1st Worldwide Internet Symposium on Drug-Induced QT Prolongation, October 2007

Drug-induced LQT-Syndrome: Sotalol-Experience, Heart failure, Susceptibility to drug induced LQT

Stefan Kääb
Ludwig-Maximilians Universität München
Klinikum Grosshadern, Med. Klinik I
Stefan.Kaab@med.uni-muenchen.de

LMU

no conflicts of interest to disclose

Objective and Outline

- review data on Sotalol as an examplary agent of drug-induced LQT syndrome
- introduce the multifactorial nature of drug-induced LQT syndrome, highlighting hypertrophy and heart failure as important co-factors for TdP in the context of drugs with QT-prolonging potential (i.E. Sotalol)
- Sotalol as a tool to study altered repolarization and susceptibility to TdP in the context of QT prolonging drugs
- common genetic variants modulate myocardial repolarization and define intrinsic individual susceptibility to drug-induced LQT syndrome

Sotalol induced changes in myocardial repolarization in healthy volunteers (n=39)

Table 1. QT Repolarization Measurements Associated With 3 Ranges Sotalol Plasma Concentration

SPC (ng/mL)	N	RR	QTc slope (B)	QTc slope (F)	QTc slope (N)	QTac 25% (N)	QTac 50% (N)	QTac97% (N)
0	558	899 ± 128	391 ± 24	384 ± 21	359 ± 32	220 ± 25	261 ± 27	346 ± 34
<0-300	69	**1011 ± 122**	391 ± 25	391 ± 22*	**393 ± 35**	**240 ± 29**	**288 ± 30**	**384 ± 36**
≤300-600	135	**1000 ± 129**	394 ± 22	**393 ± 19**	**393 ± 34**	**236 ± 26**	**285 ± 28**	**380 ± 36**
≤600	649	**1052 ± 134**	**419 ± 32**	**421 ± 39**	**434 ± 43**	**249 ± 31**	**308 ± 34**	**419 ± 46**

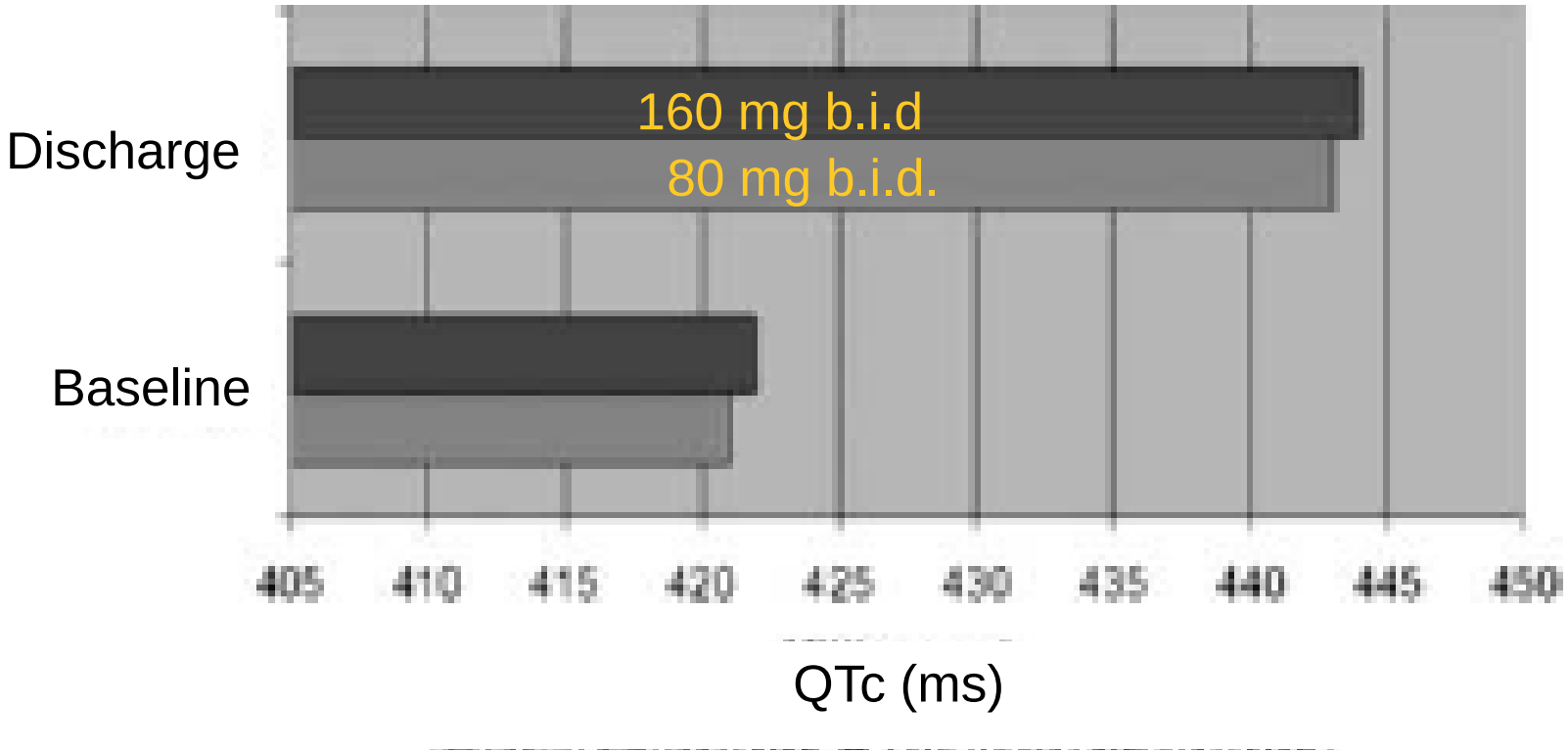
Comparing mean values in reference to plasma concentration free of sotalol, the values in bold are significantly higher ($P < .001$) than baseline values. Sotalol Plasma Concentration (SPC) is expressed in ng/ml, all other parameters are in msec. Bazett's (B), Fridericia's (F) and population-based (N) corrections are reported for QT slope (automatic measurements).

*$P = .07$, values in bold $P < .001$

Couderc JP et al. J Electrocardiol 2003; 36:115-120

QTc and area-based repolarization parameters are affected by sotalol indicating drug induced changes in T-wave morphology

Sotalol induced changes in QTc-Interval in atrial and ventricular arrhythmia patients (n=209)



Kim RJ, et al., Pace 2006; 29:1219-1225

Yield of in-hospital monitoring for initiation of sotalol in atrial arrhythmia patients (n=120)

- new or increased ventricular arrhythmias in n=7 (5.8%) (TdP in n=2)
- significant bradycardia in n=20 (16.7 %)
- excessively prolonged QTc interval in n=8 (6.7 %)

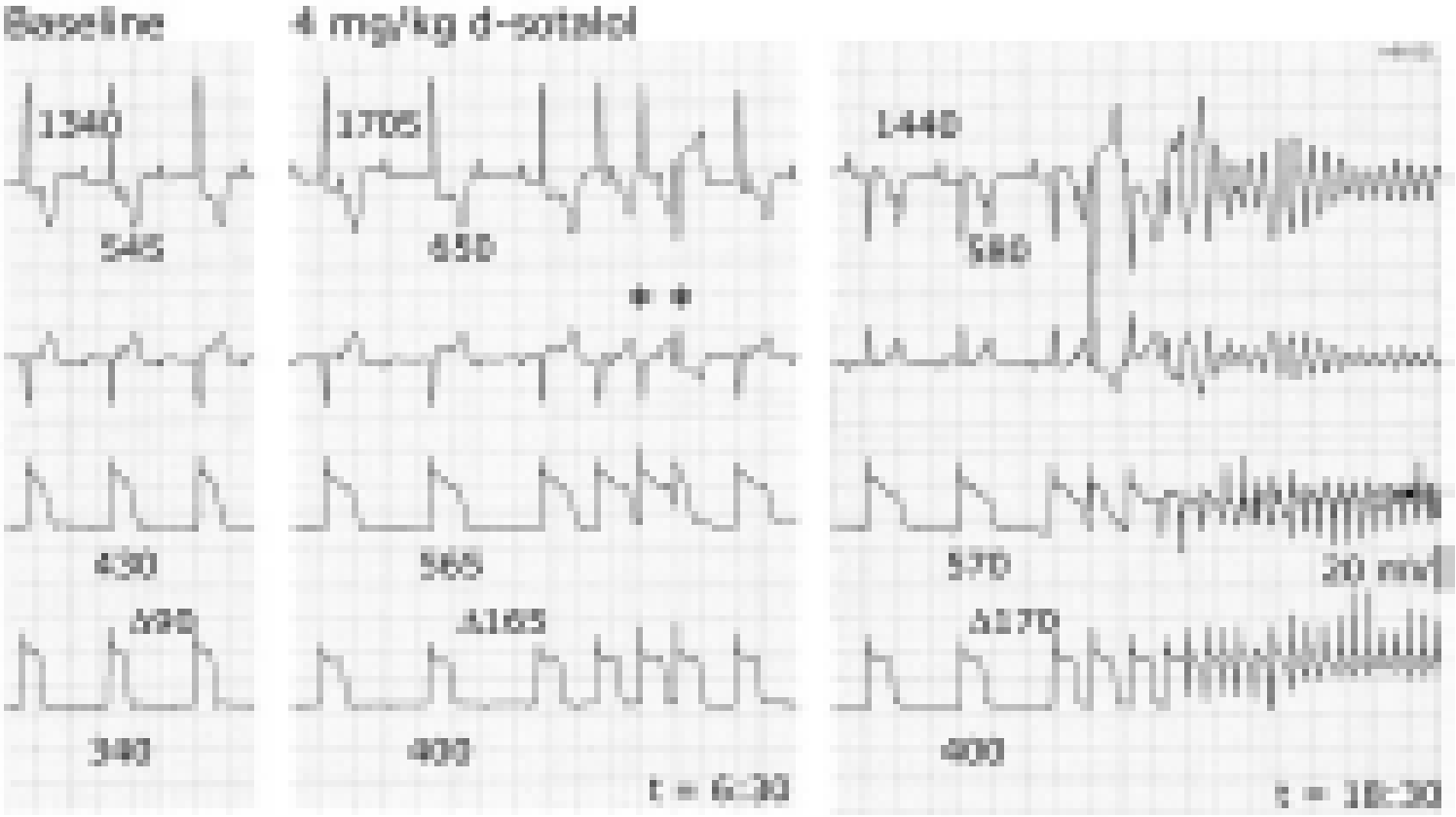
Chung MK, et al., J Am Coll Cardiol 1998;32:169-176

