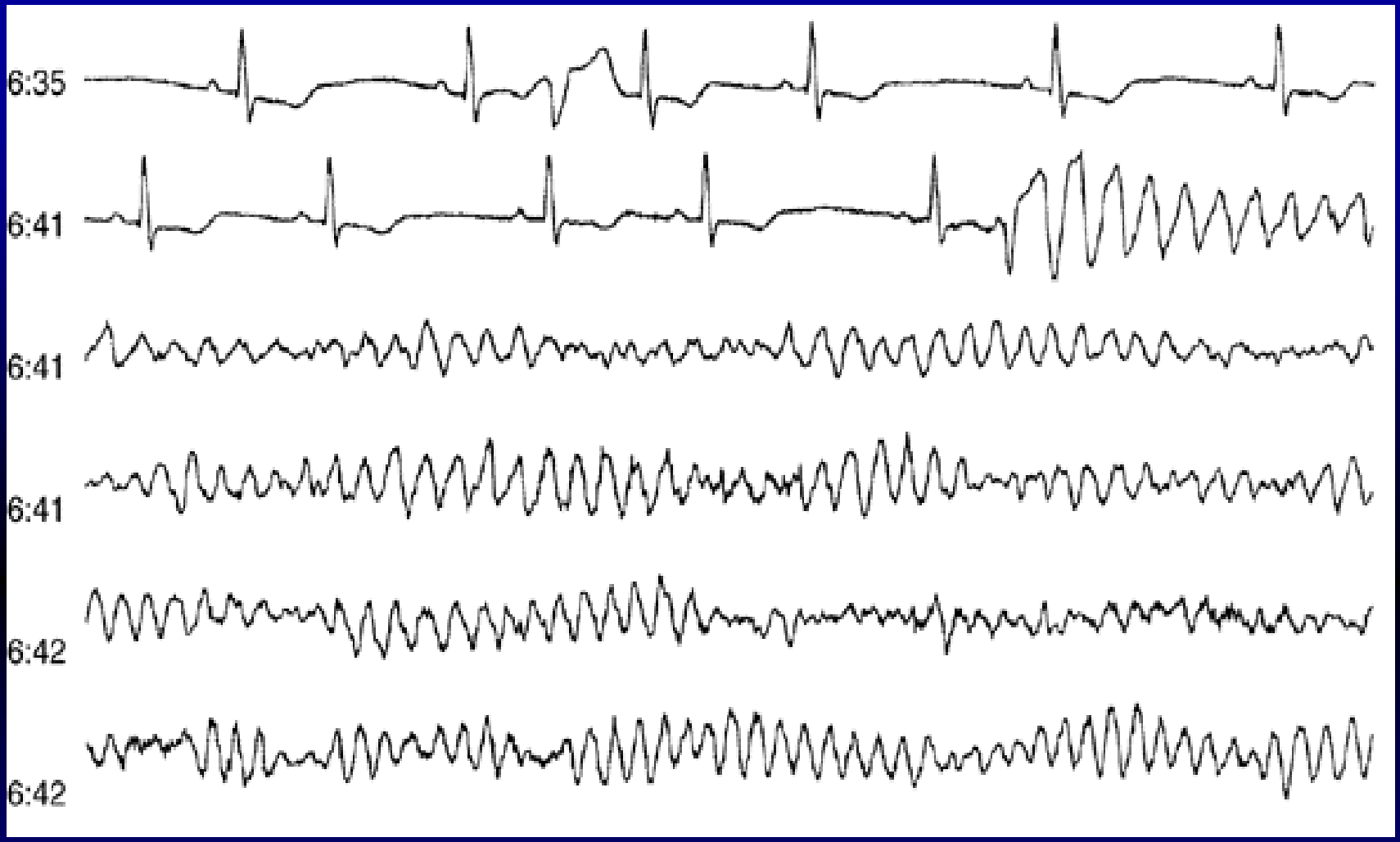
J. G. Mendel



Sudden cardiac death

(USA 400.000 deaths/year)

Paris prospective study

>7000 males followed cca 23 years

Multivariant analysis of relative risk of sudden cardiac death (SCD)

	RR	P
BMI	1,21	0,03
Smoking	1,34	0,0001
Diabetes	2,21	0,02
Heart rate	1,22	0,007
Systolic BP	1,23	0,02
Cholesterol	1,23	0,0001
Fam. history of MI	1,16	-
Family history of SCD		
- in one parent	1,8	0,01
- in both parents	**9,4**	

Familial occurence of SCD in common population

- Being aware of external risk factors shared in a particular family it is obvious that genetically determined variations of physiological proceses must exist that increase the risk of SCD.

