Repolarization reserve and sudden cardiac death in competitive athletes

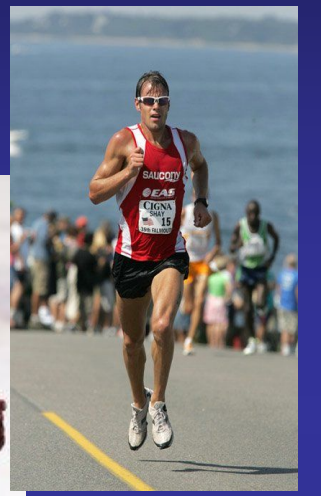
Garden view

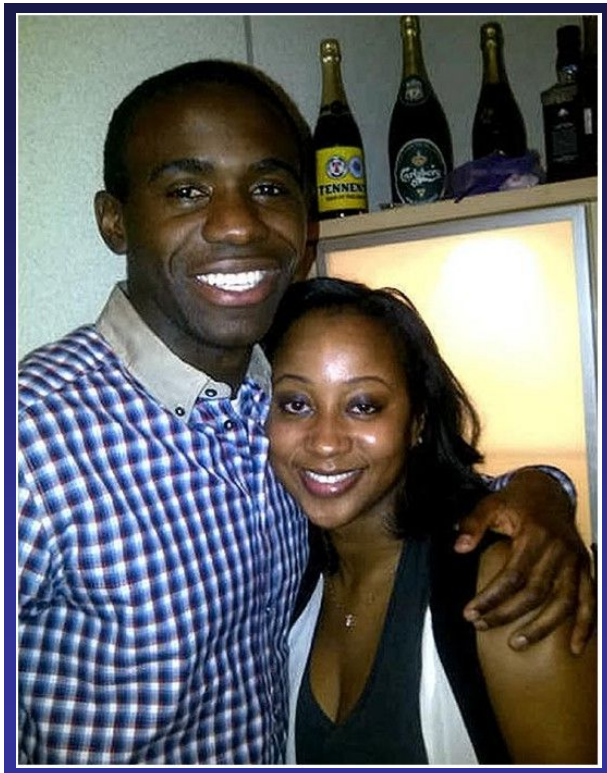
Street view

István Baczkó

[1]Department of Pharmacology & Pharmacotherapy, University of Szeged; Szeged, Hungary

SCD in competitive athletes: cardiac repolarization reserve impairment and increased arrhythmia susceptibility?





Can it be predicted? Can we screen for those individuals at high risk?

Miracle' Fabrice Muamba faced second heart alert

Published: 9 hrs ago
4

HEART-attack footballer Fabrice Muamba has revealed he endured the agony of a second scare during the summer.

The Bolton Wanderers midfielder made a miracle recovery after his heart stopped for 78 minutes during a match at Spurs last season.

He was enjoying a holiday with his family when he felt the defibrillator that doctors had fitted suddenly kick in.

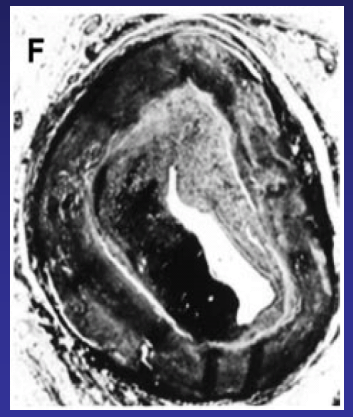
Muamba, 24, who was forced to retire from football, said: "It's like an electric shock and everything stops for a second.

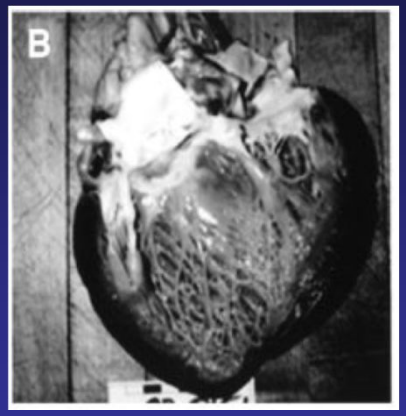
"You've got to get yourself together. It kicked in. That confirms it is working well, which is safe."

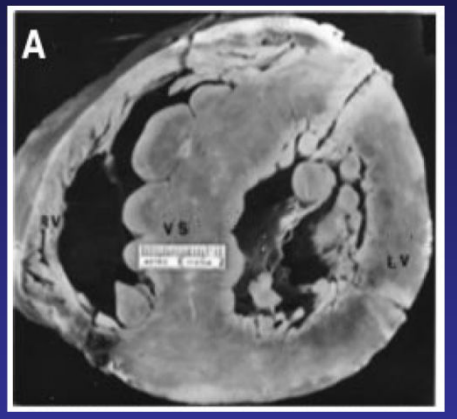
He was promoting Hearts and Goals, a campaign aiming to reduce cardiac arrest deaths.

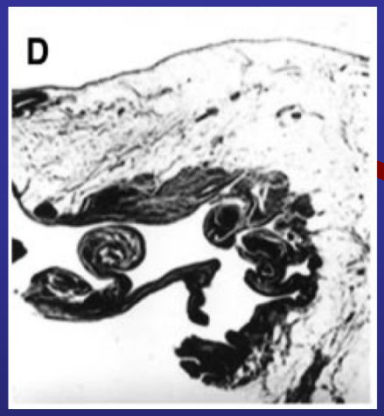
Read more: http://www.thesun.co.uk/sol/homepage/news/4591652/Miracle-Fabrice-Muamba-faced-second-heart-alert.html#ixzz29RyJJ92v

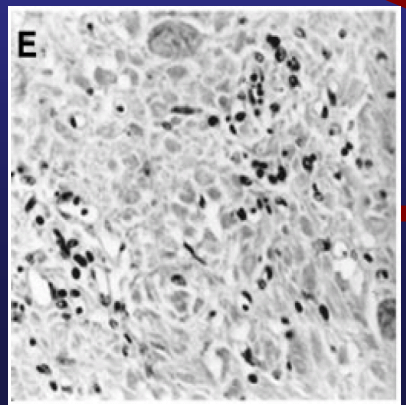
Autopsy findings in young athletes with SCD

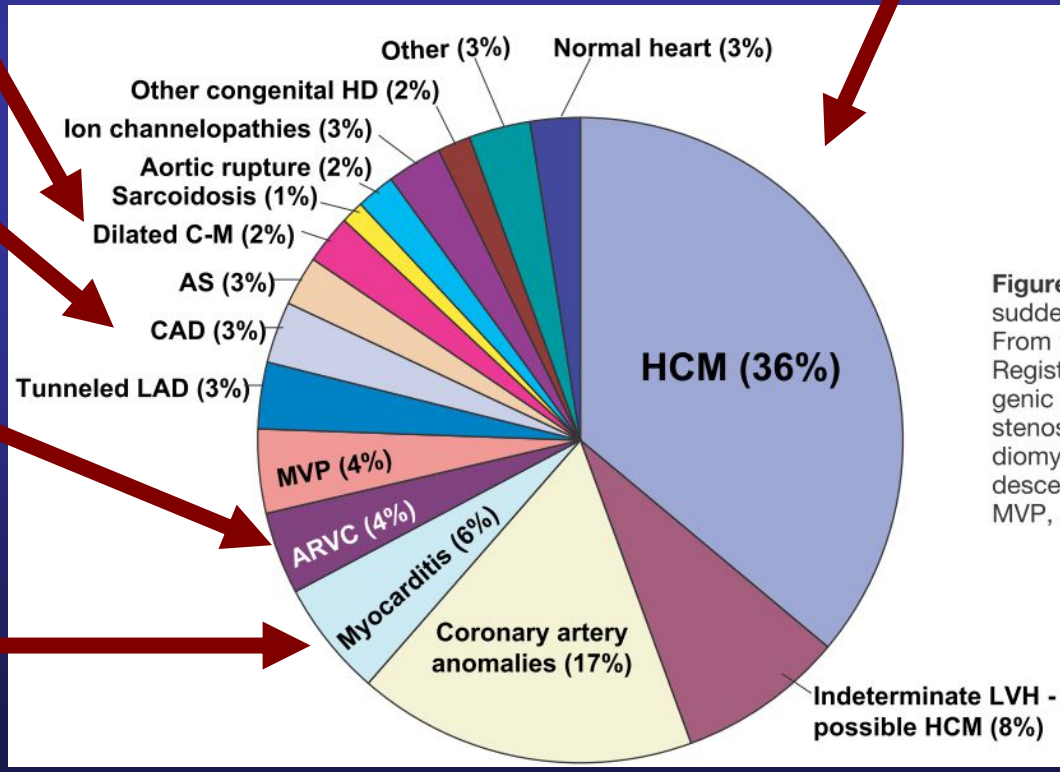












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Maron and Pelliccia
Circulation 2006;114;
1633-1644

Maron *Cardiol Clin* 25 (2007) 399–414

Decrease of SCD in competitive athletes
In Northern Italy (preparticipation screening!!!)