Proarrhythmia with sotalol

- pooled analysis of n=1.288 patients enrolled in premarketing trials showed new or increased ventricular arrhythmia occurred in 4.3% (1.9% classified as torsades de pointes)[1]
- the survival with oral d-sotalol (SWORD) trial demonstrated increased mortality in remote myocardial infarction group with LVEF between 30-40% (RR=7.9) with increased risk in women[2]
- in general proarrhythmia is reported with a range of 1% to 8% for sotalol
- sotalol causes a concentration dependent lengthening of the QT interval, increasing action potential duration and refractory periods predominantly by blocking the delayed rectifier potassium current (IKr)

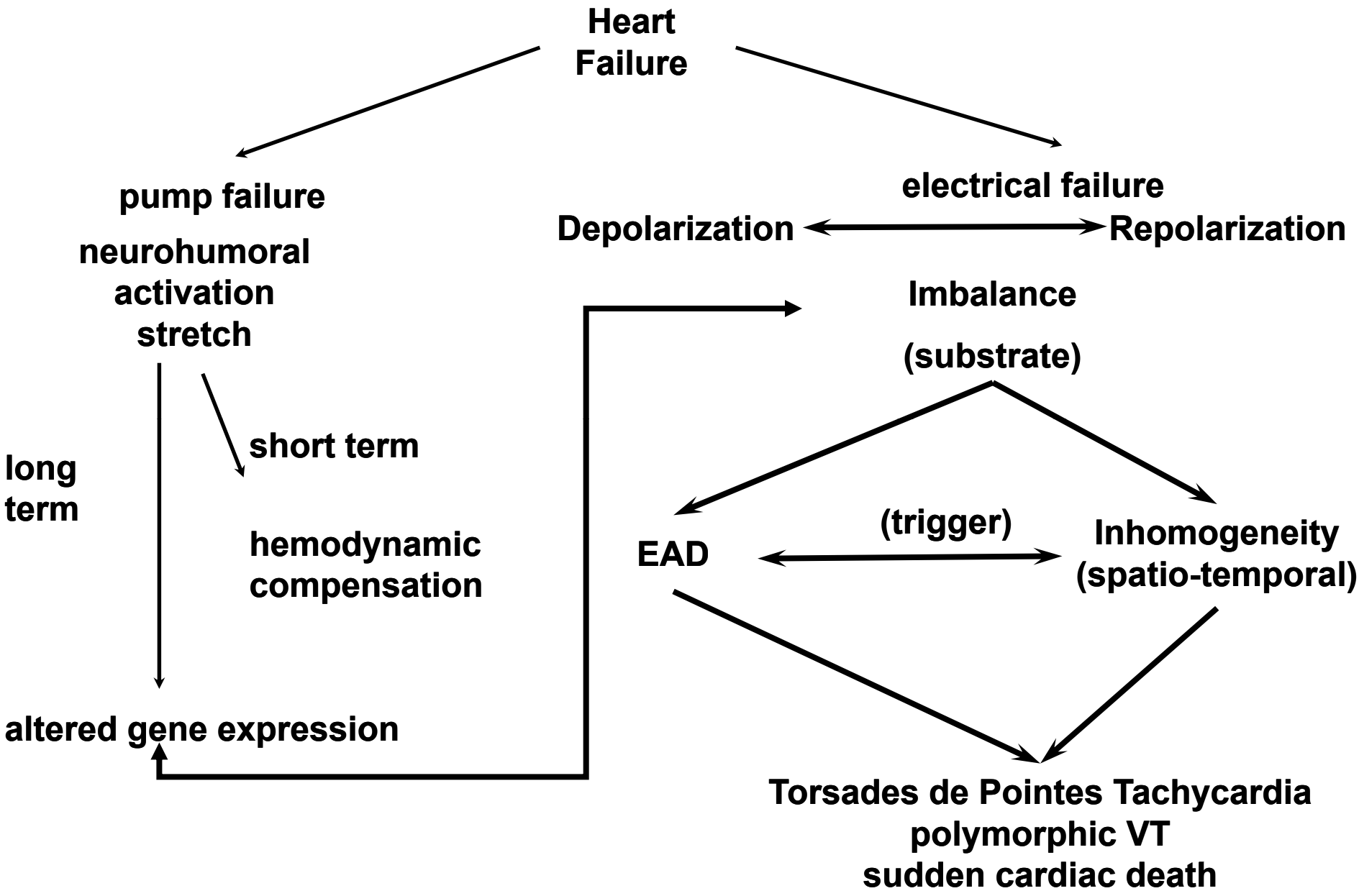
[1]Soyka LF et al., Am J Cardiol 1990; 65:74A-81A
[2]Pratt CM, et al., Am J Cardiol 1998; 81:869-876

Increased short-term variability of repolarization rather than QT prolongation predicts d-sotalol induced torsades de pointes in dogs with chronic AV block induced LV-hypertrophy



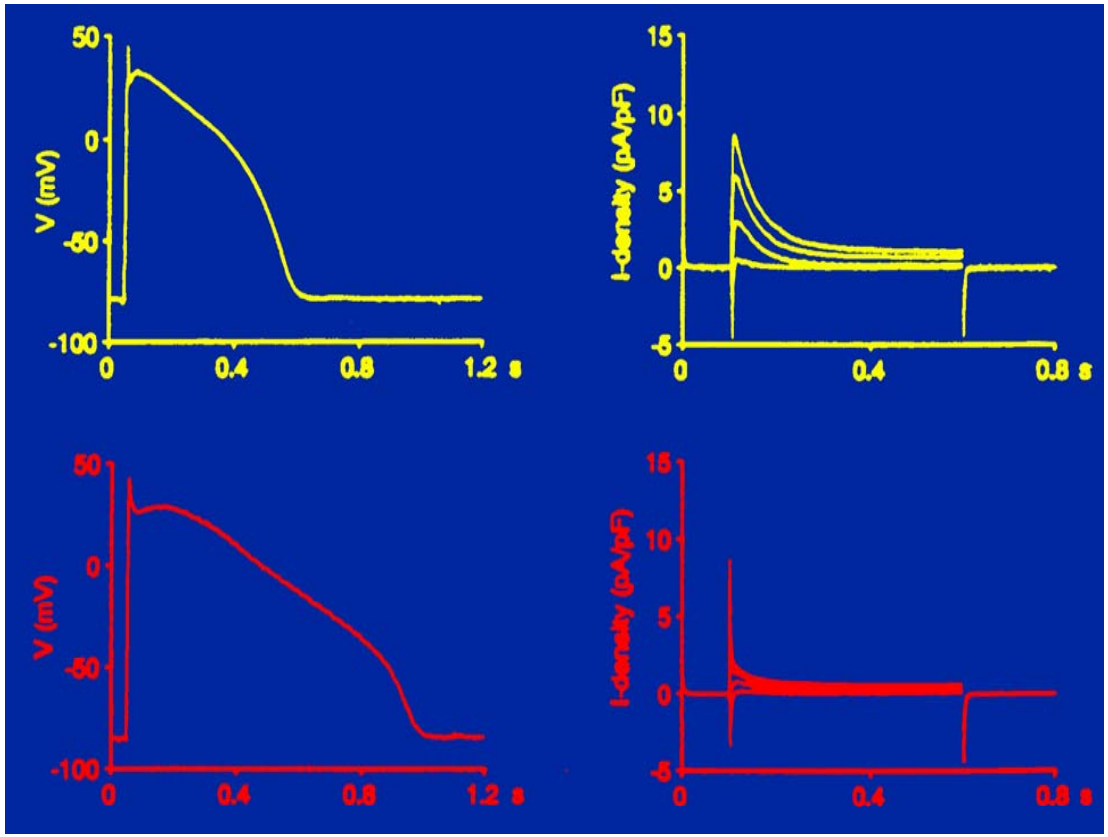
Thomsen MB, et al., Circulation 2004; 110:2453-2459

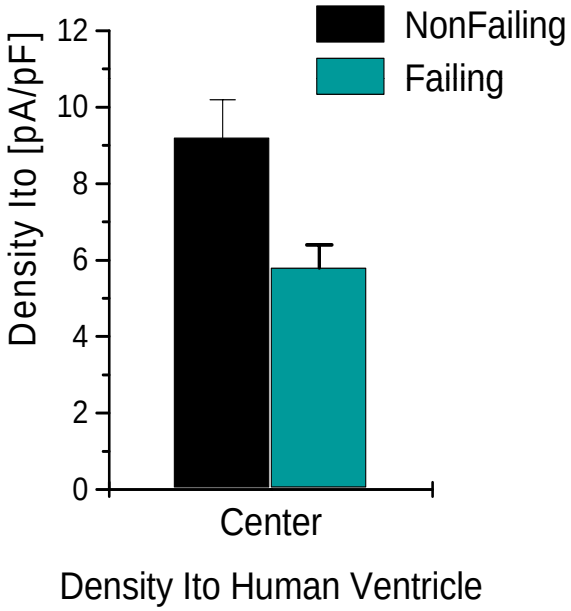
LV-Hypertrophy and congestive heart failure can be regarded as forms of acquired LQT syndrome and thus are specific risk factors for drug induced LQT syndrome



modified from: Marban E, J Cardiovasc Electrophysiol, 1999;10:1425-8

Prolongation of APD due to reduced I_{to1} in isolated human cardiomyocytes in congestive heart failure