- In these cases mutations of single genes does not play crucial role. Etiology is much more complicated.

Pathophysiology of SCD on molecular level

1) processes of electric impulse creation and propagation in myocardium

2) processes and factors of aterosclerotic plaque stability, thrombosis and ischemia in coronary vessels

3) central and local control of myocardial excitablity and vascular motorics

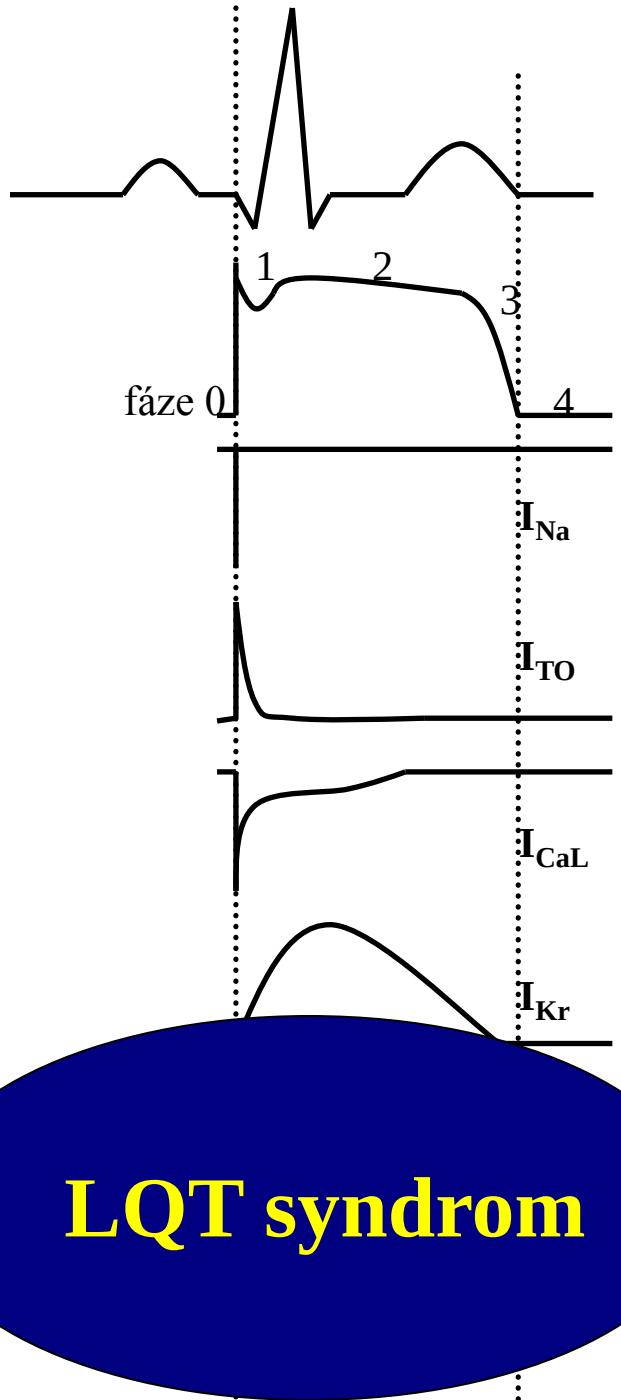
Hereditary arrhythmic diseases

=

a model of arrythmogenesis

Congenital long QT syndrome (LQTS)

- prolongation of QT interval on surface ECG
- syncopi or even sudden death due to polymorphic ventricular tachycardia (torsades de pointes)
- structurally normal heart



LQT syndrom

Ion channel genes

α subunit	**β- subunit**
SCN5A	**SCN1B**
KCND3, KCNA4	
CACNA1A	**CACNB1, B2**
KCNH2	**KCNE2**
KCNQ1	**KCNE1**
KCNJ2, KCNJ12	

LQTS types - genes and proteins

LQTS typ	chromozom	gen	protein
Romano - Ward sy (1:10 000)			
LQT 1			αI_{Ks}
LQT 2			αI_{Kr}
LQT 3			αI_{Na}
LQT 4			nkyrin B
LQT 5			βI_{Ks})
LQT 6			IIRP (βI_{Kr})
(Anders			
Jervell - L			
JLN 1			αI_{Ks}
JLN 2	21q22.1-22.2	*KCNE1*	βI_{Ks}