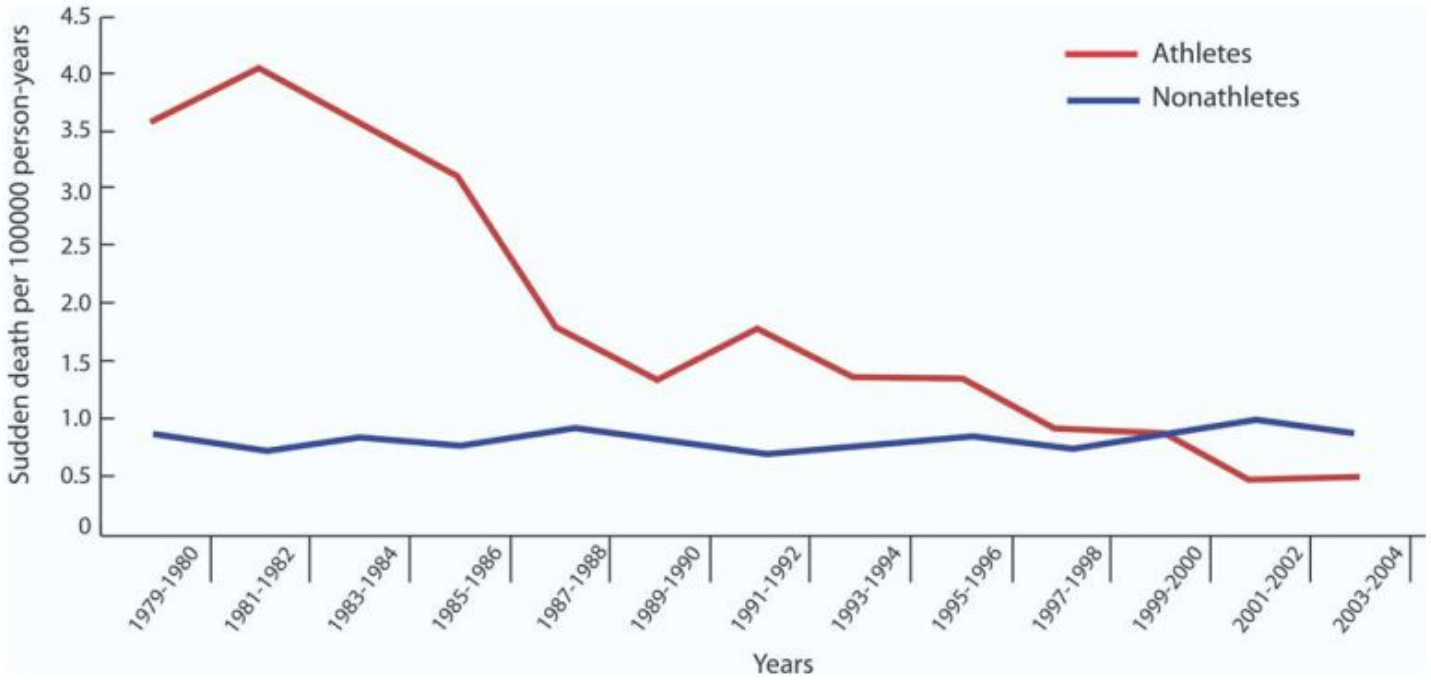
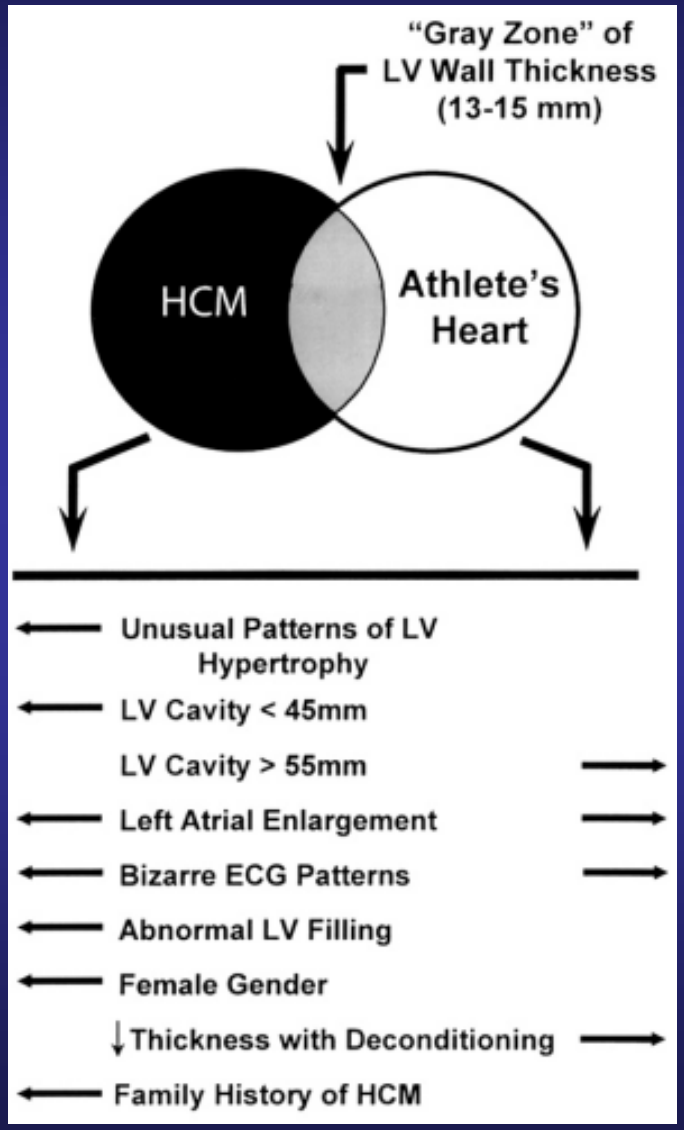
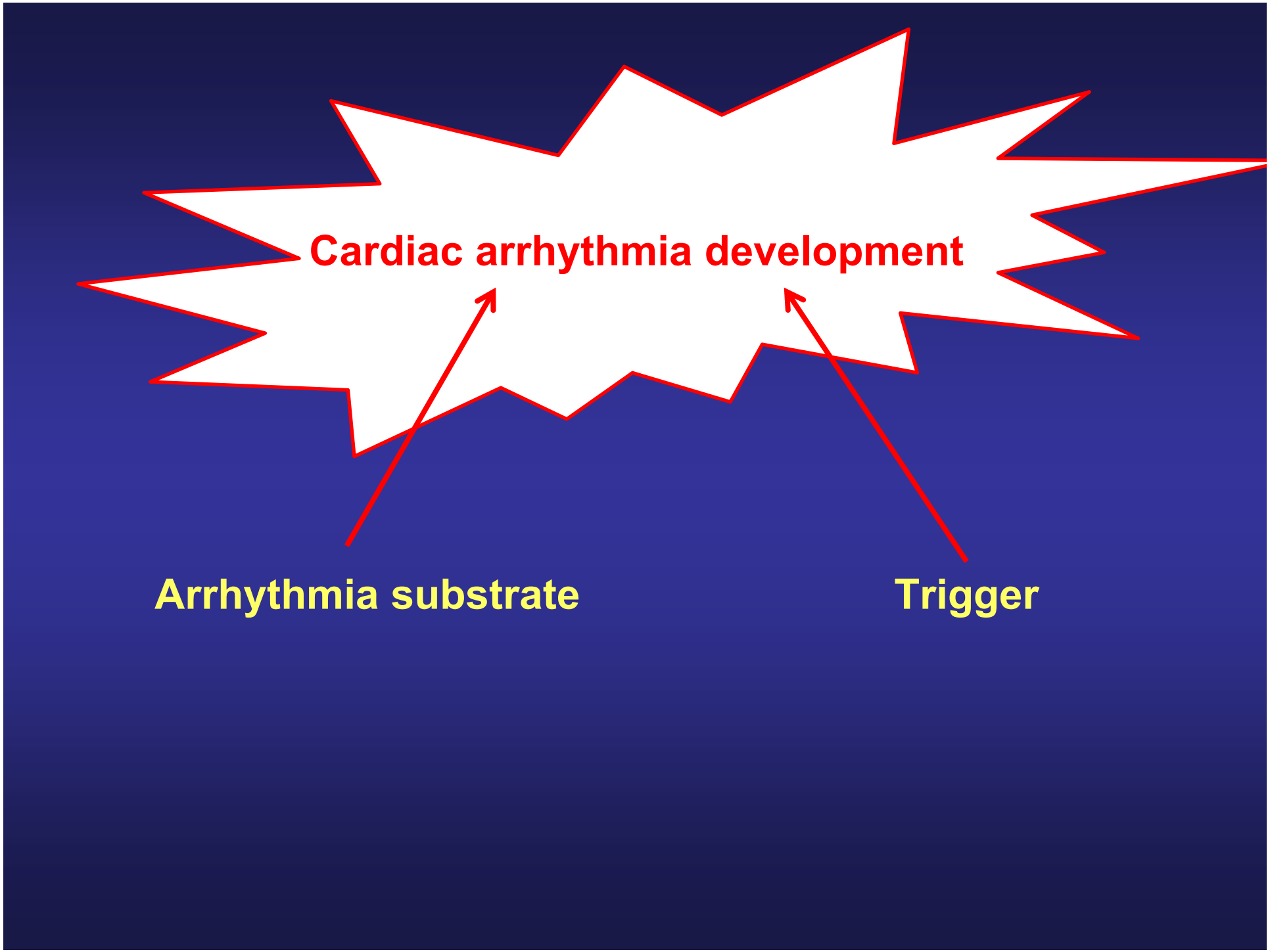


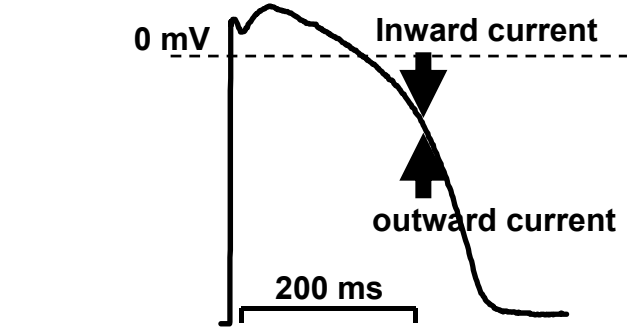
Figure 3 Annual Incidence Rates of Sudden Cardiac Death Among Screened Competitive Athletes and Unscreened Nonathletes in the Veneto Region of Italy From 1979 to 2004

Differentiating between HCM and athlete's heart




Cardiac arrhythmia development
Arrhythmia substrate
Trigger

Cardiac action potential and underlying currents



transmembrane current

channel proteins

I_{Na}	Nav1.5, Nav1.7, Nav2.1, Navβ1, Navβ2
I_{Ca}	Cav1.2, Cav3.17, Cav1.3, Cavα2d1, Cavβ2
I_{to}	Kv1.4, Kv1.7, Kv3.4, Kv4.2, Kv4.3, KCHIP2
I_{Kr}	(H)ERG, MIRP2 + MIRP3
I_{Ks}	KvLQT1 + MinK + MIRP2 + MIRP3
I_{k1}	Kir 2.1, Kir2.2, Kir2.3, Kir2.4, TWIK1, TASK2
I_{NCX}	NCX1
$I_{Na/K}$	Na/K ATP-ase α β

Cardiac repolarization reserve and the role of I_{Ks}

- When repolarization is prolonged or sympathetic tone is increased, I_{Ks} provides a safety mechanism limiting excess repolarization prolongation
- Down-regulation, genetic or acquired loss of I_{Ks} function impairs repolarization reserve

GUEST EDITORIAL

Taking the "Idio" out of "Idiosyncratic": Predicting Torsades de Pointes

DAN M. RODEN

From the Division of Clinical Pharmacology and Arrhythmia Unit, Vanderbilt University School of Medicine, Nashville, TN 37232

Journal of Physiology (2000), **523.1**, *pp.*67–81

The role of the delayed rectifier component I_{Ks} in dog ventricular muscle and Purkinje fibre repolarization

András Varró*, Beáta Baláti*, Norbert Iost*§, János Takács*, László Virág*, David A. Lathrop‖, Lengyel Csaba†, László Tálosi‡ and Julius Gy. Papp*§

Restricting Excessive Cardiac Action Potential and QT Prolongation

A Vital Role for I_{Ks} in Human Ventricular Muscle

Norbert Jost, PhD; László Virág, PhD; Miklós Bitay, MD, PhD; János Takács, MD, PhD; Csaba Lengyel, MD, PhD; Péter Biliczki, MD; Zsolt Nagy, MSc; Gábor Bogáts, MD, PhD; David A. Lathrop, PhD; Julius G. Papp, MD, DSc; András Varró, MD, DSc

(*Circulation*. 2005;112:1392-1399.)

BJP British Journal of Pharmacology

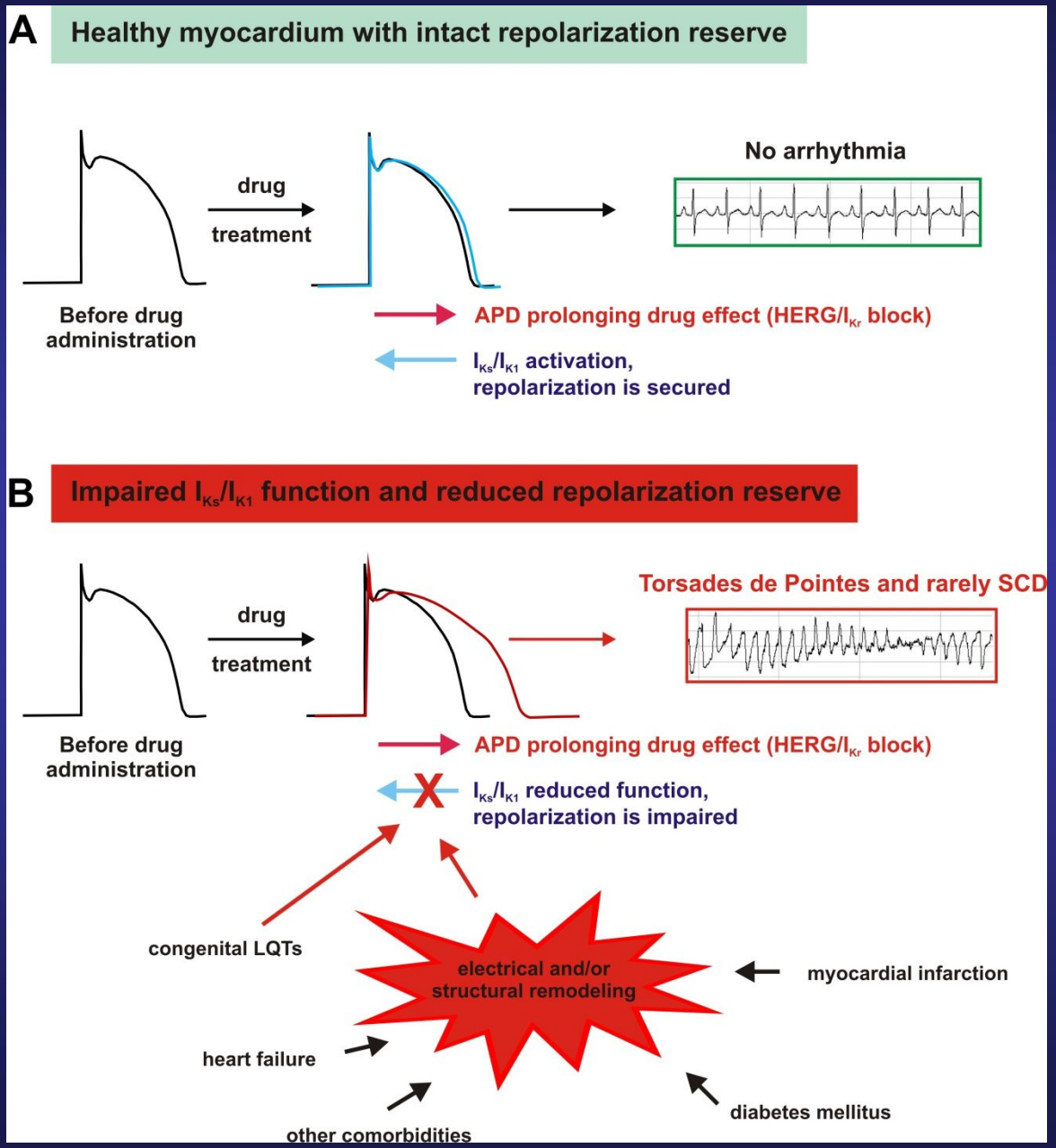
REVIEW

Cardiac ventricular repolarization reserve: a principle for understanding drug-related proarrhythmic risk