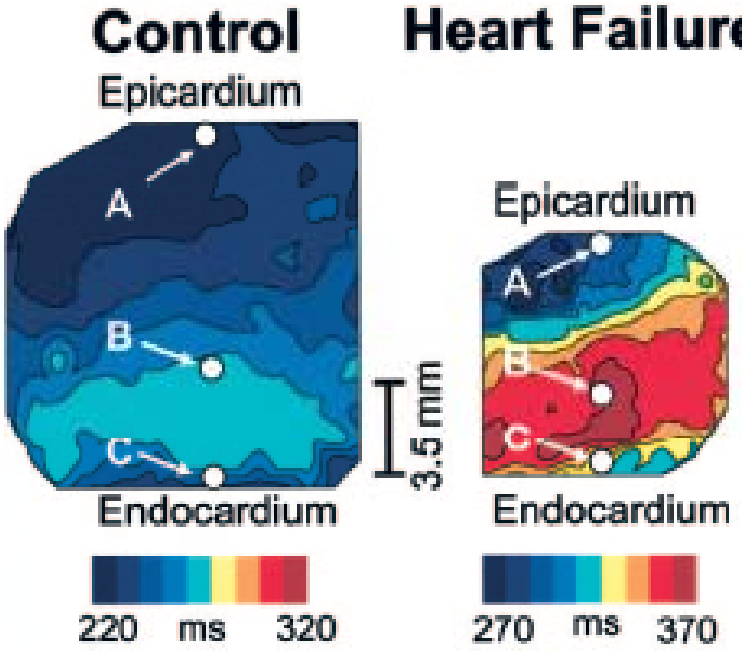


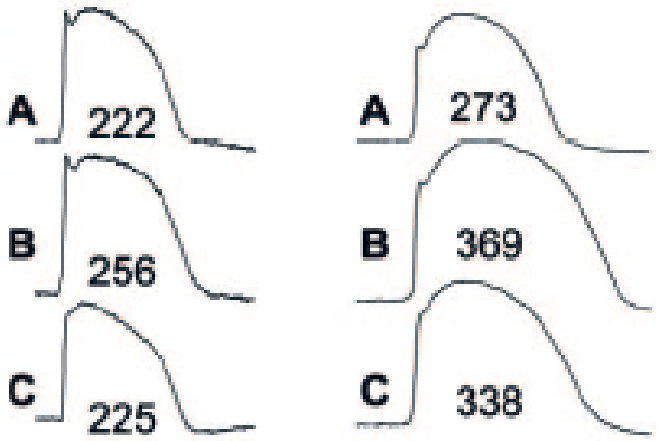


Density Ito Human Ventricle

Beuckelmann DJ, Näbauer M, Erdmann E. Circ Res 73:379 (1993)

Transmural Dispersion of Repolarization in Heart Failure





Tachycaria induced HF model

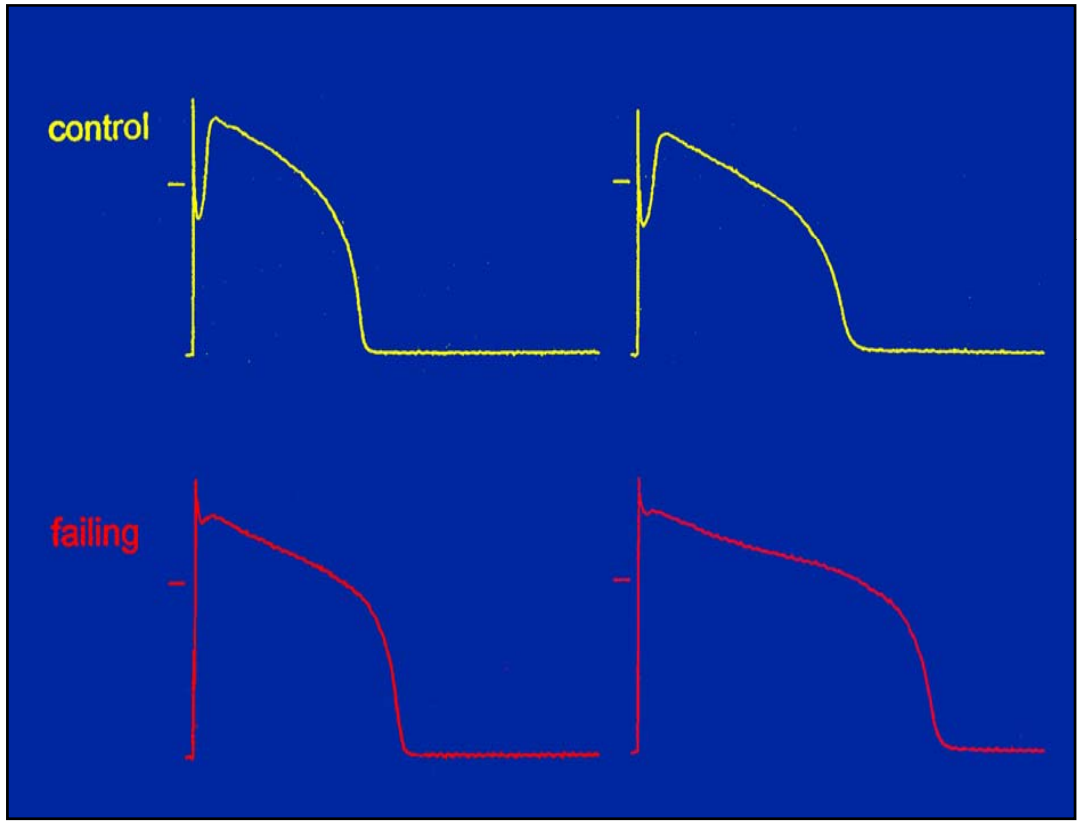
canine LV wedge preparations

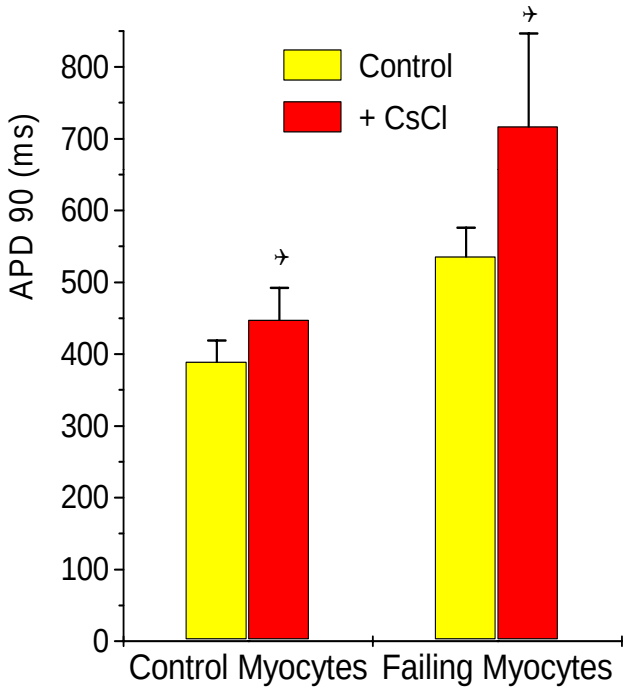
APD contour maps

APD recordings

F. Akar and D. Rosenbaum, Circ. Res. 2003; 93:638-645

Excessive AP-Prolongation by K^+ channel block (CsCl) in congestive heart failure – evidence for reduced repolarization reserve

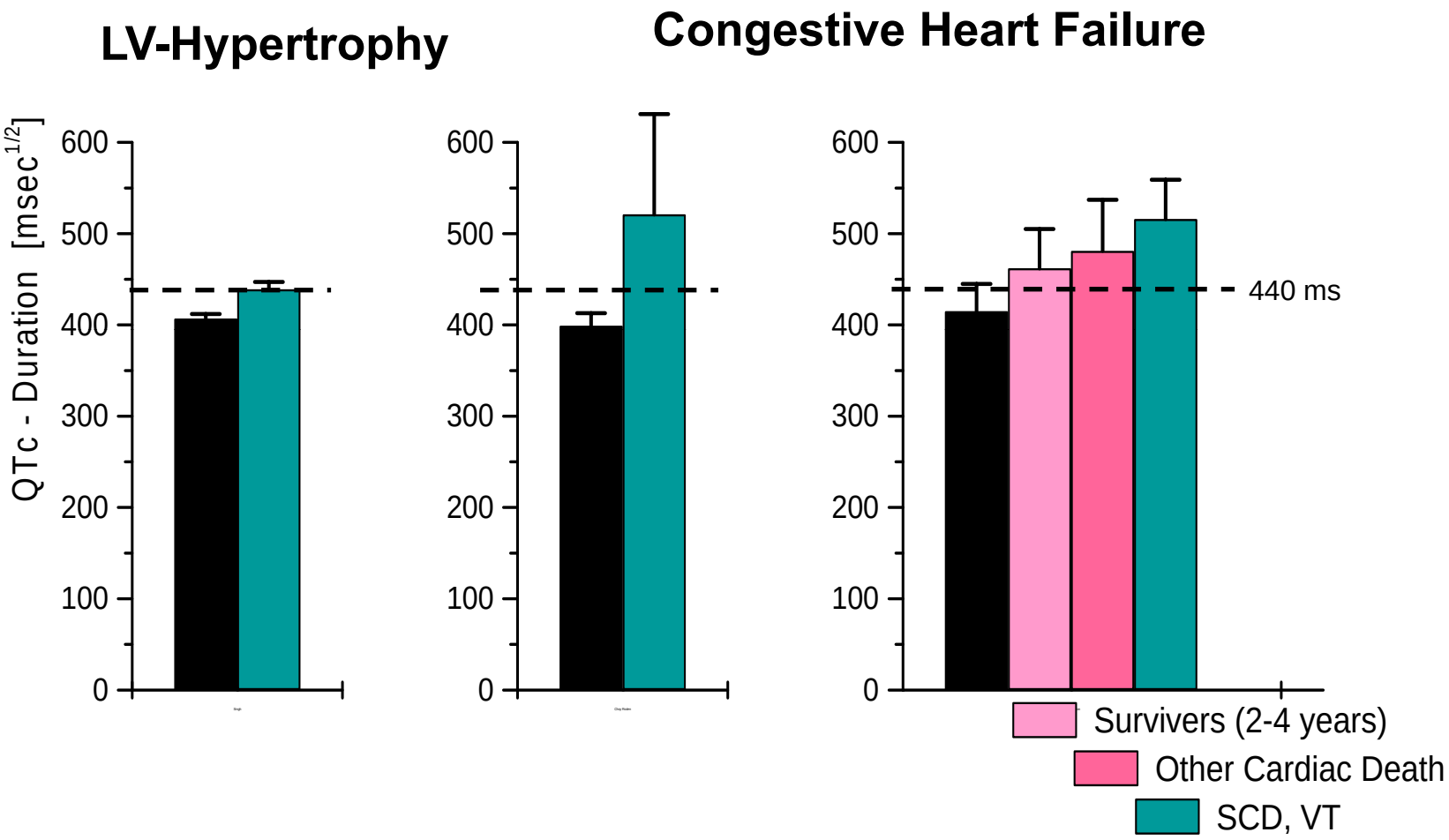




dog ventricular myocytes

Pak P, et al., JACC (1997)

