Arrhythmogenic remodeling in the elite athlete's heart: an animal study on dogs

Andras VARRO

Albert Szent-Györgyi Medical School
University of Szeged, Hungary

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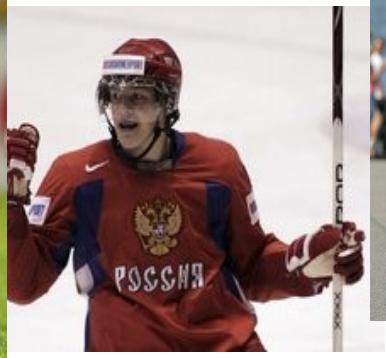
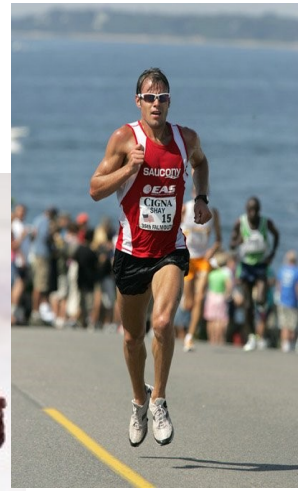
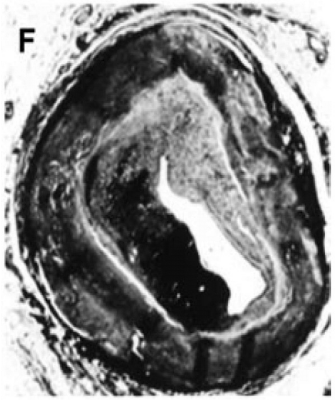
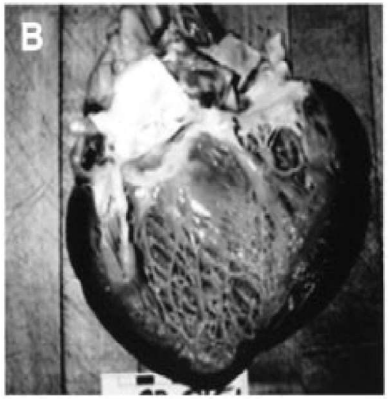
SCD in competitive athletes: cardiac repolarization reserve impairment and increased arrhythmia susceptibility?

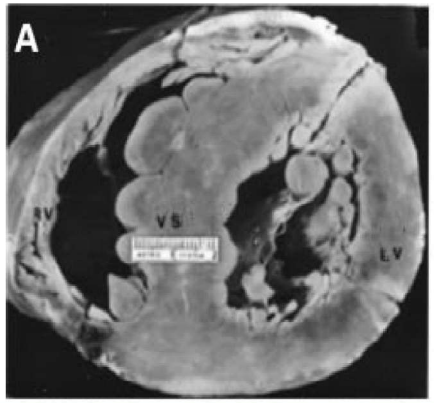


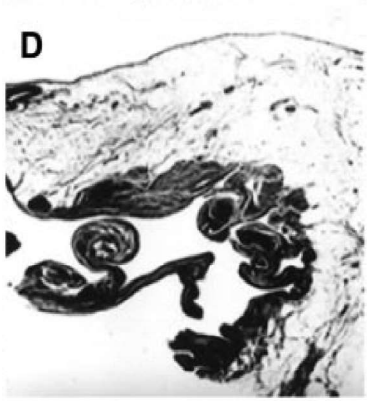


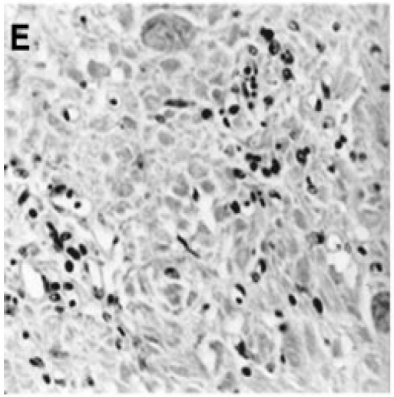
Autopsy findings in young athletes following SCD