András Varró[1,2] and István Baczkó[1]

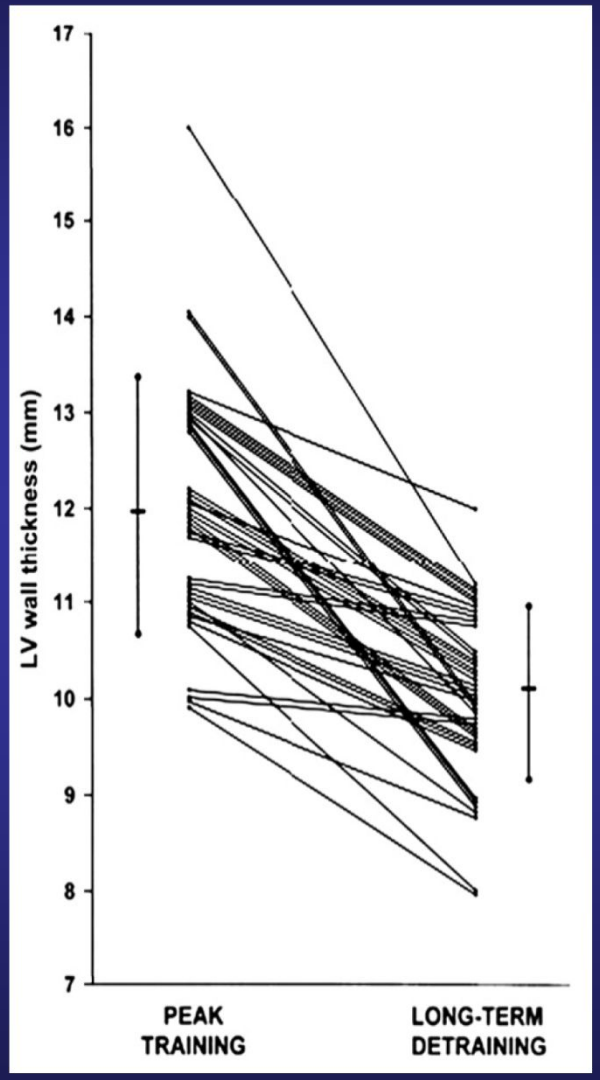
[1]*Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary, and* [2]*Division of Cardiovascular Pharmacology, Hungarian Academy of Sciences, Szeged, Hungary*

Cardiac repolarization reserve and the role of I_{Ks}

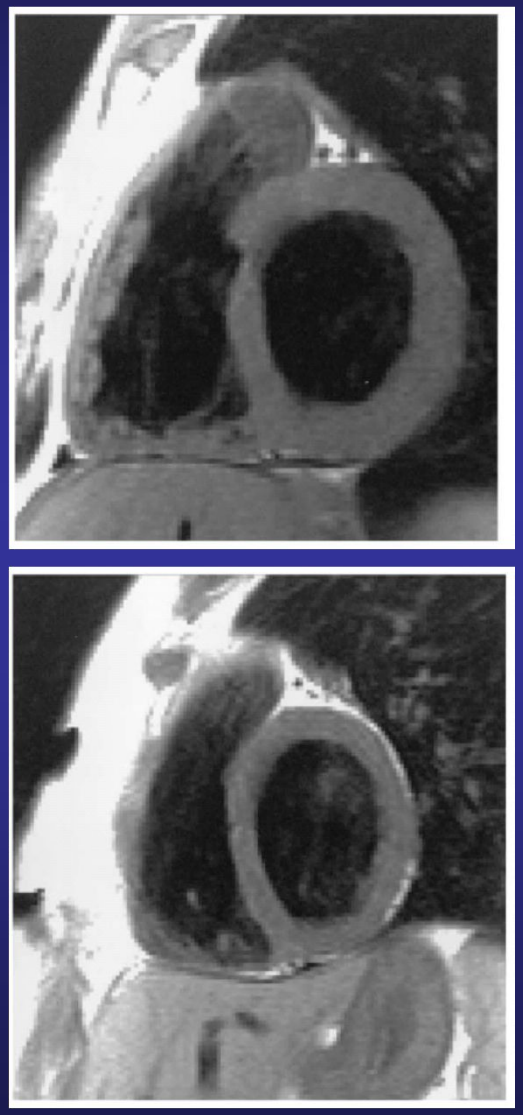


Ferdinandy P, Baczkó I *et al*., European Heart Journal, *in print*, 2018

Athlete's heart: reversible cardiac hypertrophy

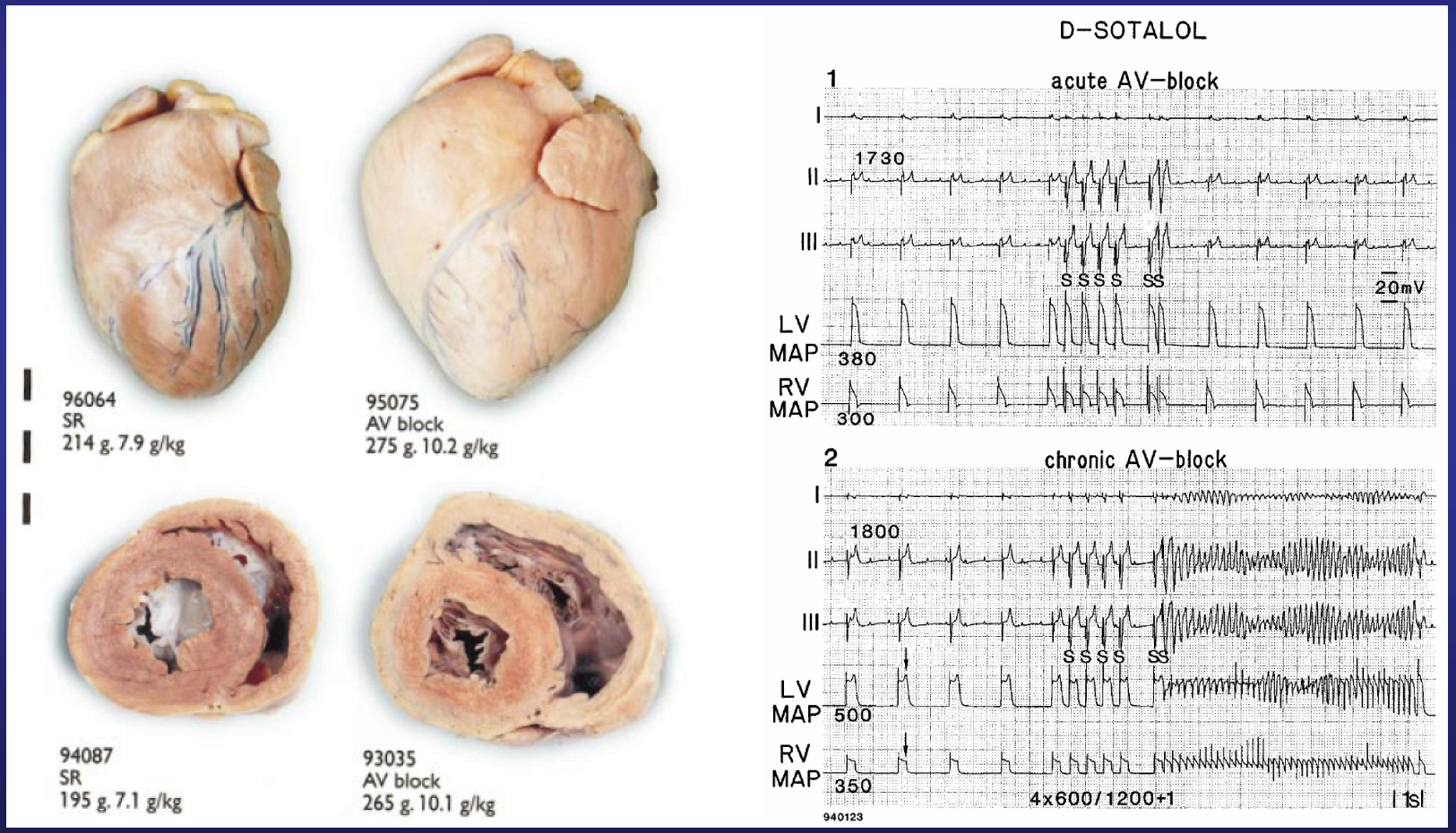


Pelliccia et al. *Circulation* 2002;105:944–9.



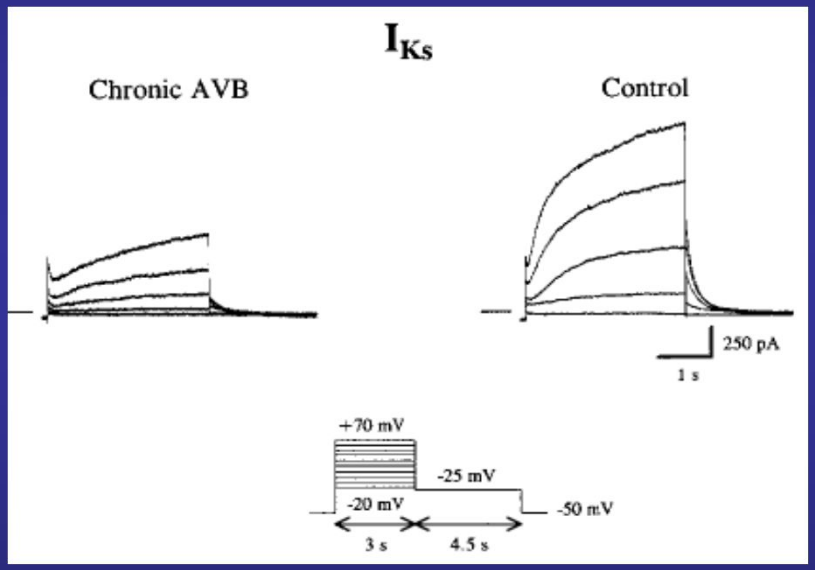
Scharhag et al. *JACC* Vol. 40, No. 10, 2002

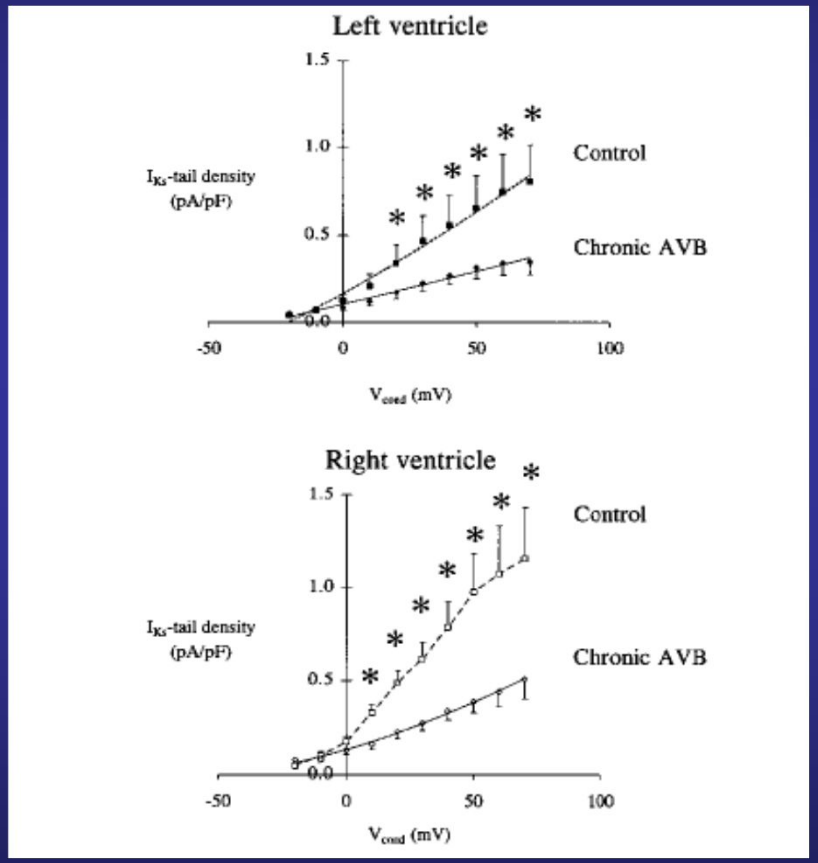
The I_{Kr} blocker d-sotalol causes TdP arrhythmia only following I_{Ks} downregulation in dogs with chronic AV-block