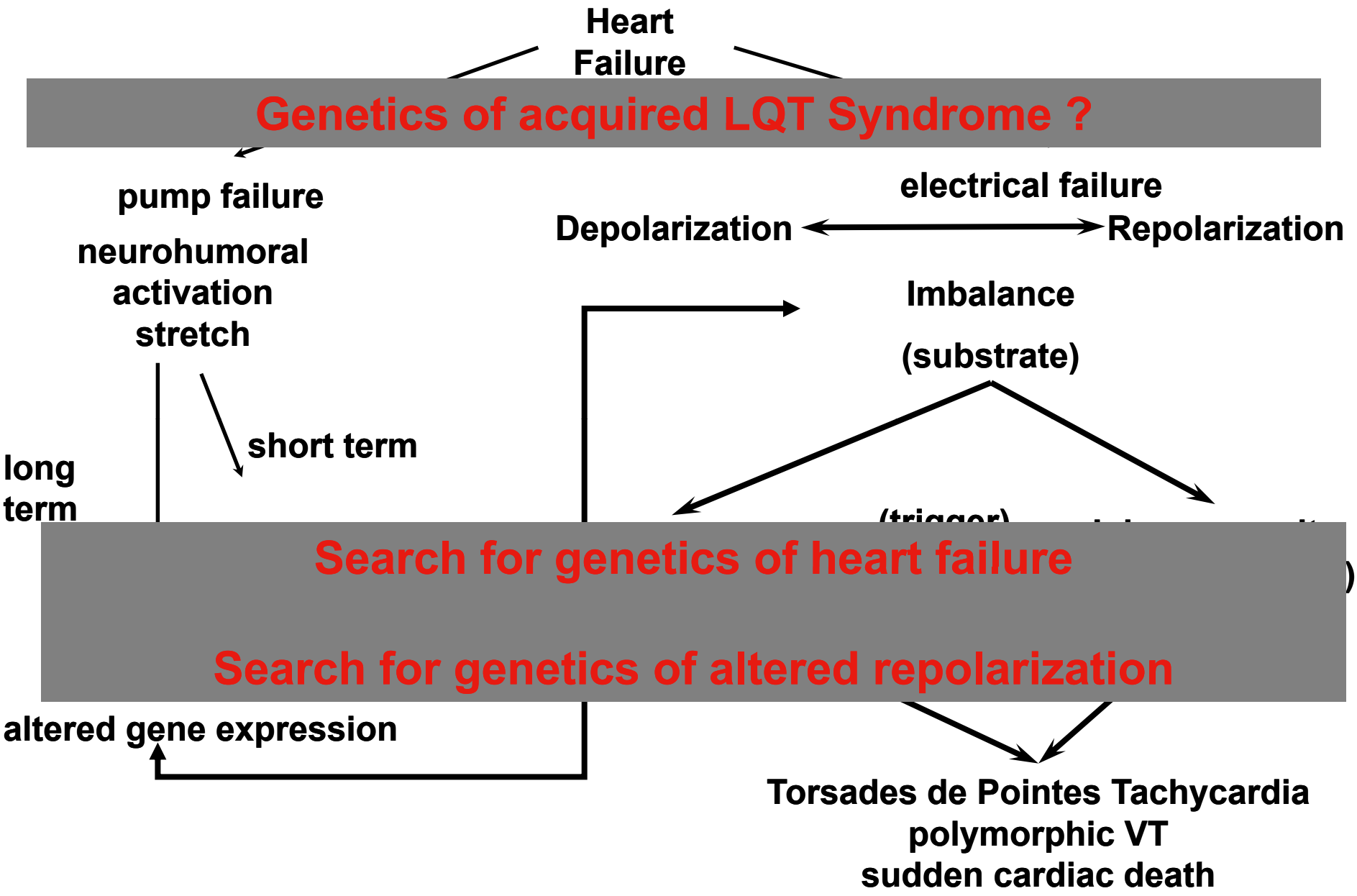
Hypertrophy and Congestive Heart Failure in Humans: an Acquired Form of Long-QT-Syndrome



Singh JP, et al. ,
JACC 29: 778 (1997)

Choy AM et al.,
Circulation 96:2149 (1997)

Fu G-S, et al. , Eur Heart J 18:281 (1997)

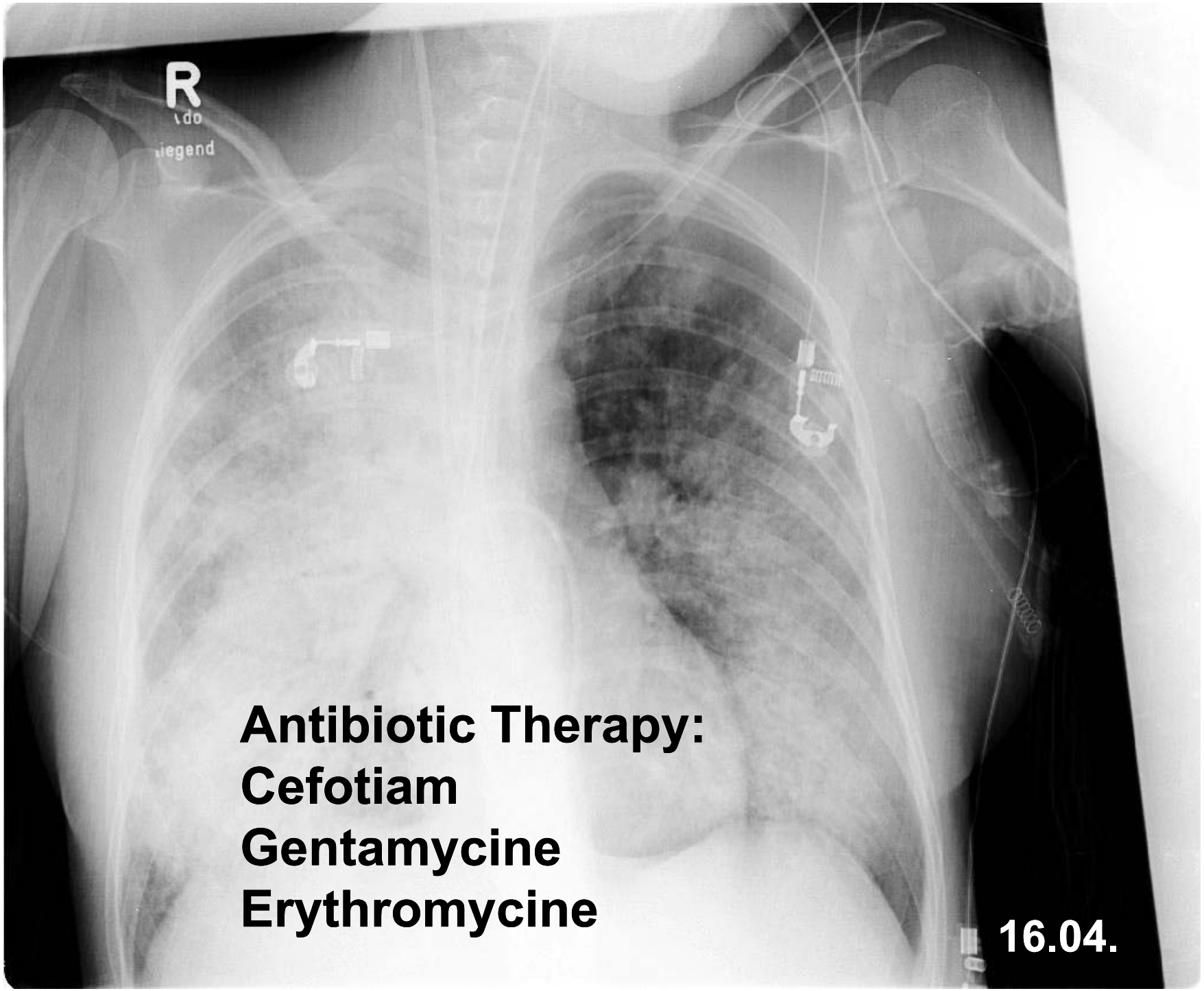


modified from: Marban E, J Cardiovasc Electrophysiol, 1999;10:1425-8

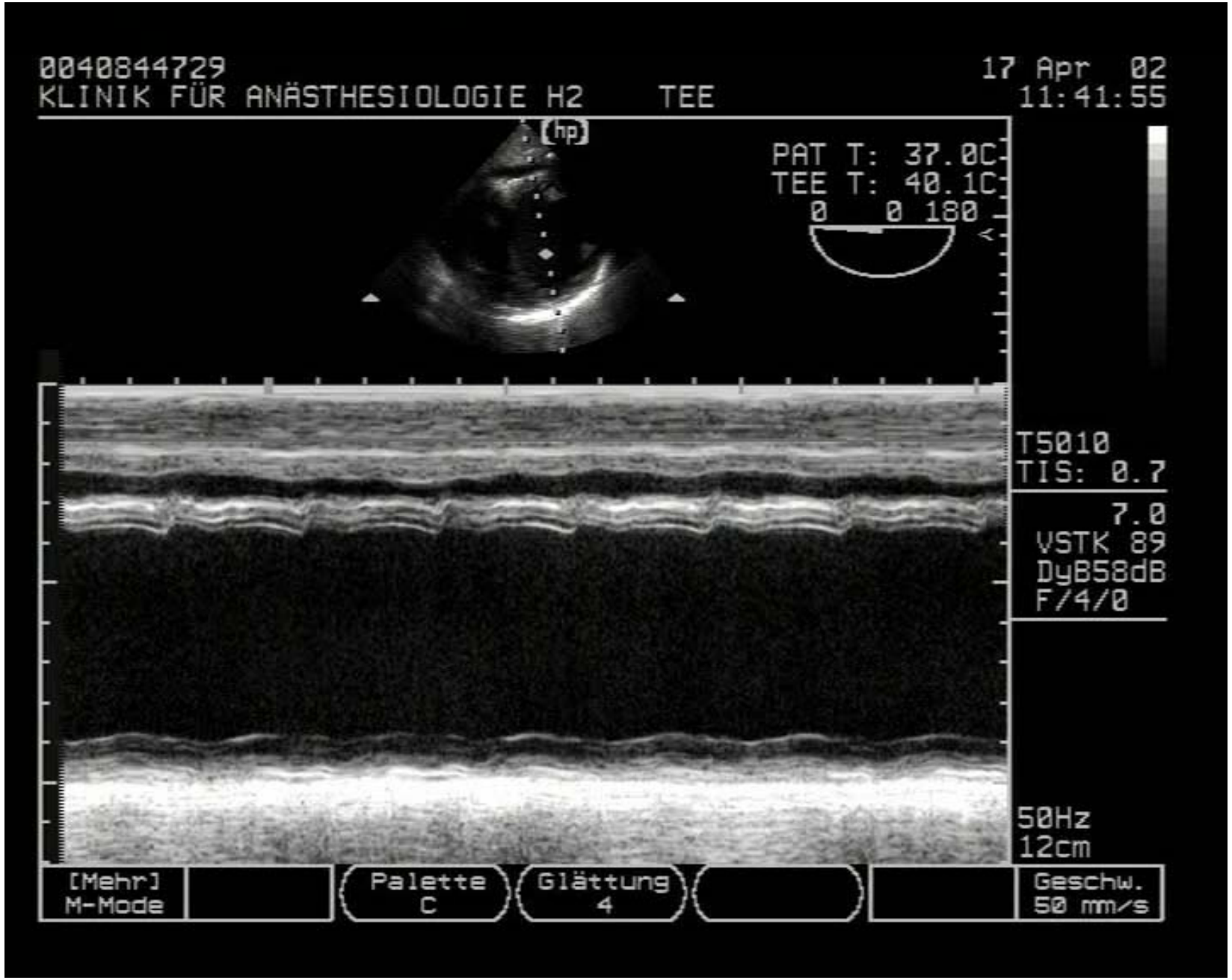
Case Report

- 25 y, female patient
- ARDS, Sepsis
- Cardiomyopathy
- repetitive polymorphic VT
- TdP, CPR

