 (97%)	18 (62%)	7 (24%)
Postma et al [7]	2005	12	42	2.0 †	50 (93%)	1 (2%)	1 (2%)
Hayashi et al [8]	2009	50	51	7.9	81 (80%)	27 (27%)	5 (5%)
Celiker et al [9]	2009	13	3	2.5	15 (94%)		4 (25%)
Haugaa et al [10]	2010	6	24	1.8	30 (100%)	1 (3%)	1 (3%)
Sy et al [11]	2011	16	11	6.2	25 (93%)	7 (26%)	2 (8%)
van der Werf et al [12]	2012	18	98	7.8, 4.7‡	98 (84%)	6 (5%)	0

Data are number (%) unless otherwise stated. SCD = sudden cardiac death. BBLs = beta-blockers.
* 3·3 years in patients with mutation in ryanodine receptor and 4·3 years in nongenotyped patients.
† Median follow-up period. ‡ 7.8 years in the probands and 4.7 years in the relatives.

(1) Circulation 1995; 91: 1512–9
(2) J Am Coll Cardiol 1999; 34: 2035–42
(3) Circulation 2001; 103: 2822–7
(4) J Am Coll Cardiol 2002; 40: 341–9
(5) Circulation 2002; 106: 69–74
(6) Heart 2003; 89: 66–70
(7) J Med Genet 2005; 42: 863–70
(8) Circulation 2009: 119: 2426
(9) Cardiol Young 2009; 19: 45–52
(10) Europace 2010; 12: 417-23
(11) Heart Rhythm 2011; 8: 814–71
(12) Circ Arrhythm Electrophysiol 2012; 5: 748-56

Two subgroups of CPVT ?

1. *« Juvenile type »* :
   - clinical symptoms at around 10 years of age
   - no gender difference,
   - more likely to have a *RyR2* mutation
   - greater risk of sudden cardiac death.

2. *« Adult type »* :
   - clinical symptoms later than 20 years of age (mean 40 y.)
   - predominantly in females
   - less likely to have a *RyR2* mutation
   - less likely to be associated with sudden cardiac death.

Sy RW et al. Heart Rhythm 2011;8:864–71.
Sumitomo N. Heart Rhythm 2011;8:872–3.