Vos et al., Circulation 1998

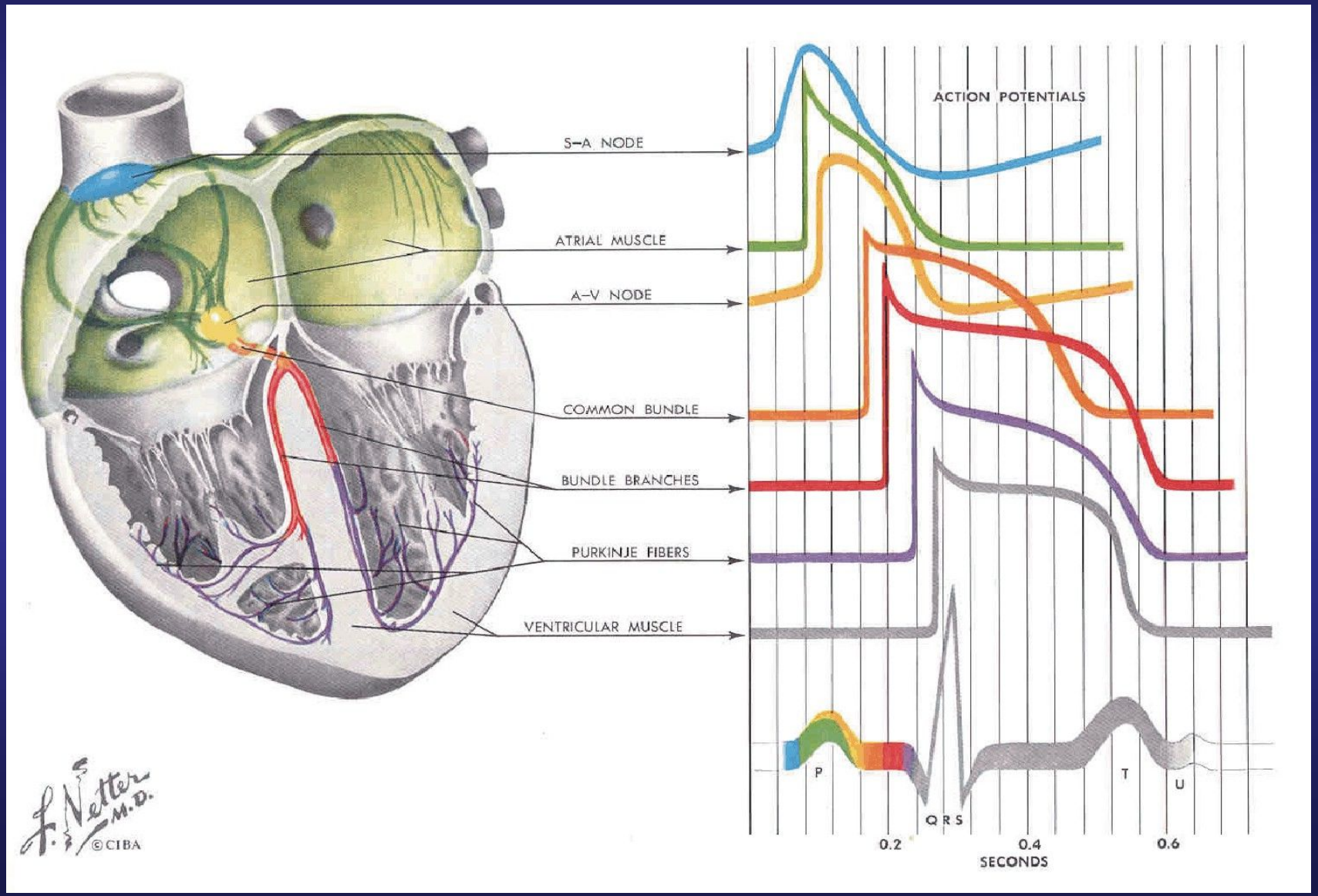
I_{Ks} downregulation in dogs with chronic AV-block: reduced repolarization reserve



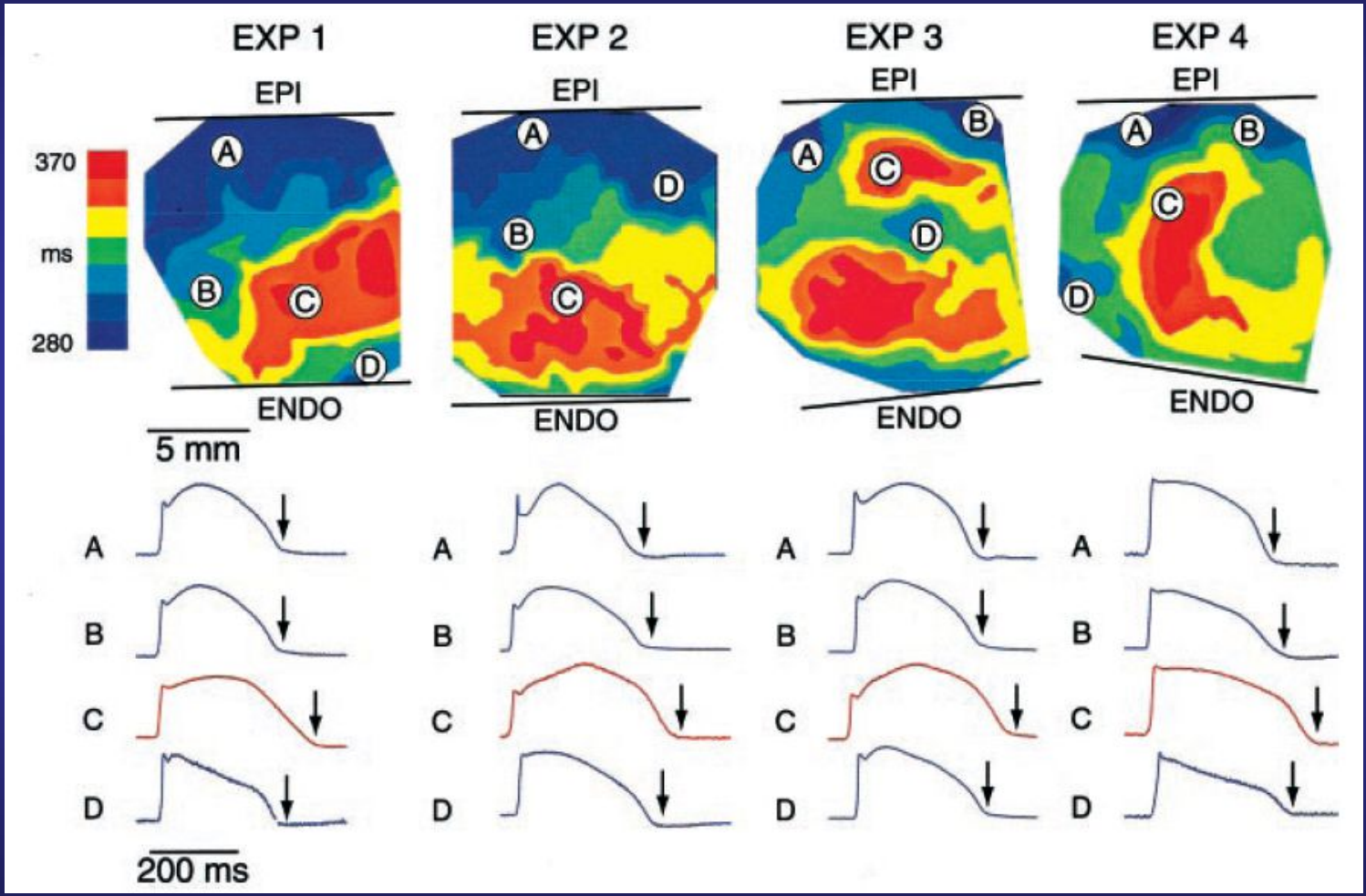


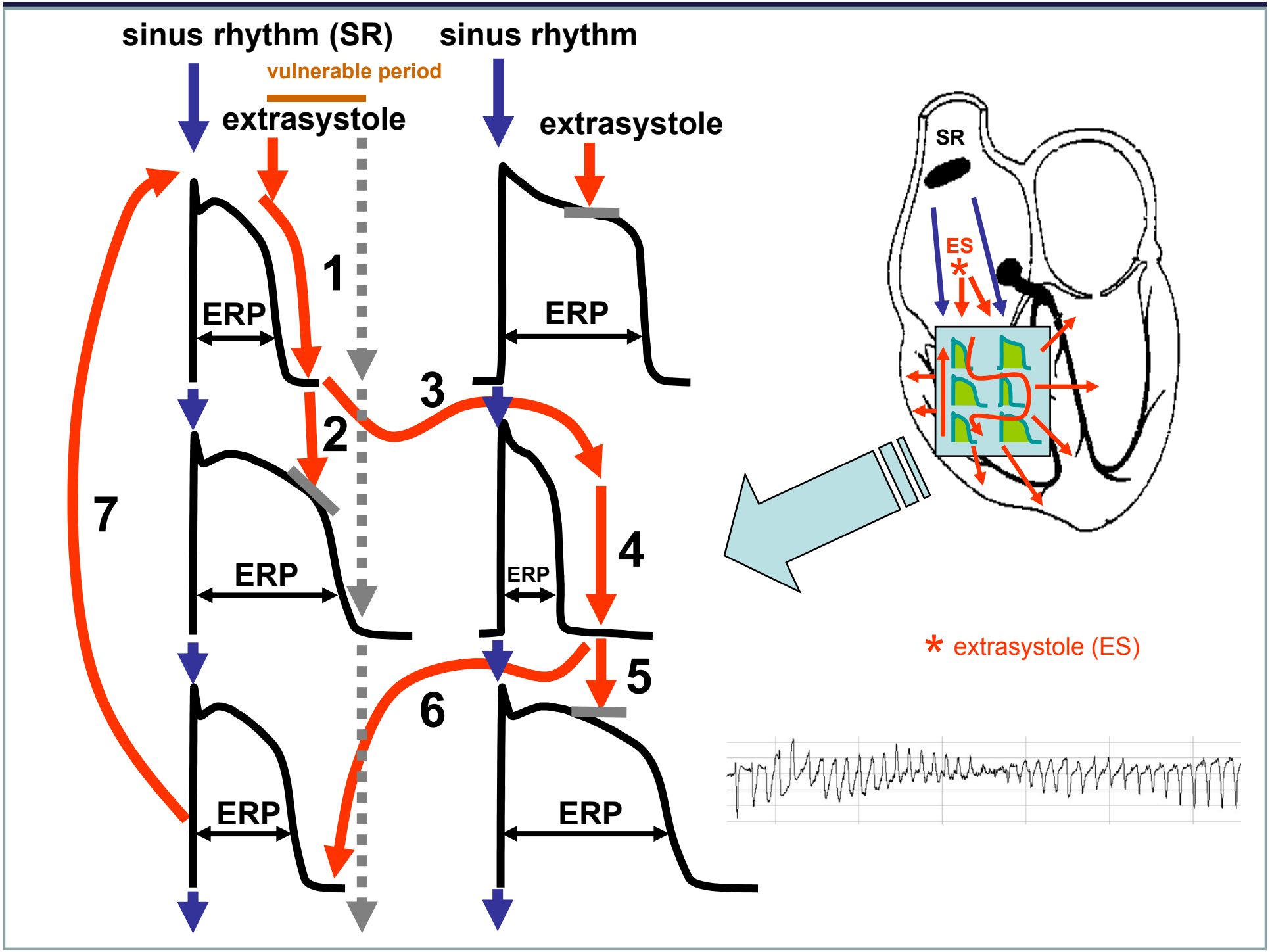
Volders et al., *Circulation*, 1999

Arrhythmia substrate: heterogeneity of repolarization duration



Transmural APD heterogeneity



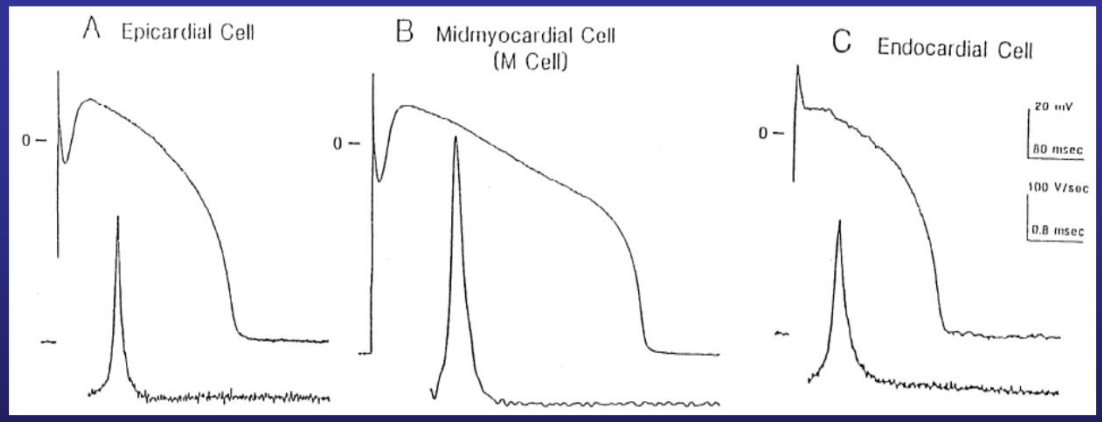

sinus rhythm (SR)
sinus rhythm
vulnerable period
extrasystole
extrasystole
ERP
ERP
ERP
ERP
ERP
ERP
1
2
3
4
5
6
7
SR
ES
* extrasystole (ES)