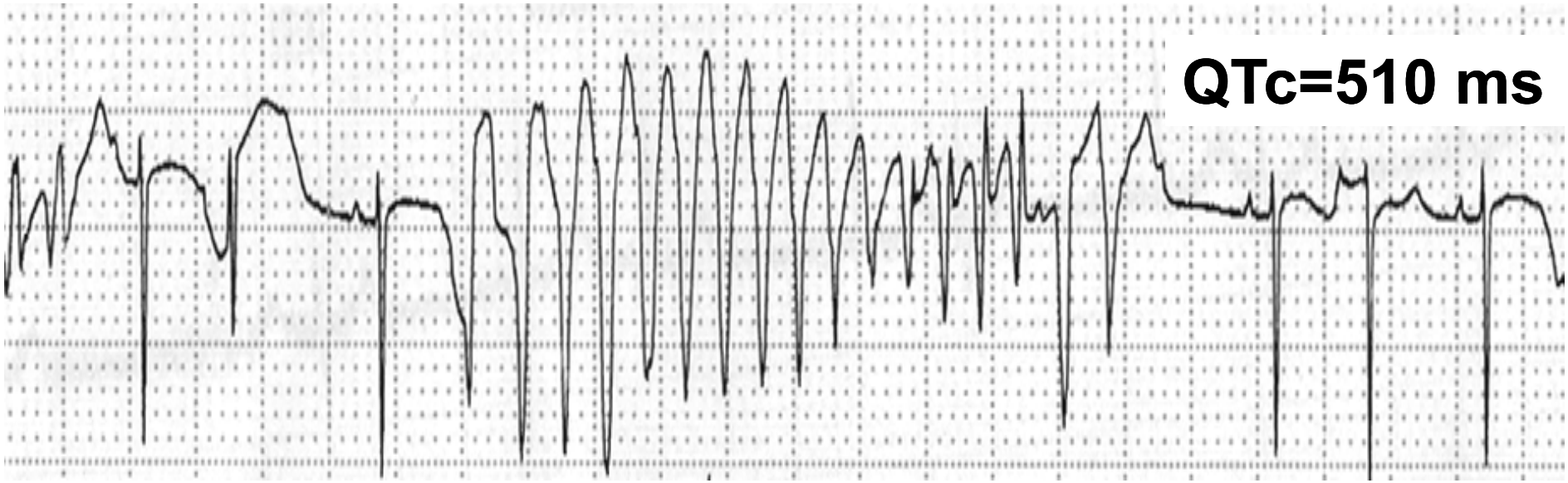
Hinterseer et al., Br J Anaesth 2006


R
Antibiotic Therapy:
Cefotiam
Gentamycine
Erythromycine
16.04.

TEE from April 17th. : LVEDD 60 ms, FS<10%



April 17th : Torsades de Pointes Arrhythmia



- polymorphic ventricular tachycardia
- changing amplitude and QRS-axis
- prolonged QT inerval
- initial short-long-short-sequence

Cardiological Evaluation
(5 weeks past acute illness)

- ECG :

  regular SR, HR 80/min, left axis deviation,
  QTc 423 ms

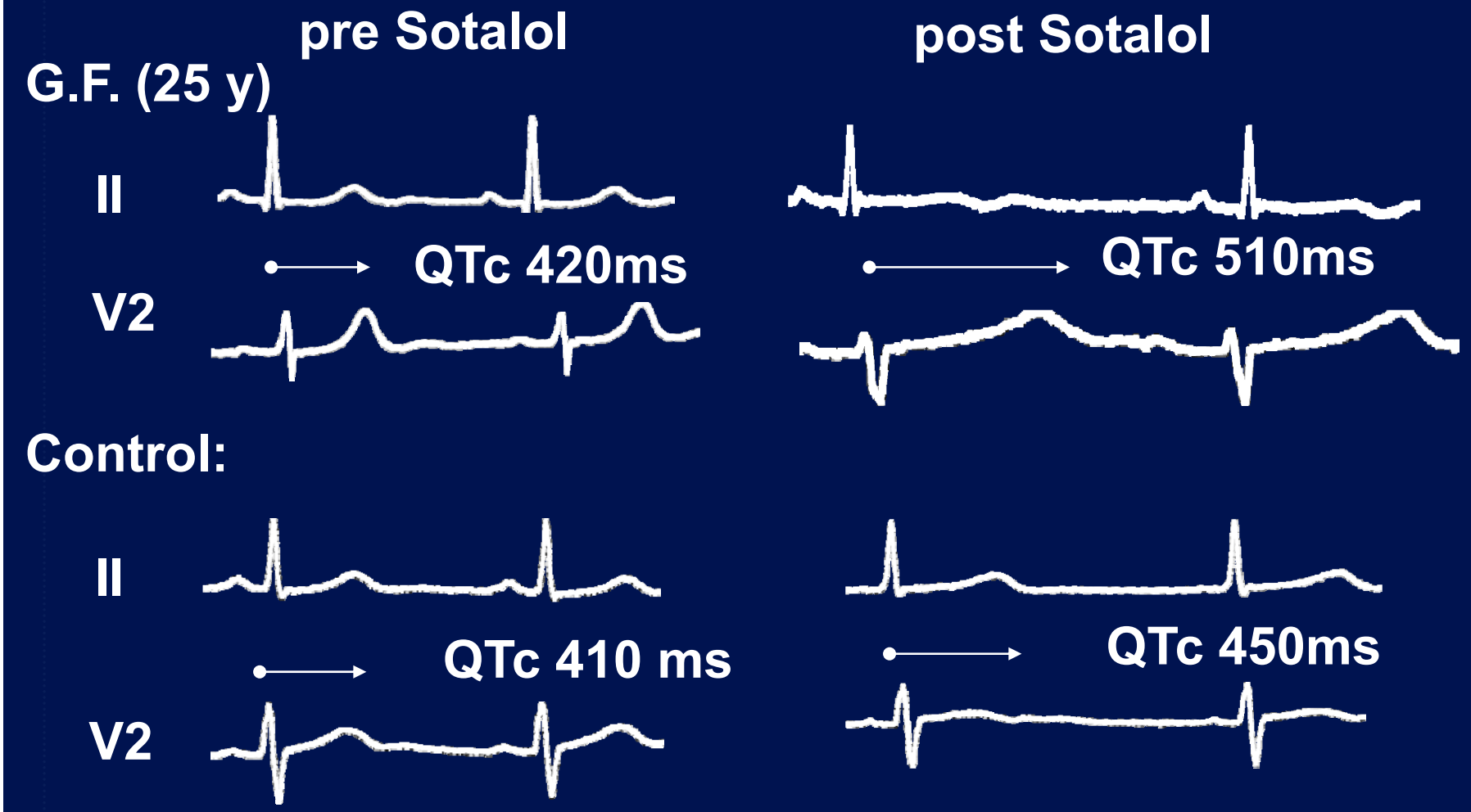
- cardiac catheterization & EP study:

  no structural heart disease
  no sustained arrhythmia induceable

- echocardiography:

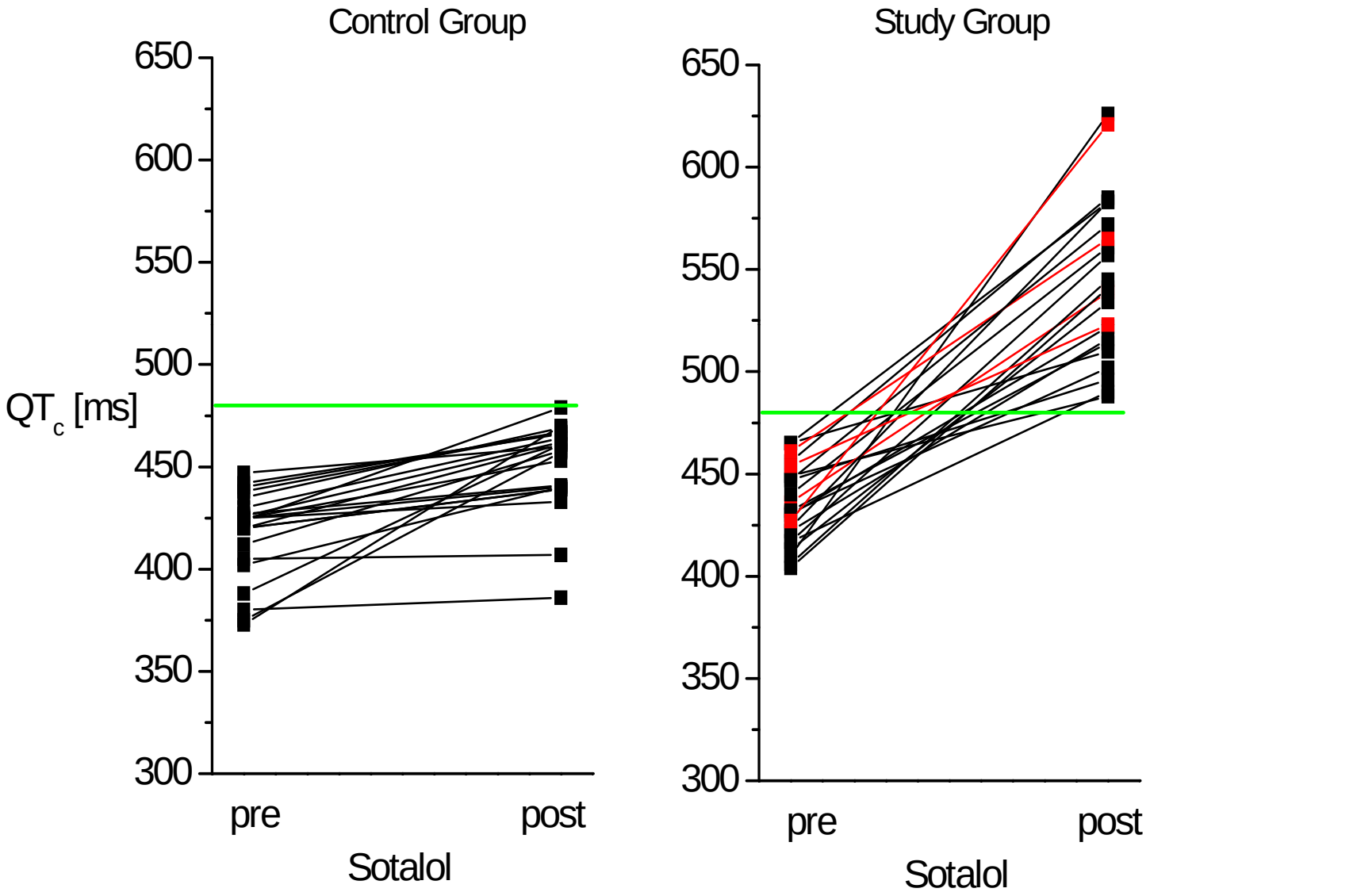
  within normal limits

Testing Myocardial Repolarisation Reserve by i.v. Sotalol



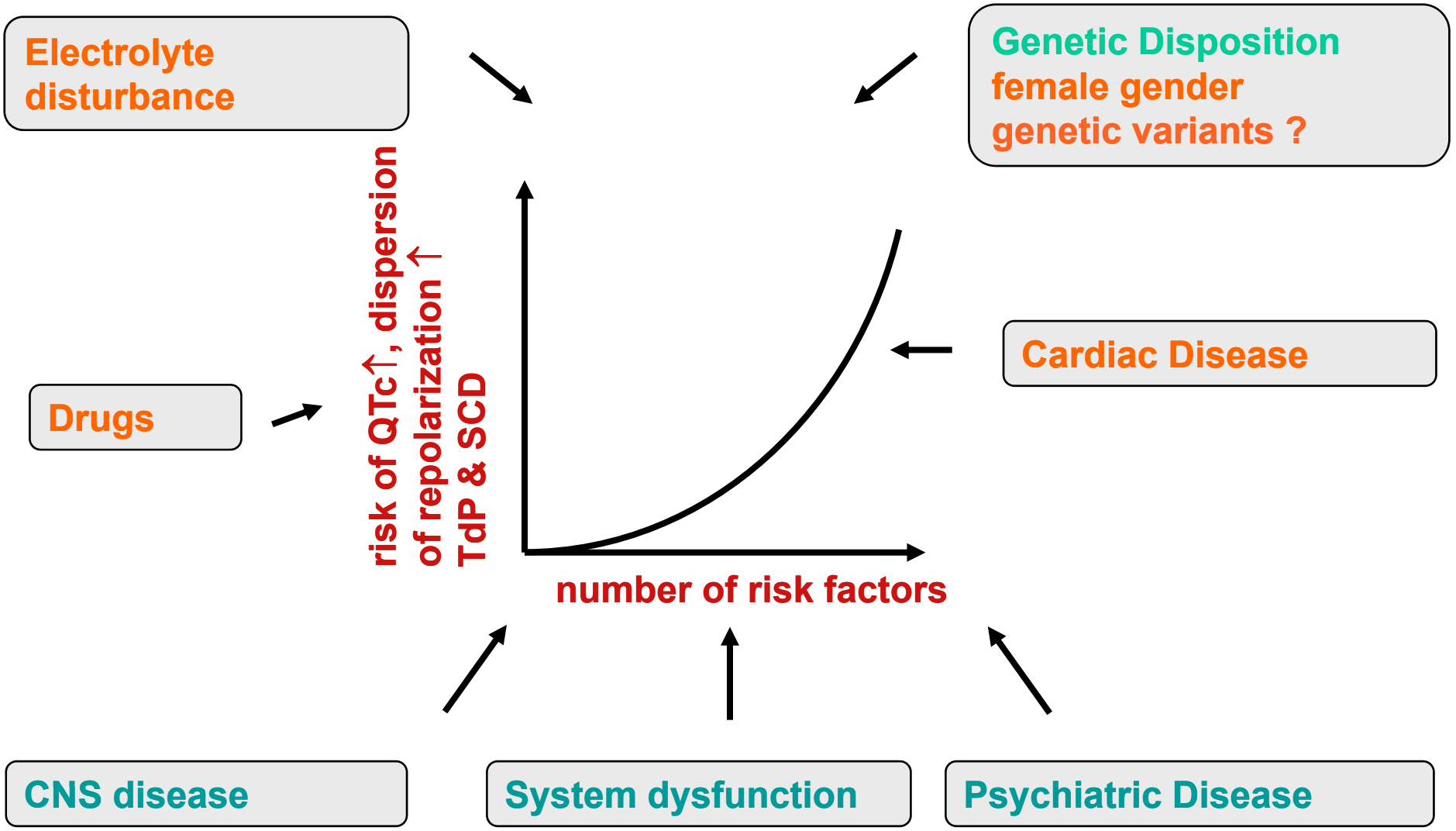
according to protocol in Kaab et al, *Eur Heart J*. 2003; 24: 649-657

Sotalol testing unmasks reduced repolarization reserve in patients with history of drug induced LQT syndrome



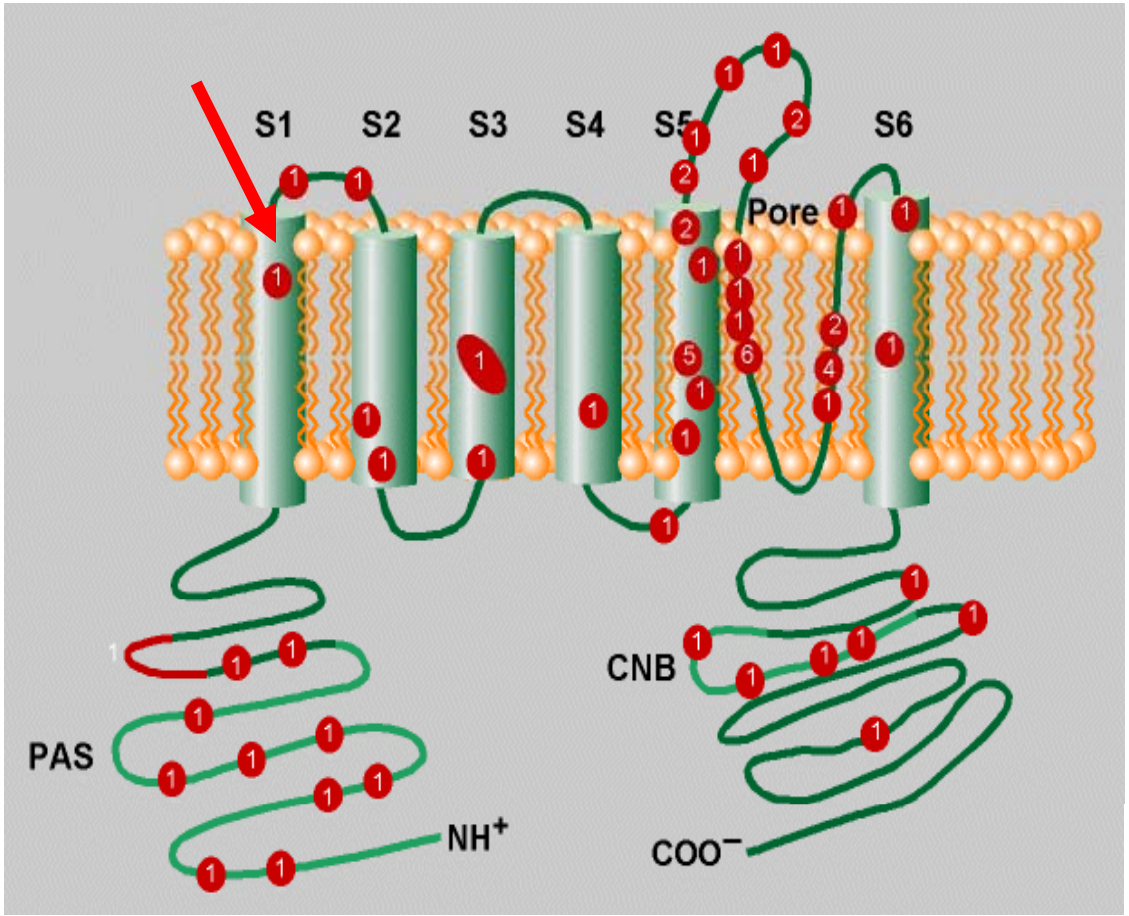
Kääb et al., Eur Heart J, 2003;24:649-657