Prevalence of the Congenital Long-QT Syndrome

Peter J. Schwartz, MD*; Marco Stramba-Badiale, MD, PhD*; Lia Crotti, MD, PhD; Matteo Pedrazzini, PhD; Alessandra Besana, PhD; Giuliano Bosi, MD; Fulvio Gabbarini, MD; Karine Goulene, MD, PhD; Roberto Insolia, PhD; Savina Mannarino, MD; Fabio Mosca, MD; Luigi Nespoli, MD; Alessandro Rimini, MD; Enrico Rosati, MD; Patrizia Salice, MD; Carla Spazzolini, DVM, MS

ECG was performed in 44 596 infants 15 to 25 days old

whites). In infants with a corrected QT interval (QTc) >450 ms, the ECG was repeated within 1 to 2 weeks. Genetic analysis, by screening 7 LQTS genes, was performed in 28 of 31 (90%) and in 14 of 28 infants (50%) with, respectively, a QTc >470 ms or between 461 and 470 ms. A QTc of 451 to 460, 461 to 470, and >470 ms was observed in 177 (0.41%), 28 (0.06%), and 31 infants (0.07%). Among genotyped infants, disease-causing mutations were found in 12

prevalence of at least 1:2534 apparently healthy live births

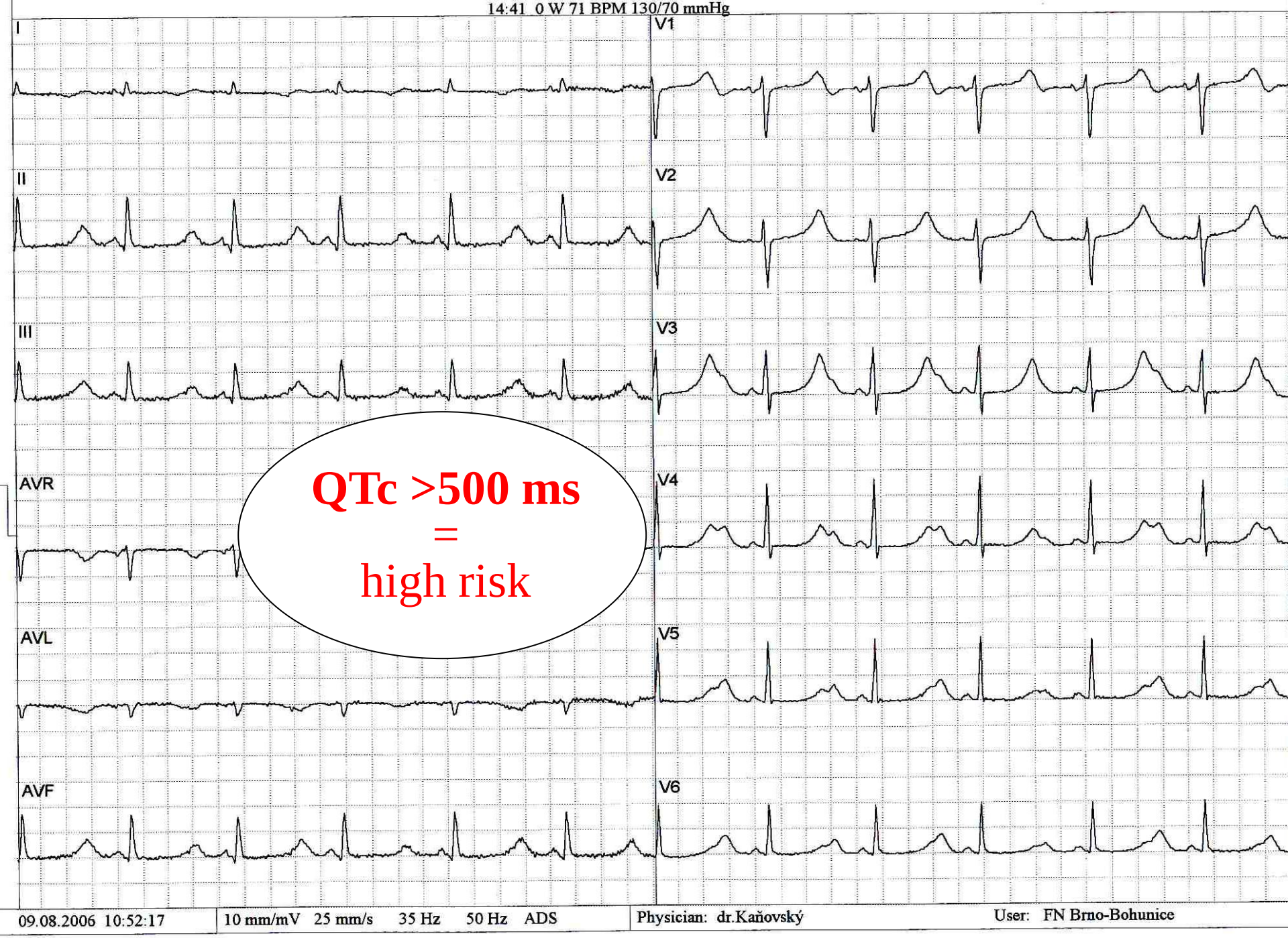
Conclusions—This study provides the first data-based estimate of the prevalence of LQTS among whites. On the basis of the nongenotyped infants with QTc betv close to 1:2000. ECG-guided molecula relatives, thus allowing effective preven