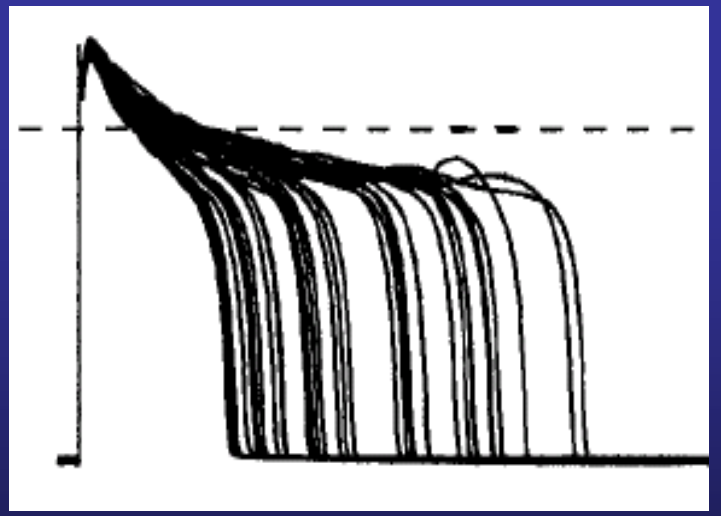
Variability in repolarization

What does it mean?

spatial
Purkinje fibre, M-cell, Subendocardial, Subepicardiali Base, Apex

temporal
beat-to-beat

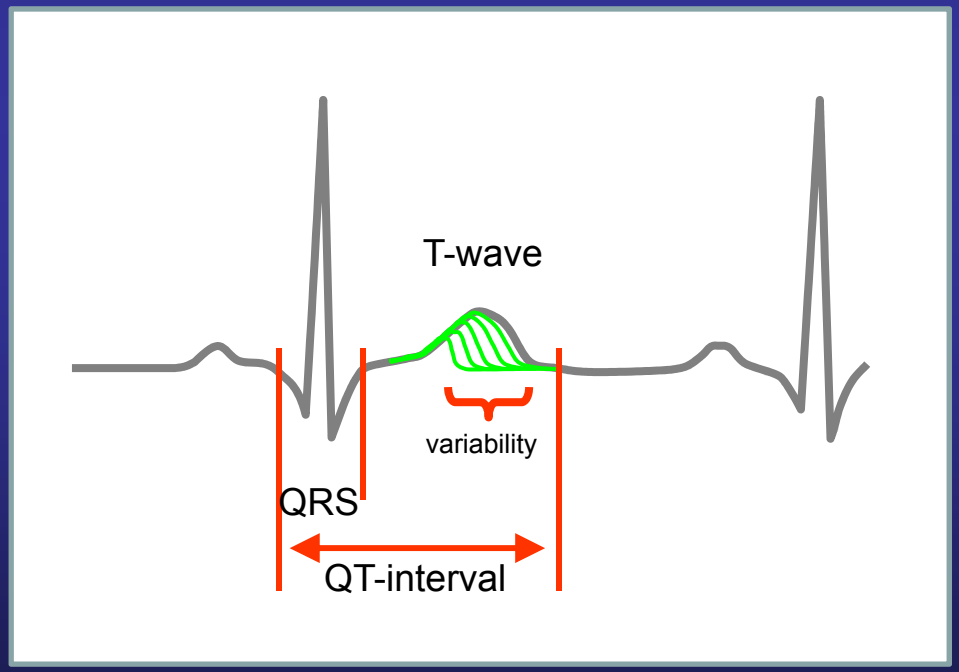


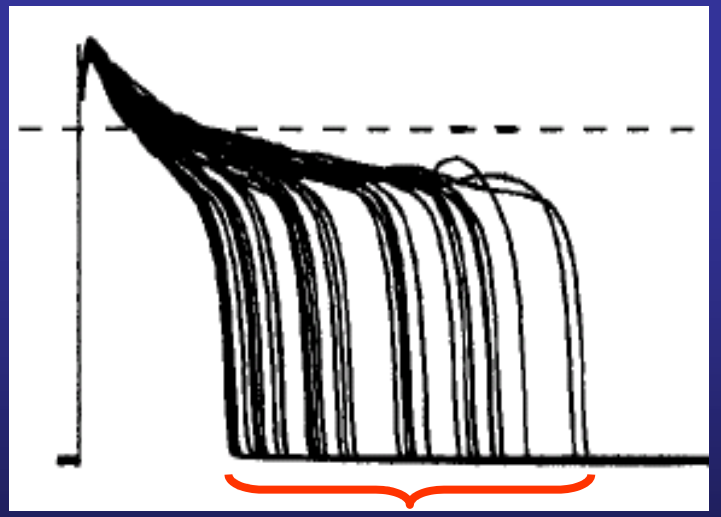


Short-term variability (STV) as a parameter for repolarization reserve

In vivo, clinical (ECG)

Cellular (action potential)





How can we measure repolarization variability?

QT or APD

Variability index

$$QT_{vi} = \log_{10}\left[\frac{QT_v / QT_m^2}{HR_v / HR_m^2}\right]$$

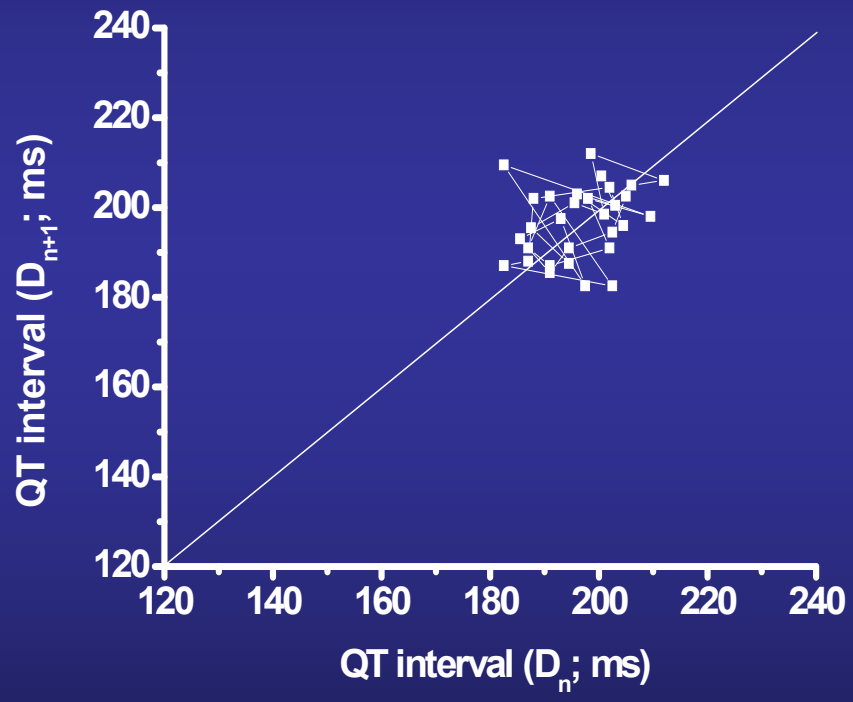
Berger et al., Circulation, 1997

Short-term beat-to-beat variability

$$STV = \frac{\sum |D_{n+1} - D_n|}{30 \cdot \sqrt{2}}$$

Brennan et al. *IEEE,* 2001; 48:1342-47.

Poincaré plot



Cardiosys ECG system for QT variability

Cardiosys-A01/C01 computerized recording and analyzing system with integrated ECG and blood pressure monitoring, and resting Holter

Increased temporal instability in professional soccer players: increased arrhythmia susceptibility?

OPEN ACCESS Freely available online

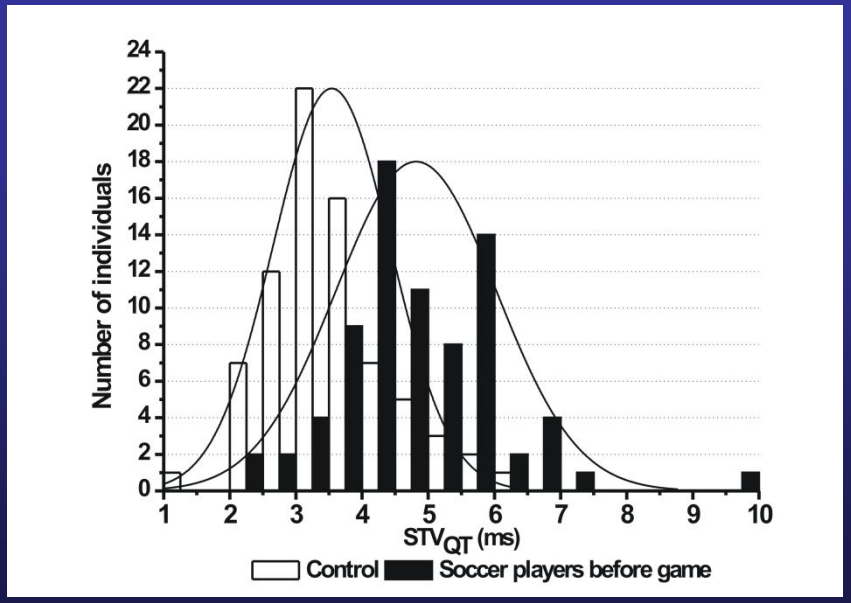
PLoS one

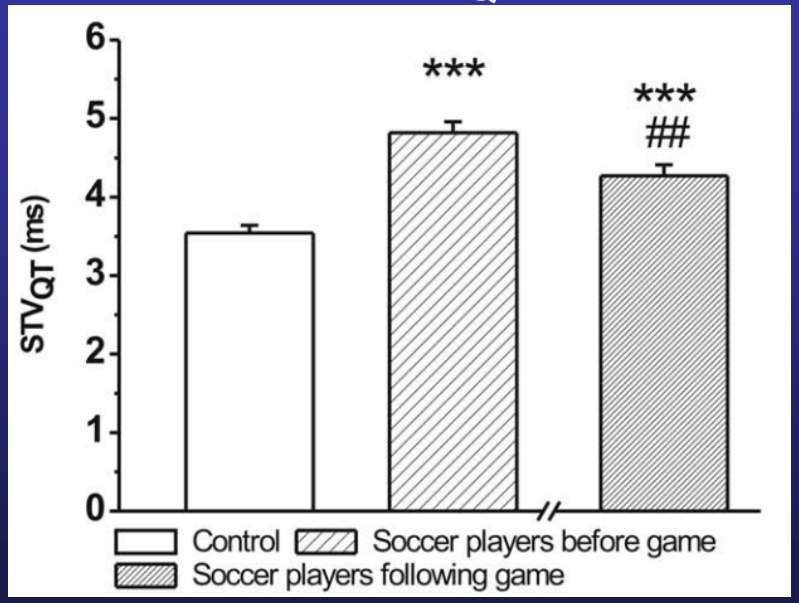
Increased Short-Term Variability of the QT Interval in Professional Soccer Players: Possible Implications for Arrhythmia Prediction