Repolarization Reserve

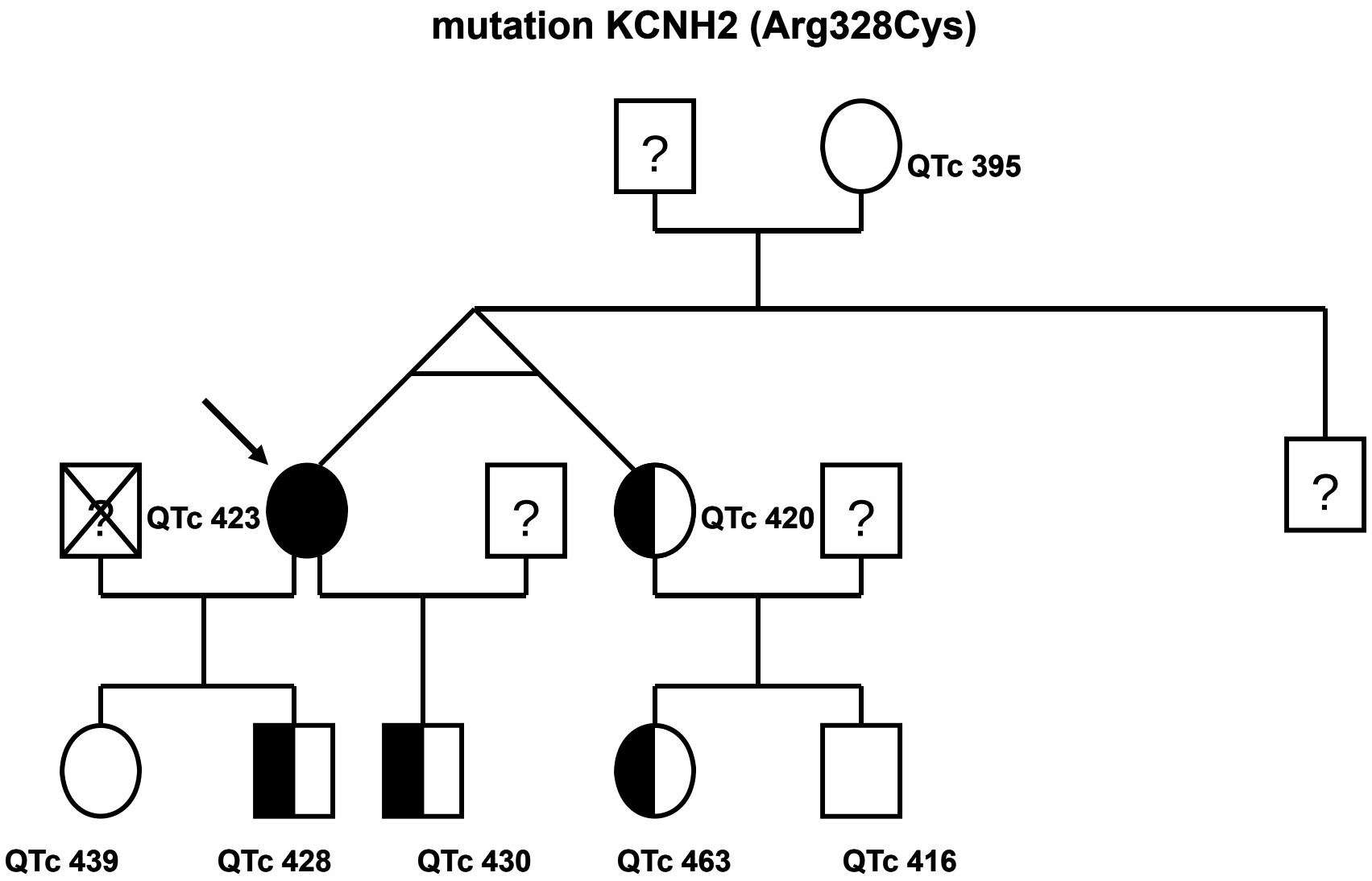


KCNH2: alpha-subunit of I_{Kr}

new mutation KCNH2 (Arg328Cys)



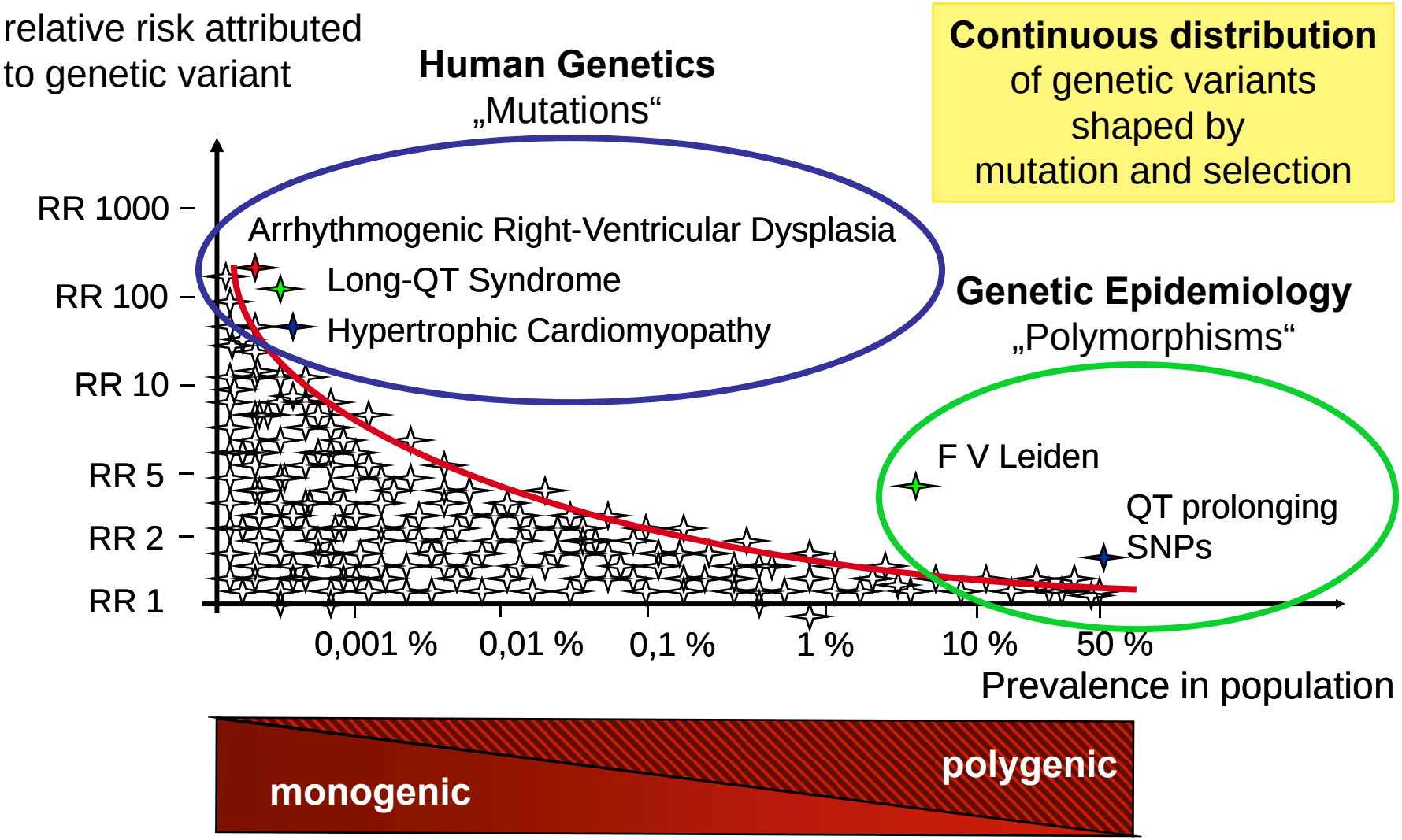
Family


mutation KCNH2 (Arg328Cys)
?
QTc 395
?
QTc 423
?
QTc 420
?
?
QTc 439
QTc 428
QTc 430
QTc 463
QTc 416

Questions

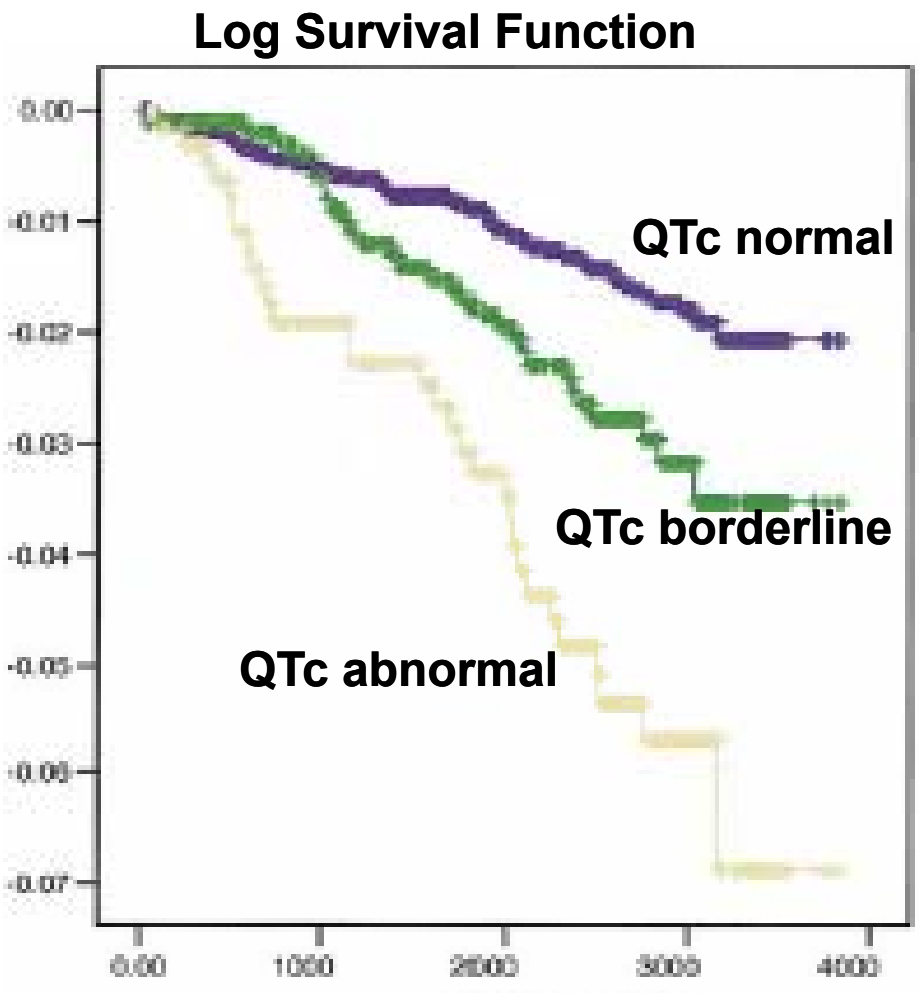
- Is genetic susceptibility to acquired LQT syndrome relevant?
- What is the substrate of genetic susceptibility to acquired LQT syndrome?

Monogenic and Complex Genetic Diseases



adapted from : N.E. Morton et al.