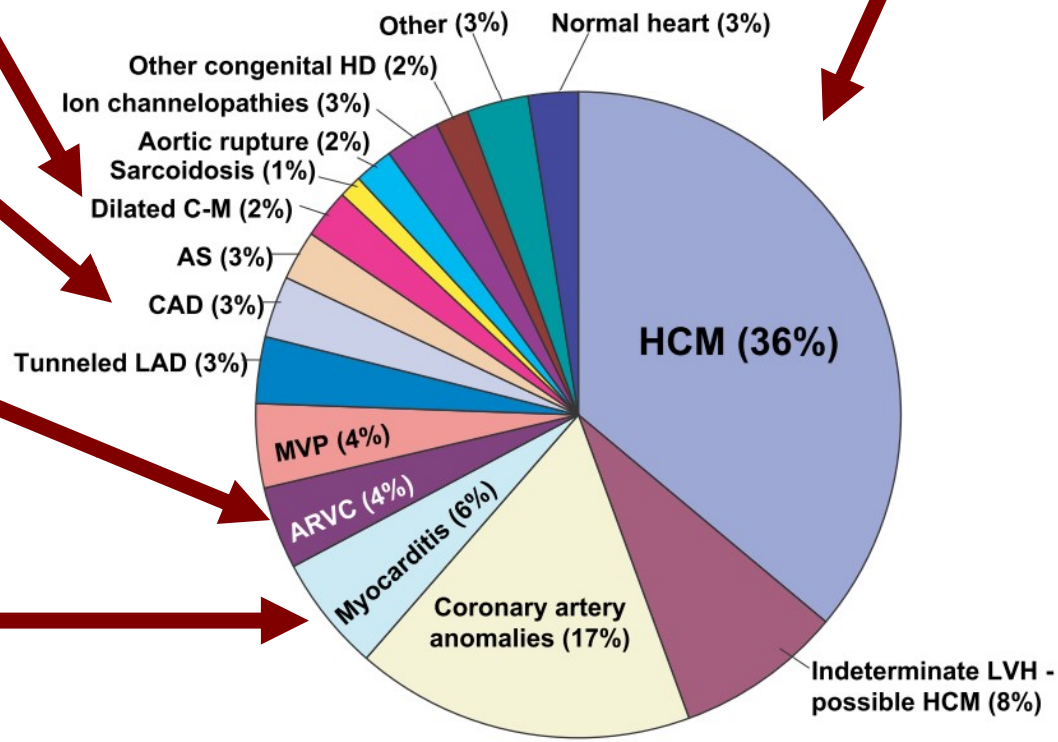












Maron and Pelliccia, *Circulation* 2006;114; 1633-1644

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

Research aims

To ***develop an experimental model*** of long-term intensive endurance exercise

ether exercise training induces ***potentially adverse myocardial morphological and/or electrical remode especially at a cellular level***