Circulation 2009;120:1761-1767

LQTS diagnostic score (Schwartz et al., 1993)

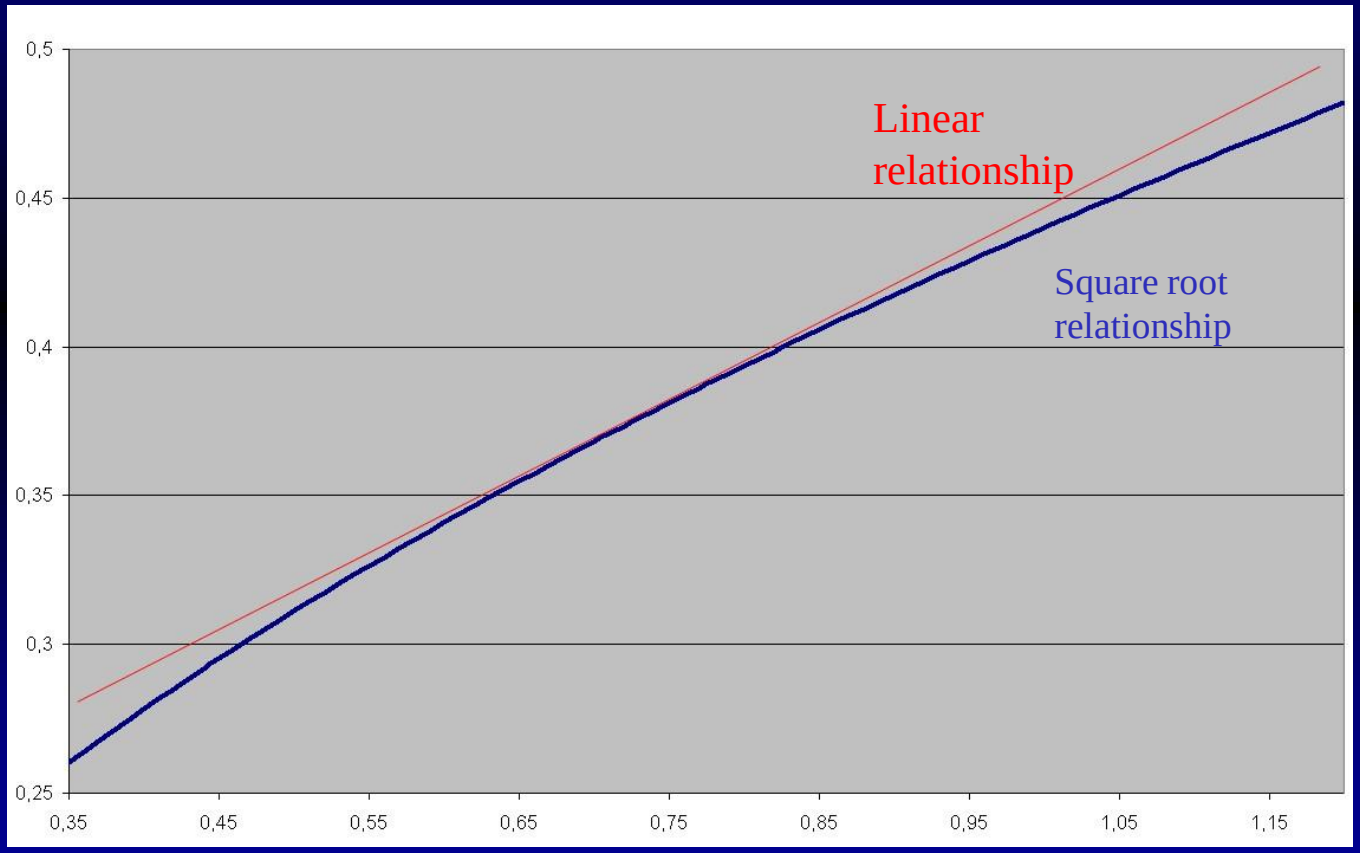
ECG signs:	A. QT_c (Bazett) $\geq$ 480 ms	**3**
	460 - 470 ms	**2**
	450 ms in male	**1**
	B. Torsades de pointes	**2**
	C. T wave alternans	**1**
	D. Notched T wave in 3 leads	**1**
	E. Low heart rate in children	**0,5**
History	A. Syncope with exercise	**2**
	without exercise	**1**
	B. Congenital deafness	**0,5**
Family H.	A. Direct relative with dg. LQTS	**1**
	B. Sudden death in family below age 30	**0,5**