Csaba Lengyel[1], Andrea Orosz[2], Péter Hegyi[1], Zsolt Komka[3], Anna Udvardy[3], Edit Bosnyák[3], Emese Trájer[3], Gábor Pavlik[3], Miklós Tóth[3], Tibor Wittmann[1], Julius Gy. Papp[2,4], András Varró[2,4], István Baczkó[2]*

1 1st Department of Internal Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary, 2 Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary, 3 Department of Health Sciences and Sports Medicine, Faculty of Physical Education and Sports Sciences, Semmelweis University, Budapest, Hungary, 4 Division of Cardiovascular Pharmacology, Hungarian Academy of Sciences, Szeged, Hungary

Short-term variability of the QT interval (STV_{QT})



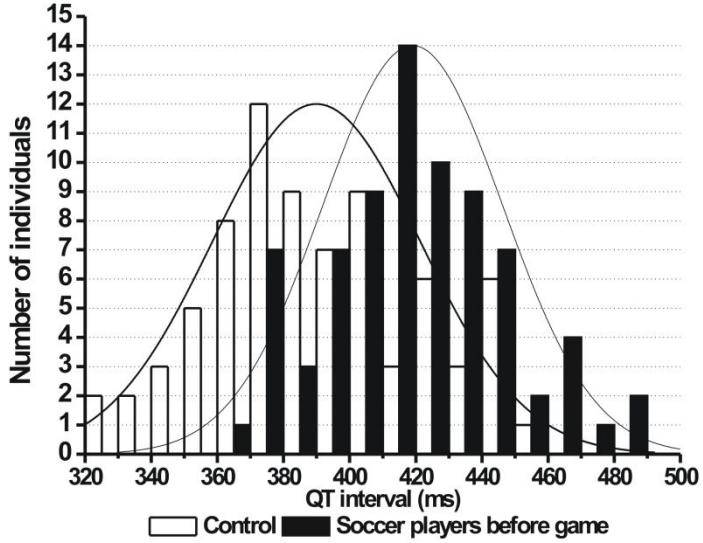


n = 76 in both groups

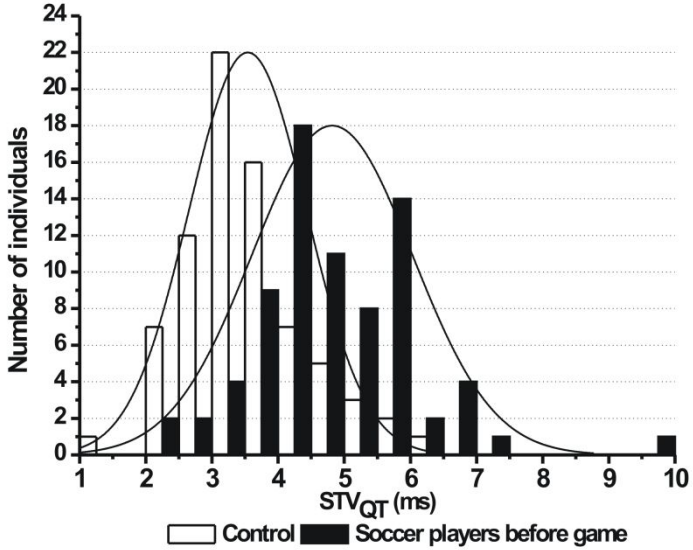
Lengyel, Orosz, …, Varró, Baczkó, PLoS ONE, 2011

Short-term QT variability in soccer players

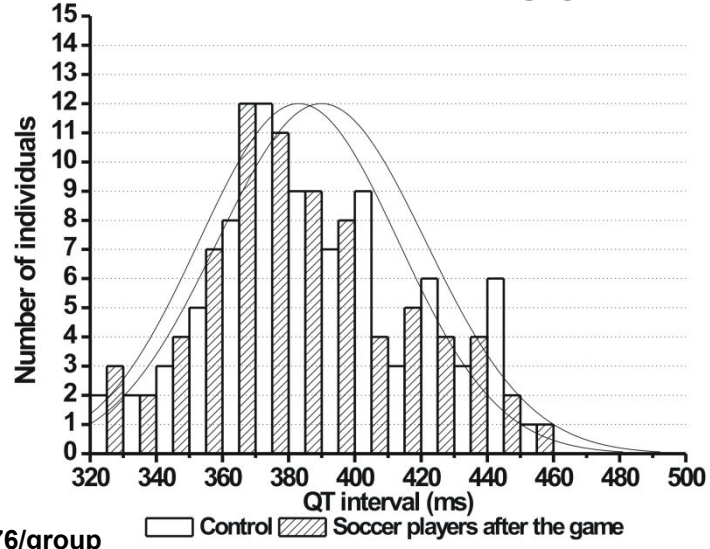
QT interval before game



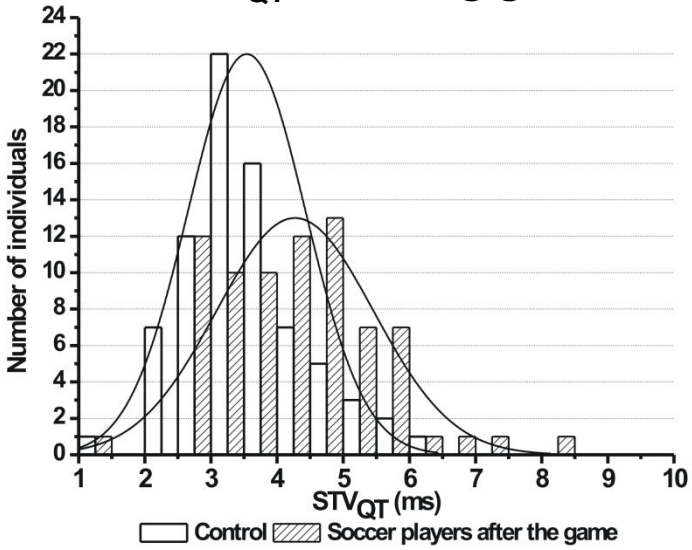
STV_{QT} before game



QT interval following game



STV_{QT} following game



n = 76/group

Lengyel et al., *PLoS ONE*, 2011

PLOS | ONE

RESEARCH ARTICLE

Increased Short-Term Beat-To-Beat Variability of QT Interval in Patients with Acromegaly

Andrea Orosz[1], Éva Csajbók[2], Csilla Czékus[2], Henriette Gavallér[3], Sándor Magony[2], Zsuzsanna Valkusz[2], Tamás T. Várkonyi[2], Attila Nemes[3], István Baczkó[1], Tamás Forster[3], Tibor Wittmann[2], Julius Gy. Papp[1,4], András Varró[1,4], Csaba Lengyel[1,2]*

1 Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Szeged, Szeged, Hungary, **2** 1st Department of Internal Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary, **3** 2nd Department of Internal Medicine and Cardiology Center, Faculty of Medicine, University of Szeged, Szeged, Hungary, **4** MTA-SZTE Research Group of Cardiovascular Pharmacology, Hungarian Academy of Sciences, Szeged, Hungary

NRC Research Press

ARTICLE

Short-term beat-to-beat variability of the QT interval is increased and correlates with parameters of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy[1]

Andrea Orosz, István Baczkó, Viktória Nagy, Henriette Gavallér, Miklós Csanády, Tamás Forster, Julius Gy. Papp, András Varró, Csaba Lengyel, and Róbert Sepp

Abstract: Stratification models for the prediction of sudden cardiac death (SCD) are inappropriate in patients with hypertrophic cardiomyopathy (HCM). We investigated conventional electrocardiogram (ECG) repolarization parameters and the beat-to-beat short-term QT interval variability (QT-STV), a new parameter of proarrhythmic risk, in 37 patients with HCM (21 males, average age 48 ± 15 years). Resting ECGs were recorded for 5 min and the frequency corrected QT interval (QTc), QT dispersion (QTd), beat-to-beat short-term variability of QT interval (QT-STV), and the duration of terminal part of T waves (*T*peak–*T*end) were calculated. While all repolarization parameters were significantly increased in patients with HCM compared with the controls (QTc, 488 ± 61 vs. 434 ± 23 ms, $p < 0.0001$; QT-STV, 4.5 ± 2 vs. 3.2 ± 1 ms, $p = 0.0002$; *T*peak–*T*end duration, 107 ± 27 vs. 91 ± 10 ms, $p = 0.0015$; QTd, 47 ± 17 vs. 34 ± 9 ms, $p = 0.0002$), QT-STV had the highest relative increase (+41%). QT-STV also showed the best correlation with indices of left ventricular (LV) hypertrophy, i.e., maximal LV wall thickness normalized for body surface area (BSA; $r = 0.461$, $p = 0.004$) or LV mass (determined by cardiac magnetic resonance imaging) normalized for BSA ($r = 0.455$, $p = 0.015$). In summary, beat-to-beat QT-STV showed the most marked increase in patients with HCM and may represent a novel marker that merits further testing for increased SCD risk in HCM.

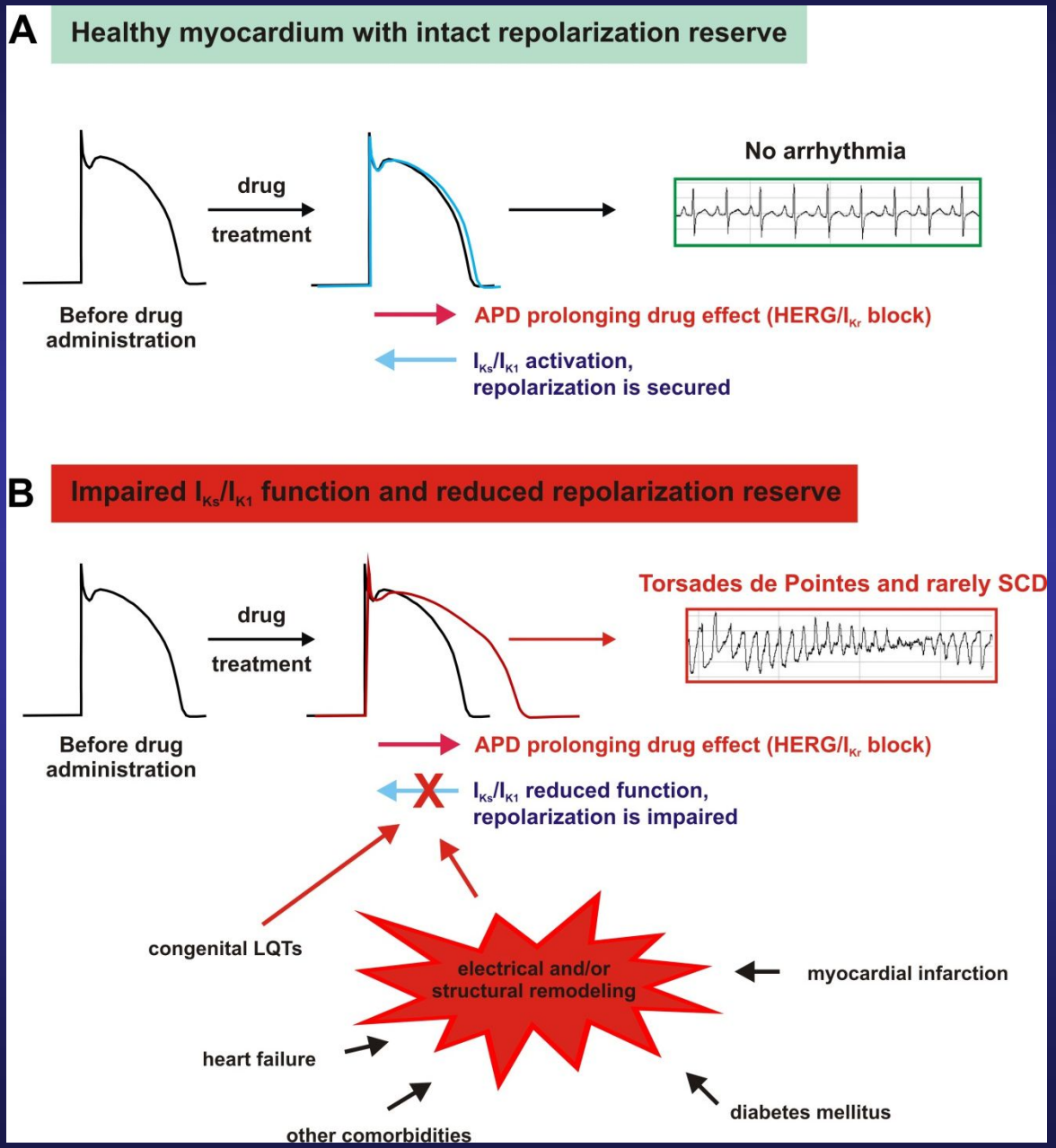
Pflugers Arch - Eur J Physiol (2010) 460:31–40
DOI 10.1007/s00424-010-0798-0

CARDIOVASCULAR PHYSIOLOGY

Possible mechanisms of sudden cardiac death in top athletes: a basic cardiac electrophysiological point of view

András Varró · István Baczkó

Cardiac repolarization reserve and the role of I_{Ks}



Ferdinandy P, Baczkó I *et al*., European Heart Journal, *in print*, 2018

Impaired repolarization reserve and SCD in competitive athletes

- Myocardial hypertrophy: I_{Ks} downregulation (athlete's heart)
- Sweating: chance for hypokalaemia: I_{Kr} decrease
- Seemingly harmless drugs e.g. antibiotics, antihistamines, NSAIDs (?)