Experimental groups

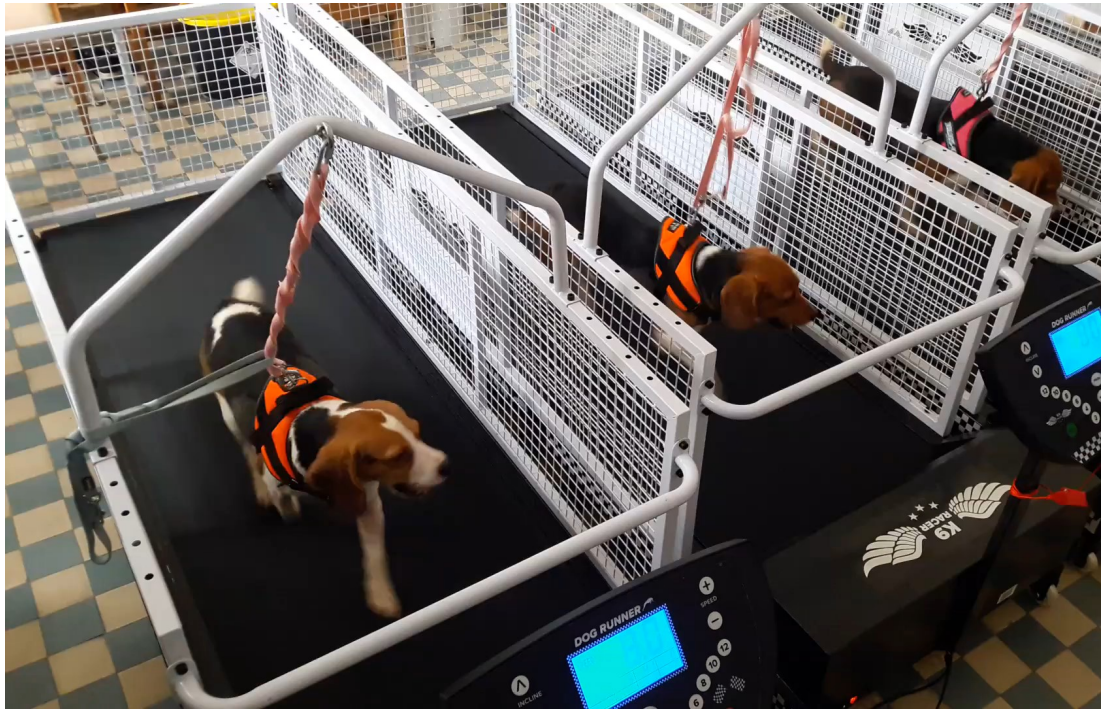
'Control' *(n=12)*

'Trained' *(n=12)*

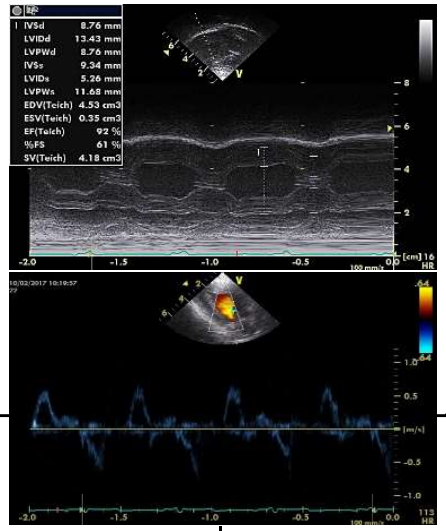
ning program duration:	**16-week treadmill running**
of trainings:	5 times /week
ning sessions:	2x90 min long-distance running +
	2x50 min interval running
nation:	0% - 5% - 12%
k daily distance:	**80 km**
k running speed:	**22 km/h**

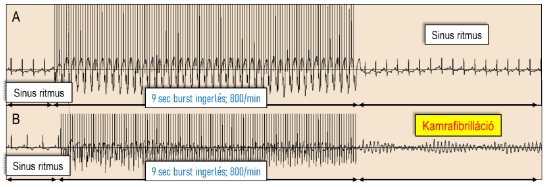
Sex ratio

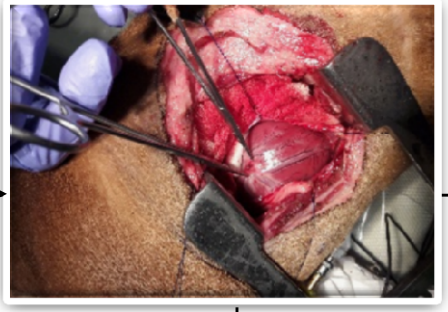
50% 50%

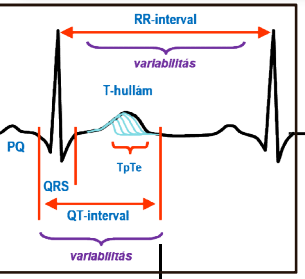


Methods









ECG characteristics

Conscious dogs
Precordial leads
Baseline measurements (RR, PQ, QT, Tpeak-Te)
Beat-to-beat variability
Ectopic activity after I_{Kr} block *(35 µg/kg dofetilide)*

Echocardiography

- M-mode parasternal long axis view
- LV morphological parameters

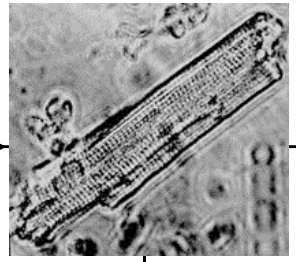
Burst stimulation

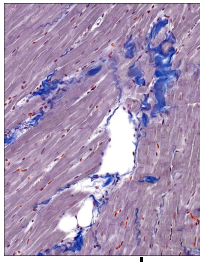
- Anaesthetized dogs open-chest burst pacing
- *duration: 9 sec*
- *800/min, equal to 13.3 Hz*