Scoring: **≤1 point** – low, **2-3 points** – intermediate,
≥3,5 – high probability of the dg


14:41 0 W 71 BPM 130/70 mmHg
I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
QTc >500 ms
=
high risk
09.08.2006 10:52:17
10 mm/mV 25 mm/s 35 Hz 50 Hz ADS
Physician: dr.Kaňovský
User: FN Brno-Bohunice

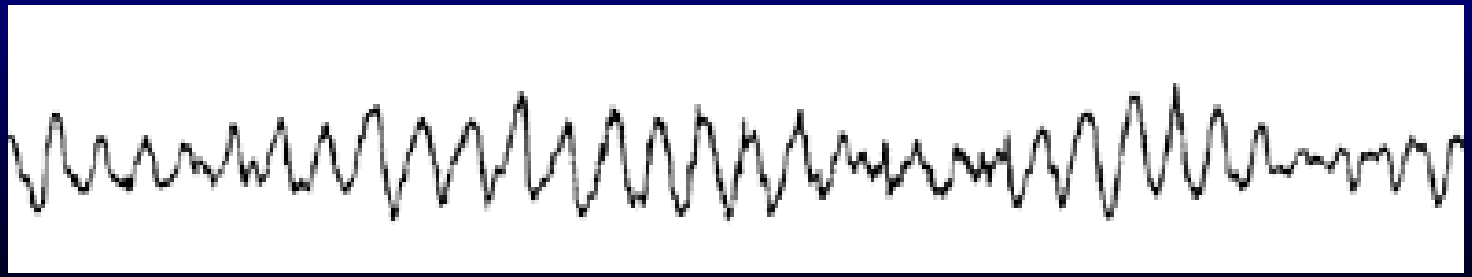
QT interval correction to the heart rate

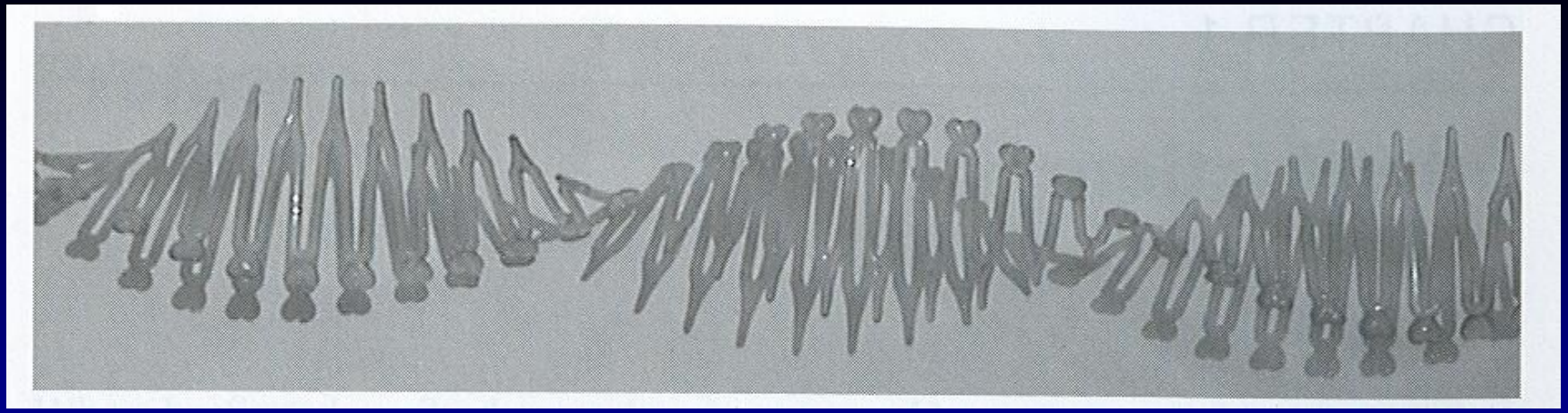
Bazett – $\frac{QT}{\sqrt{RR}}$ Fridericia – $\frac{QT}{\sqrt[3]{RR}}$