Miklós Fehér

- Genetic alterations, I_{Ks} impairment
- Stress situation (trigger!)
- Dietary constituents (e.g. grapefruit juice)

Impaired repolarization reserve and SCD in competitive athletes

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Miklós Fehér

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FRIDAY 22 SEPTEMBER 2006

Could common painkillers be cause of so many players' deaths?

DOUG GILLON
DOUG GILLON

THE Danish football federation is to investigate the deaths of two players after a TV documentary linked their heart failures to the use of painkillers available without prescription.

The programme, "When Death Plays Along, " stated the four used anti-inflammatory drugs before they died. Ibuprofen and diclofenac (also known as Voltaren) were mentioned.

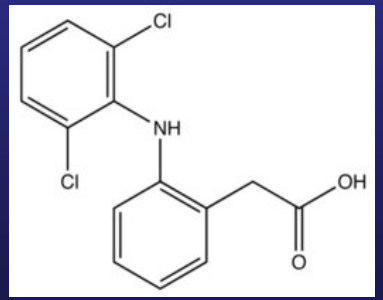
Such drugs are known to increase the risk of heart failure, though generally in people prone to cardiac problems.

Allan Hansen, the Danish federation chairman, said medical experts would review the circumstances surrounding the deaths of the two Danes and, "make a report which we can discuss and adopt an attitude to internally."

Mogens Kreutzfeldt, the Danish team doctor, said it was possible there was "inexpedient use [of non-specific anti-inf lammatory drugs] among players, " but added that the Danish team bans players from taking painkillers before matches.

Diclofenac

- Diclofenac - NSAID, nonselective COX inhibitor
- Widely used as analgesic, antiinflammatory drug
- Some preparations are OTC
- Also used by athletes for sports injuries, most likely often in higher than recommended dose
- Accumulating evidence suggests increased cardiovascular risk associated with NSAID use



diclofenac

Introduction: NSAIDs and cardiovascular safety

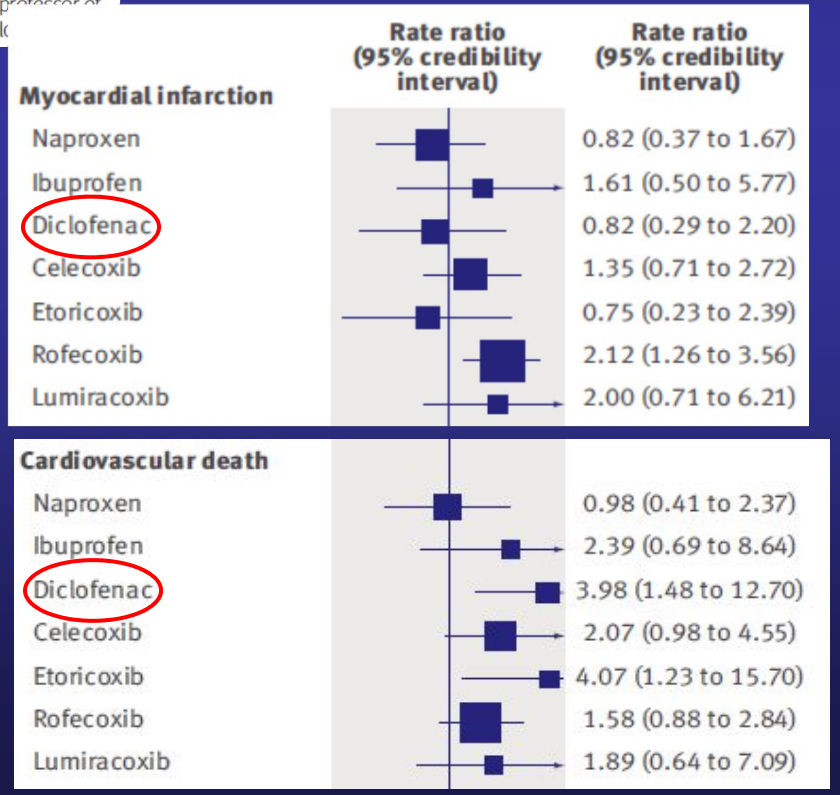
BMJ

RESEARCH

Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis

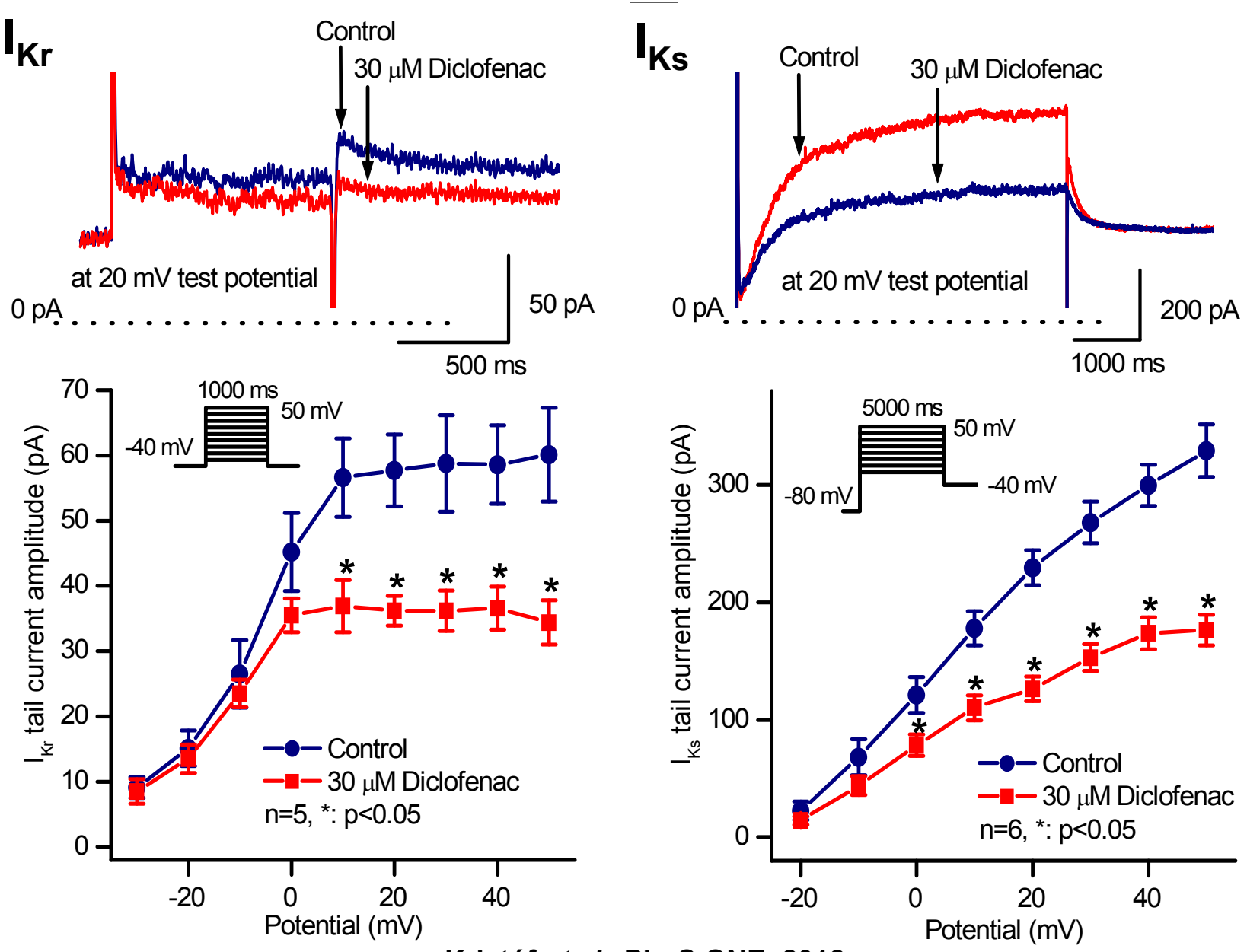
Sven Trelle, senior research fellow,[1,2] Stephan Reichenbach, senior research fellow,[1,4] Simon Wandel, research fellow,[1] Pius Hildebrand, clinical reviewer,[3] Beatrice Tschannen, research fellow,[1] Peter M Villiger, head of department and professor of rheumatology,[4] Matthias Egger, head of department and professor of epidemiology and public health,[1] Peter Jüni, head of division and professor of clinical epidemiol

Conclusions Although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms. Naproxen seemed least harmful. Cardiovascular risk needs to be taken into account when prescribing any non-steroidal anti-inflammatory drug.



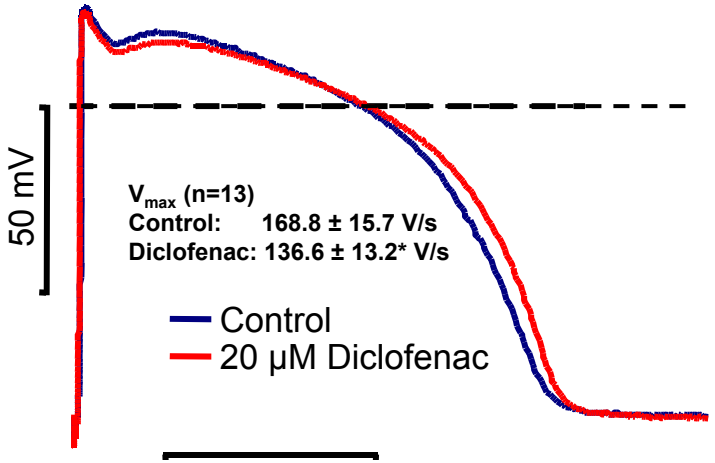
Trelle S *et al.*, BMJ 2011, 342: c7086

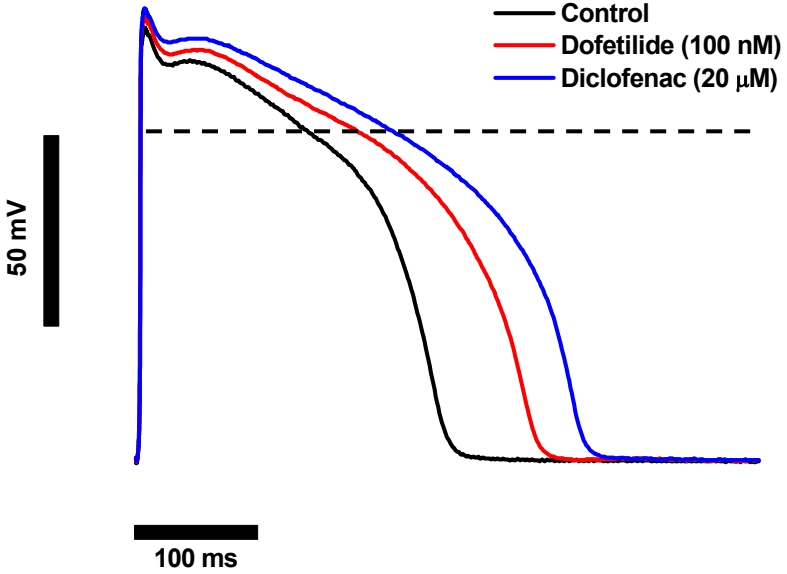
Effect of diclofenac on I_{Kr} and I_{Ks}