QTc Associated with Risk of SCD in the General Population (Rotterdam Study, n=4.344)



QTc normal	m: ≤ 430
	f: ≤ 450
QTc borderline	m: 431- 450
	f: 451- 470
QTc abnormal	m: > 450
	f: > 470

QTc and Risk for SCD (< Median age 55-68 y)	
borderline	1.6 (0.9-3.1)
(n=1.109 / 514)	3.7 (1.1-14.0)
abnormal	2.5 (1.3-4.7)
(n=681 / 212)	8.0 (2.1-31.3)

Straus et al., JACC 2006;47:362-7

Genetic Variants and Risk for Arrhythmias

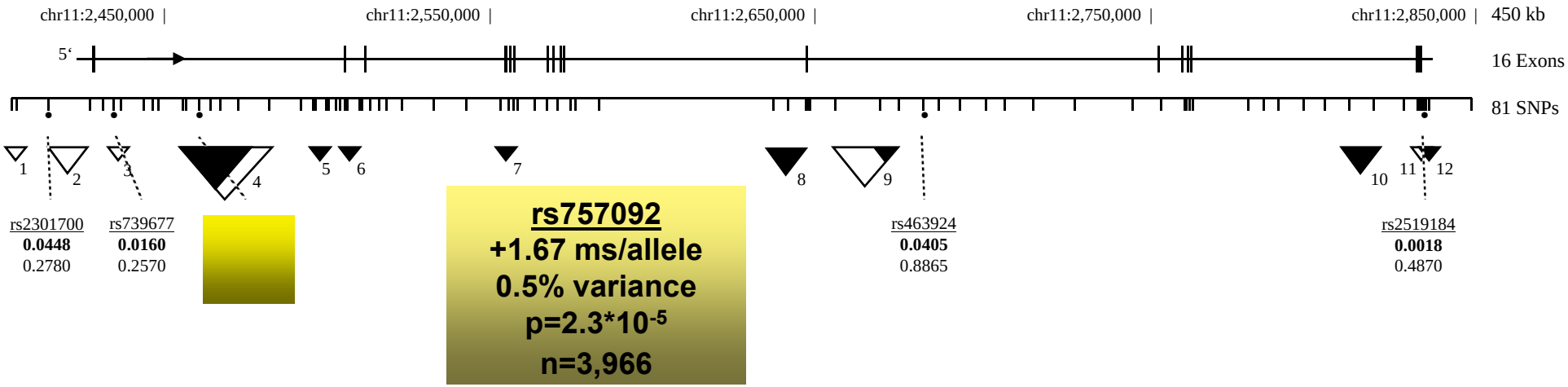
Common Disease Common Variant (?)

- From Rare to Common Diseases
- From Rare to Common Gene Variants

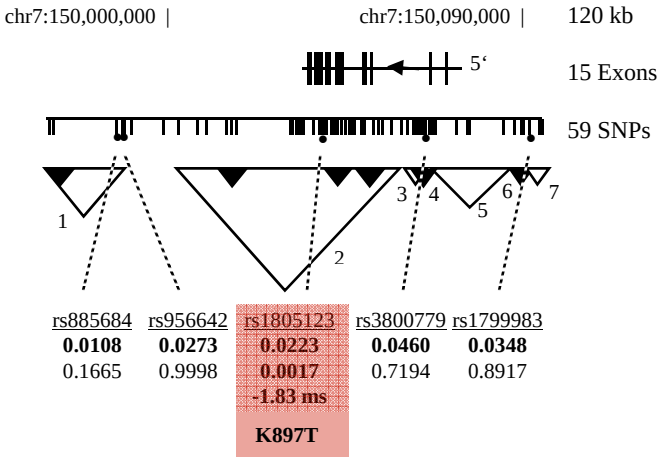
Genetic susceptibility to Arrhythmias in the context of drugs may follow the common disease common variant hypothesis

LD-mapping in 4 LQT disease genes

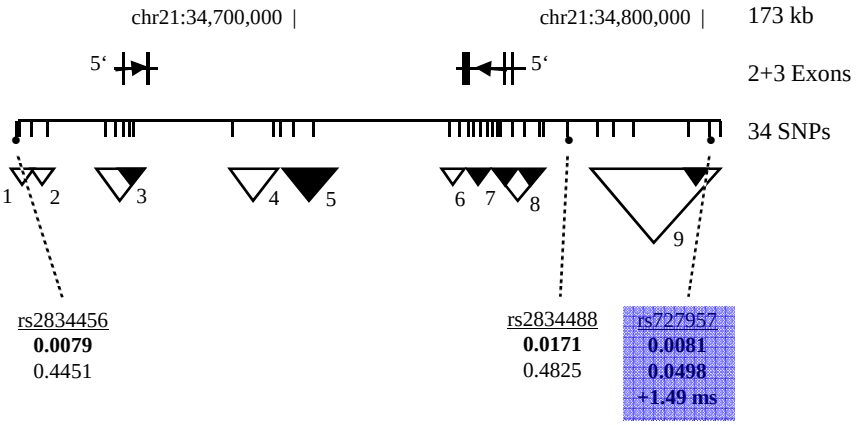
KCNQ1 (11p15.5-p15.4)



KCNH2 (7q36)



KCNE2 (21q22.11-q22.12) KCNE1



Pfeufer et al., Circ Res. 2005

Common variants (SNPs) in LQT disease genes modulate QT interval in the general population

Combined effect of 3 SNPs (6 alleles) on QT-interval

QT-prolonging allele	QTc_RAS ± SD	n
0	412.3 ± 13.8	70
1	415.8 ± 17.1	432
2	416.7 ± 16.4	905
3	417.7 ± 17.3	955
4	420.3 ± 17.7	561
5	420.4 ± 19.7	162
6	426.6 ± 18.2	19

Analysis of 174 LD based SNPs in 4 LQT-disease genes shows positive association in 3 loci and explains 15 ms of QT-interval variance

Pfeufer et al. Circ Res 2005

Hypotheses on genetic disposition to acquired LQTS

common gene variants in LQT disease genes and genes modulating cardiac repolarization or cardiac electrical properties are associated with risk for arrhythmia in acquired LQT syndrome

(e.g. in the context of QT prolonging drugs)

Searching for novel genes involved in QT regulation as the surrogate marker for cardiac repolarization

w/ hypothesis -> disease genes

w/o hypothesis -> genome wide

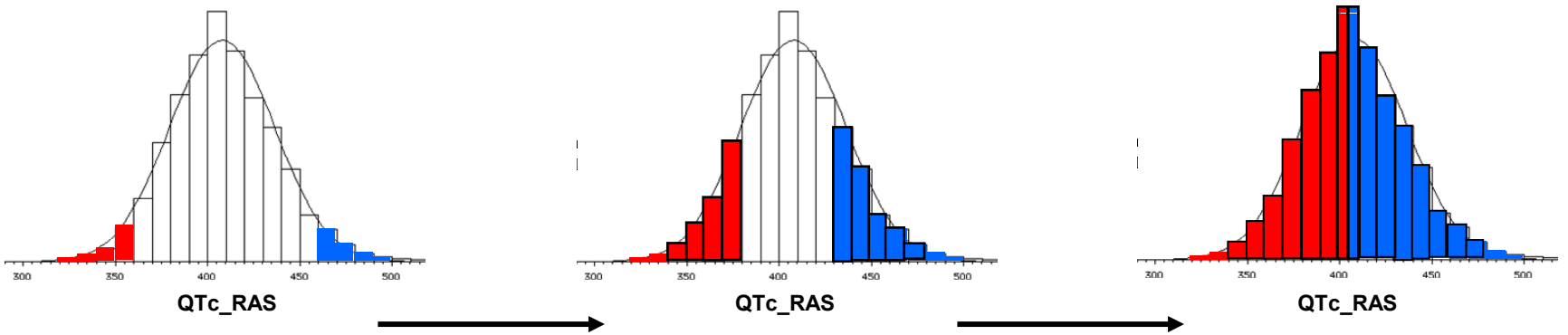
GWA of QT interval in the General Population (KORA) using 100 K SNP Chip

Three stage design:

Stage 1
- n=103/103 from each extreme (top and bottom 7.5th %tile)
- strict exclusion criteria
- females only
- Genomewide genotyping

Stage 2
- n=300/300 from each extreme
- relaxed exclusion criteria (s AF,pacer, pregnancy)
- females only
- SNPs that passed stage 1

Stage 3
- n=3,966, KORA S4 survey
- relaxed exclusion criteria (s AF,pacer, pregnancy)
- both genders
- SNPs that passed stage 2



NOS1AP (Capon) modulates QT interval by 5-10 ms (1,5% var.)

An hypothesis free genome wide association study was useful to identify a novel gene variant that modulates QT in the general population and may be a risk factor for drug induced LQT syndrome

Arking, Pfeufer et al., Nat. Genet 2006;38:644-651

Summary

- sotalol causes a concentration dependent lengthening of the QT interval, increasing action potential duration and refractory periods predominantly by blocking the delayed rectifier potassium current (IKr)
- for sotalol proarrhythmia is reported with a range of 1% to 8%
- hypertrophy and heart failure are acquired states with reduced repolarization reserve due to downregulation of repolarizing currents and thus are important co-factors for TdP in the context of drugs with QT-prolonging potential (i.E. Sotalol)
- Sotalol as a predominantly IKr blocking agent is a valid tool to study altered repolarization and susceptibility to TdP in the context of QT prolonging drugs
- common genetic variants modulate myocardial repolarization, define intrinsic individual repolarization stability and are likely to define intrinsic individual susceptibility to drug-induced LQT syndrome
- Combinations of multiple extrinsic and intrinsic factors (multiple allels) are defining the overall individual risk for drug induced LQT syndrome

Collaborations

LMU München
Großhadern
Med. Klinik I
Moritz Sinner
Martin Hinterseer
Britt-Maria Beckmann

TU München IHG, & GSF
Arne Pfeufer
Shapour Jalilzadeh
Mahmut Akyol
Thomas Meitinger

GSF, EPI & IMEI
Siegfried Perz
Thomas Illig
H.-Erich Wichmann

Vanderbilt University
Dan Roden

Amsterdam University
Arthur Wilde
Connie Beccina

University Münster
Eric Schulze-Bahr

Nantes, INSERM
Jean-Jaques Schott
Denis Escande (†)

Johns Hopkins University
Cardiology
Peter M. Spooner
Gordon Tomaselli
Eduardo Marbán

University Miami
Robert Myerburg
Nanette Bishopric

Johns Hopkins University
& McKusick-Nathan Institute
Dan E. Arking
Wendy Post
W.H. Linda Kao
Aravinda Chakravarti

University Medical Center
Utrecht
Marc Vos
Morten Thomsen

University of Rochester
Jean-Philippe Couderc
Wojciech Zareba
Arthur Moss

Grant Support

Nationales
Genomforschungsnetz

Krankheitsorientierte
Genomnetze

German National Genome Research Network

Fondation leducq Transatlantic Network of Excellence

http://www.allianceagainstscd.org/