Any formula represents a substantial simplification of a much more complicated natural reality!!

polymorphic ventricular tachycardia „torsade de pointes“





Dessertenne F. Le tachycardie ventriculaire a deux foyers opposes variables. Arch Mal Coeur Vaiss. 1966;59:263-72.

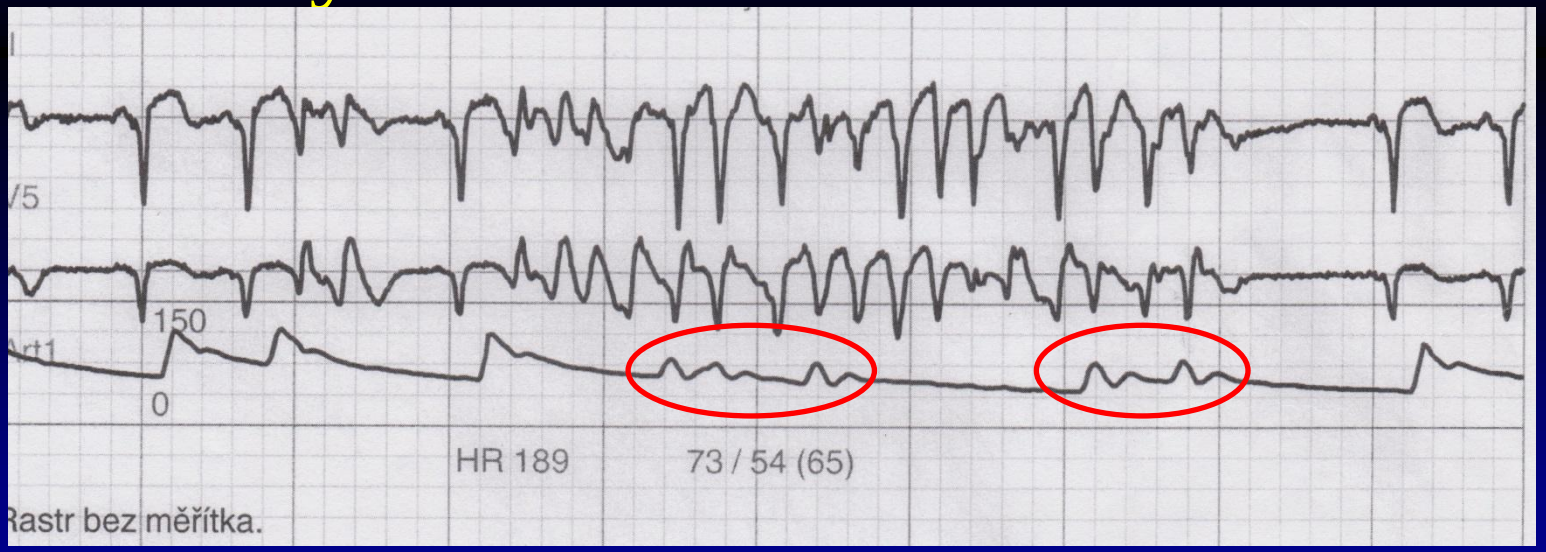
Camm AJ, Malik M, Yap YG. Acquired long QT syndrome. Blackwell Futura, 2004.