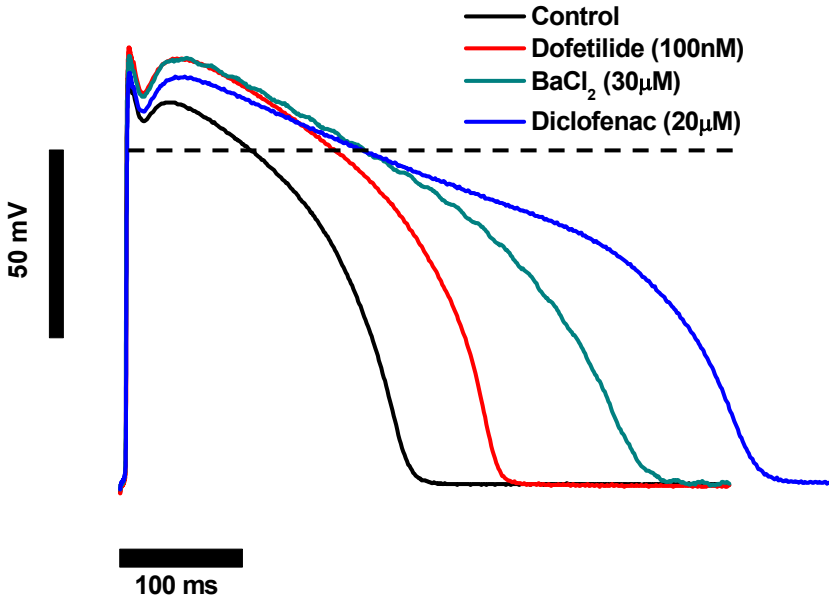


Kristóf *et al.*, PLoS ONE, 2012

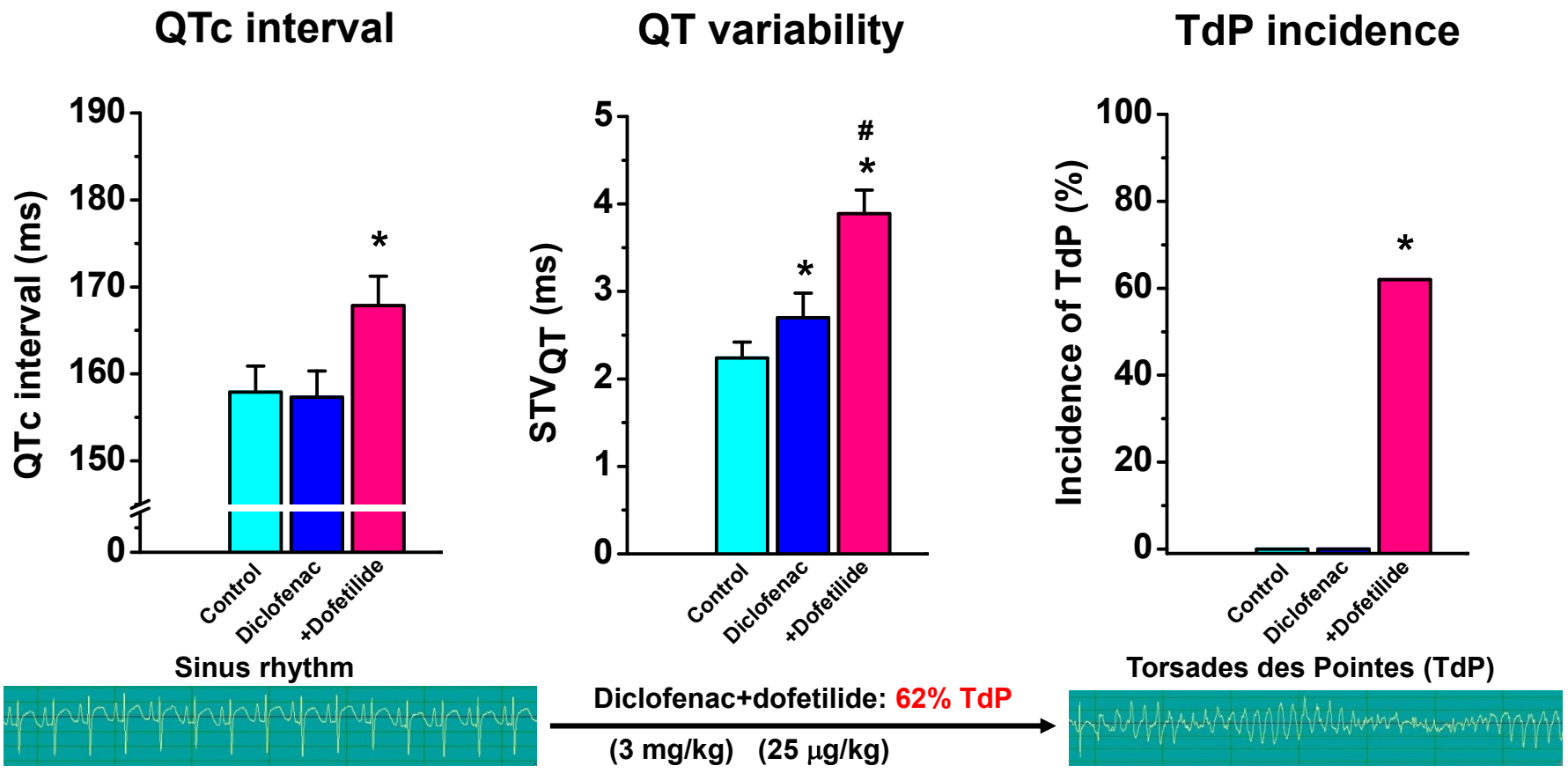
Effect of diclofenac on APD in right ventricular muscle







Effect of diclofenac administration on QTc, short-term QT variability and the incidence of TdP in anaesthetized rabbits



*p<0.05 vs. control, #p<0.05 vs diclofenac; n= 13-15 animals/group

Kristóf *et al.*, PLoS ONE, 2012

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PLOS ONE

Diclofenac Prolongs Repolarization in Ventricular Muscle with Impaired Repolarization Reserve

Attila Kristóf[2], Zoltán Husti[1], István Koncz[1], Zsófia Kohajda[2], Tamás Szél[1], Viktor Juhász[1], Péter Biliczki[1], Norbert Jost[2], István Baczkó[1], Julius Gy Papp[1,2], András Varró[1,2]*, László Virág[1,2]

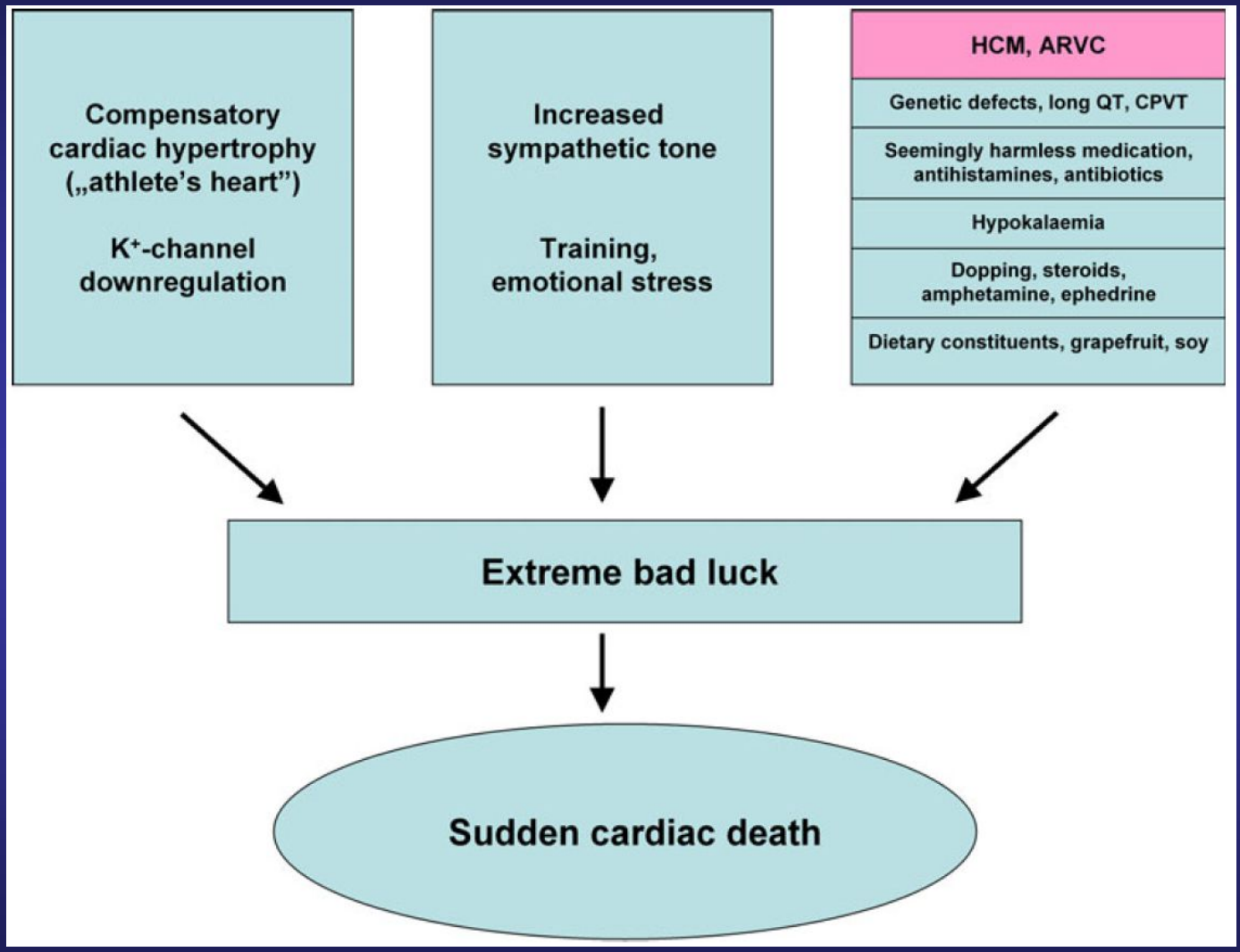
1 Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary, **2** Division of Cardiovascular Pharmacology, Hungarian Academy of Sciences, Szeged, Hungary

Drugs causing acquired long-QT syndrome

Antibiotics	ampicillin, macrolides, kinolones, trimethoprim + sulfamethoxasol, etc.
Antimycotics	fluconazole, ketoconazole, etc.
Hypokalaemia, hypomagnesaemia by drugs	diuretics, glucocortikoids, etc.
Nonsteroid anti-inflammatory drugs (NSAIDS)	diclofenac, etc.
β_2-receptor agonists	fenoterol, salbutamol, salmeterol, etc.
Antihistamines	astemizole, terfenadine, stb.
Prokinetics	domperidone
Antipsychotics	1st & 2nd generation antipsychotics
Antidepressants	tri- and tetracyclic antidepressants serotonin reuptake inhibitors
Other drugs	vardenafil, tamoxifen vinpocetin, etc.
Anti-arrhythmics prolonging ventricular repolarization	Class I/A, I/C, III drugs
Dietary supplements	grapefruit juice, flavonoids, etc.

Summary

- In response to physical training, athlete's heart develops that involves the development of cardiac hypertrophy
- Cardiac hypertrophy is associated with electrical remodeling, including downregulation of I_{Ks}
- I_{Ks} downregulation reduces ventricular repolarization reserve and increases arrhythmia susceptibility
- When repolarization reserve is impaired, other (even mild) hits on repolarization may induce serious ventricular arrhythmias and SCD
- Such additional hits can be caused by non-cardiovascular drugs
- NSAIDs are associated with increased morbidity and mortality in patients with cardiovascular disease, including diclofenac.
- Diclofenac does not influence ventricular repolarization markedly at therapeutic concentrations *in the normal heart*
- However, diclofenac may enhance proarrhythmic risk *when repolarization reserve is impaired*


Compensatory cardiac hypertrophy („athlete's heart")
K+-channel downregulation
Increased sympathetic tone
Training, emotional stress
HCM, ARVC
Genetic defects, long QT, CPVT
Seemingly harmless medication, antihistamines, antibiotics
Hypokalaemia
Dopping, steroids, amphetamine, ephedrine
Dietary constituents, grapefruit, soy
Extreme bad luck
Sudden cardiac death

Acknowledgements

- András Varró, MD, DSc
- Julius Gy. Papp, MD, DSc
- Norbert Jost, PhD
- László Virág, PhD
- Csaba Lengyel, MD
- Andrea Orosz, MD
- Zoltán Husti, MD
- Viktor Juhász, MD
- Attila Kristóf, MSc
- Zsófia Kohajda, MSc
- Tamás Szél, MD
- Mária Kosztka Győrfiné

SZÉCHENYI 2020

Pályázat címe: A 21. század követelményeinek megfelelő, felsőoktatási sportot érintő differenciált, komplex felsőoktatási szolgáltatások fejlesztése a Dél-alföldi Régió felsőoktatásában
Pályázati azonosító: TÁMOP-4.1.2.E-13/1/KONV-2013-0011