Leading symptome - syncope

- during exercise, jumps in water

- but also at rest, strong acoustic signals

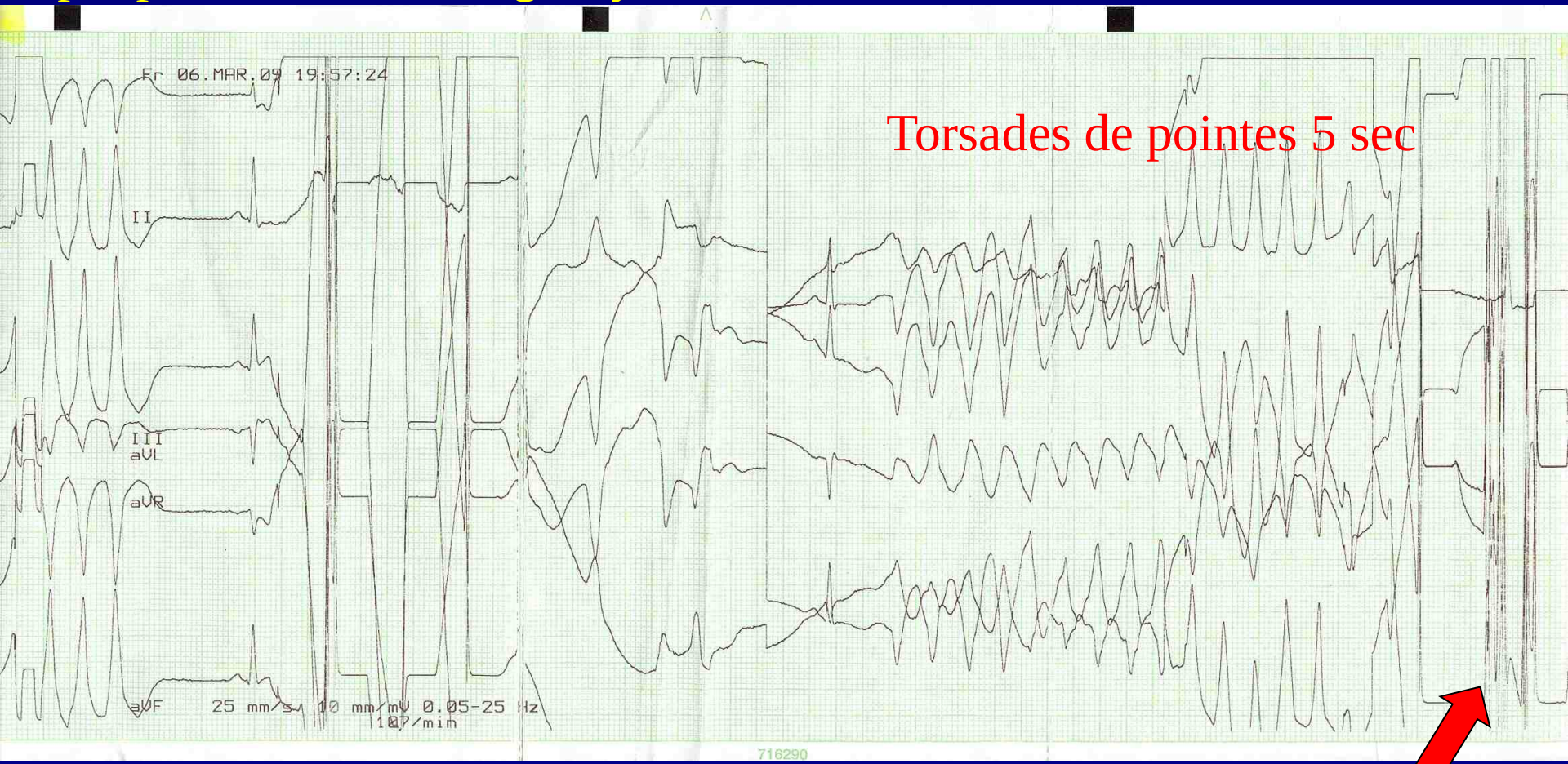
Very often seizures!!!



Torsade is an incomplete circulatory arrest causing non-coordinated muscular acitivity – seizures.

A case report

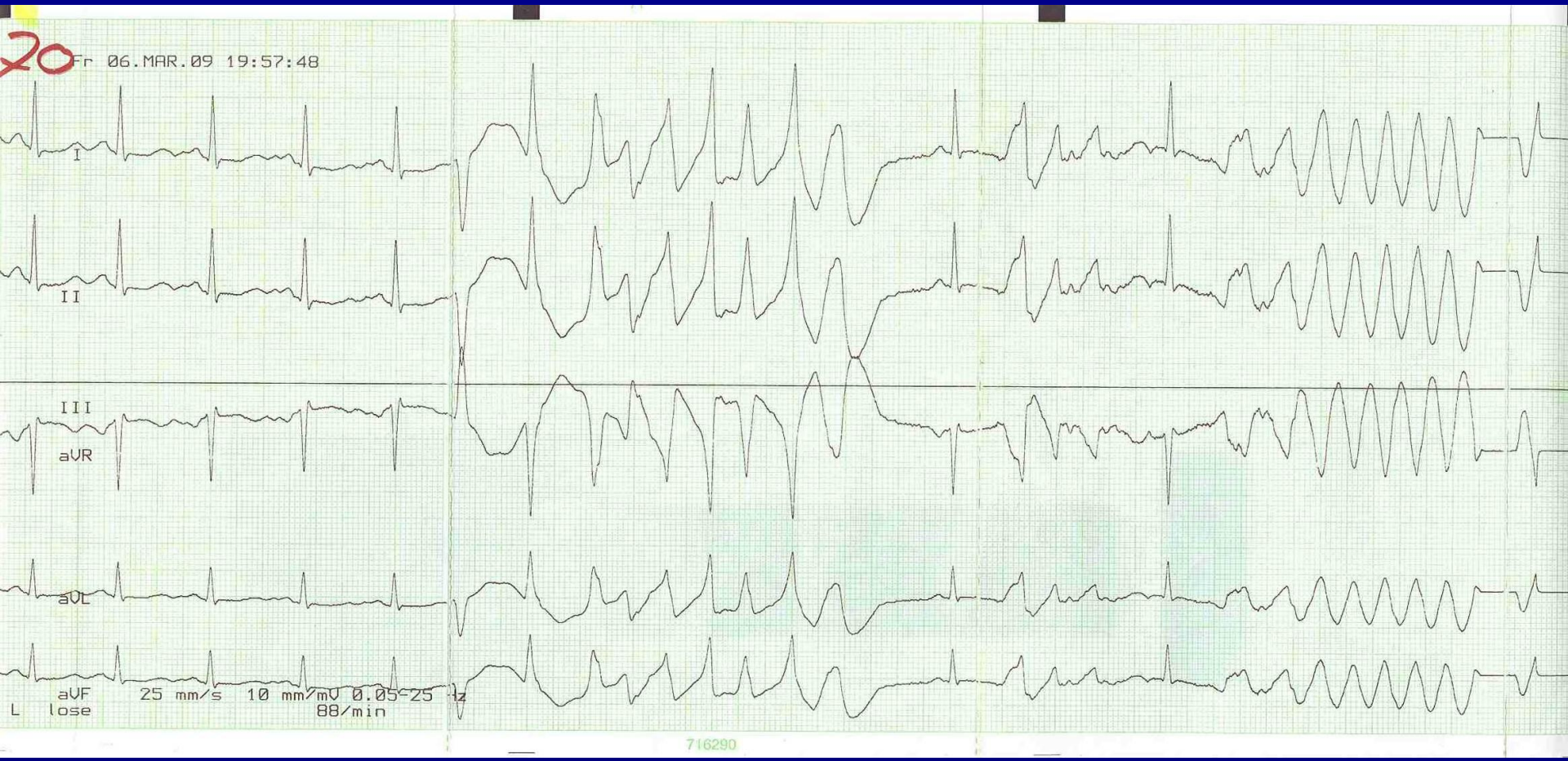
47-year old female with repeated seizures clasified as status epilepticus at the Emergency



Torsades de pointes 5 sec

Movement artefacts = seizures

Continuing ECG shows QT interval prolongation



The lady had low potassium level and was on antirheumatoid drug plaquenil = drug induced long QT syndrome

QT interval prolonging drugs

Antiarrhythmics - ajmaline, amiodarone, bretylium, dofetilide, disopyramide, ibutilide, prokainamide, propafenone, chinidin, sotalol

Antibiotics, chemotherapeutics, antimycotics - amantadine, clarytrhomycine, chloroquine, cotrimoxazole, erythromycine, fluconazole, halofantrine, itraconazole, ketoconazole, pentamidine, chinine, spiramycine, sparfloxacine

Antihistaminics - astemizole, loratadine, terfenadine

Psychopharmacs - amitryptiline, clomipramine, clozapine, chlorpromazine, citalopram, desipramine, doxepine, droperidol, fl
m
pr
thioridazine, timiperone, trifluoperazone, venlataxine, zimeldine, ziprasidone

Other - cisapride, indapamide, ketanserine, probucol, plaquenil, sildenafil vasopresin