***In vivo* measurements**

Enzymatic isolation

***Ex vivo* measurements**





Action potential duration measurements

- Patch-clamp technique
- Perforated patch
- Current-clamp, 37 °C

Transmembrane ionic current measurements

- Patch-clamp technique
- Whole-cell
- Voltage-clamp, 37 °C

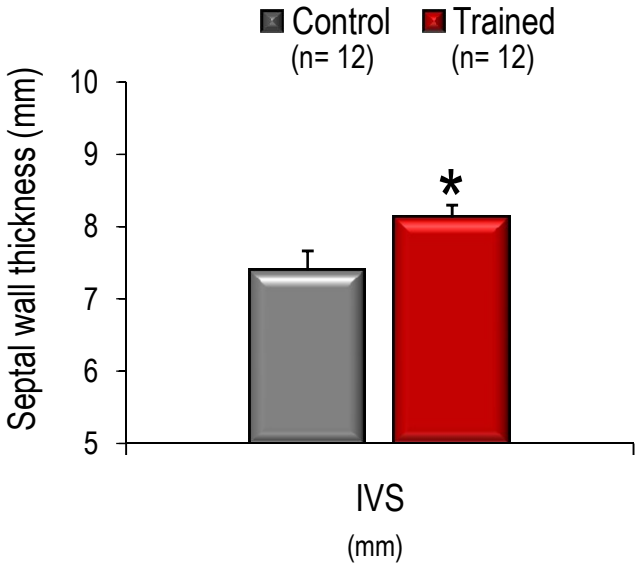
Biological markers

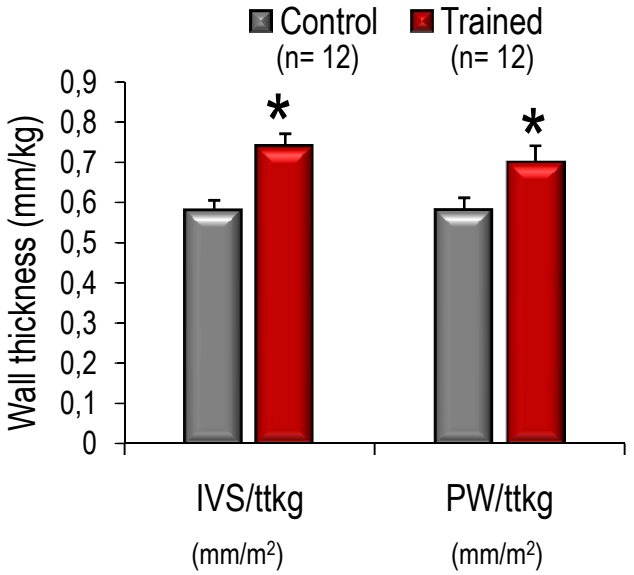
- Immunocytochemistry

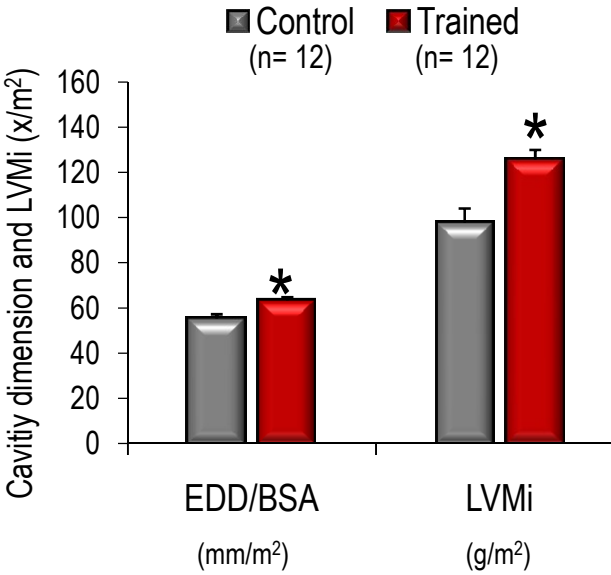
Presence of fib

- Crossmon's trichrome stair
- Semi-quantitat analysis

Echocardiography: Left ventricular hypertrophy







viations:

**p<0.05 Trained 16th week vs. Control*

terventricular septal wall thickness

eft ventricular posterior wall thickness

Left ventricular end diastolic diameter

Body surface area (m^2) = 10,1 × (body mass $(g)^{2/3}$) × 10^{-4} *(1)*

Left venticular mass (g)=0.8*(1,04*(EDd+PWd+IVSd)^3-(EDd)^3)+0,6))/1000. *(2)*

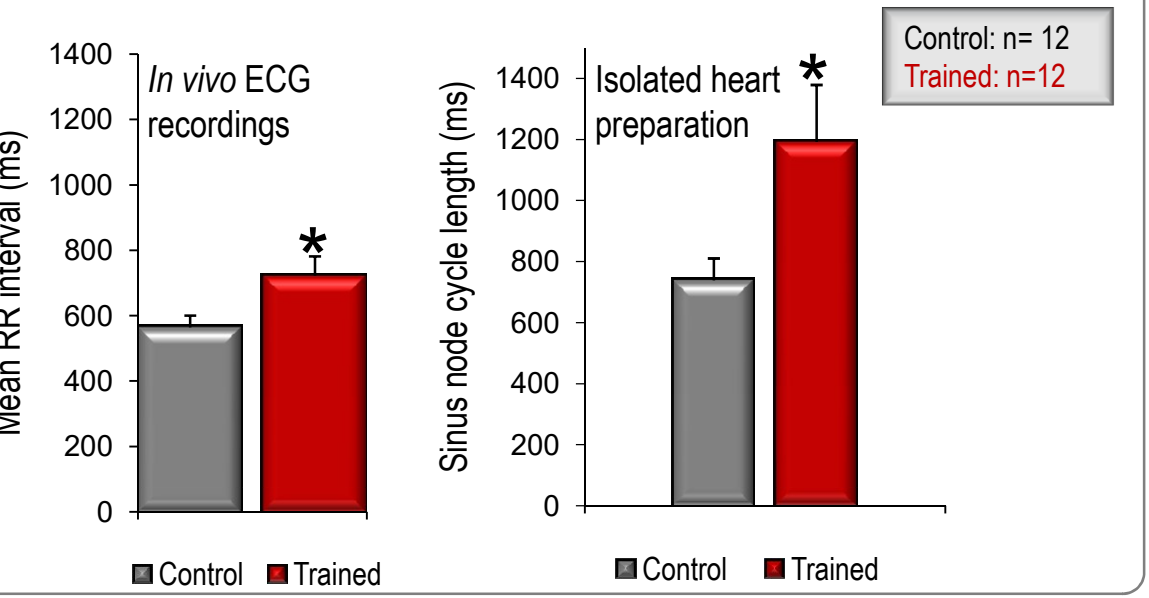
Left ventricular mass index: LVM/BSA (g/m^2)

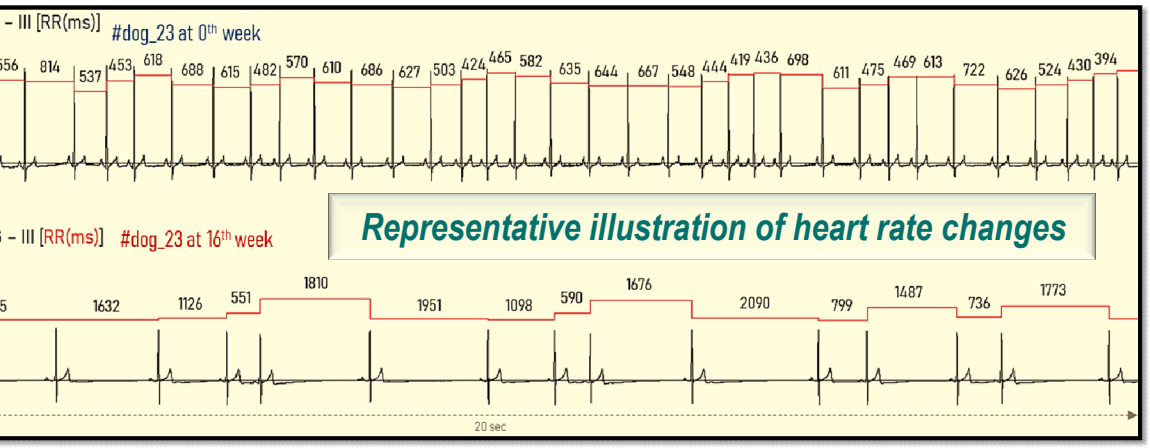
[1] Wey et al. Allometric Scaling of M-Mode Cardiac Measurements in Normal Ad

[2] Troy et al. Measurement of left ventricular wall thickness and mass by echoca

Bradycardia and increased heart rate variability

A) Bradycardia

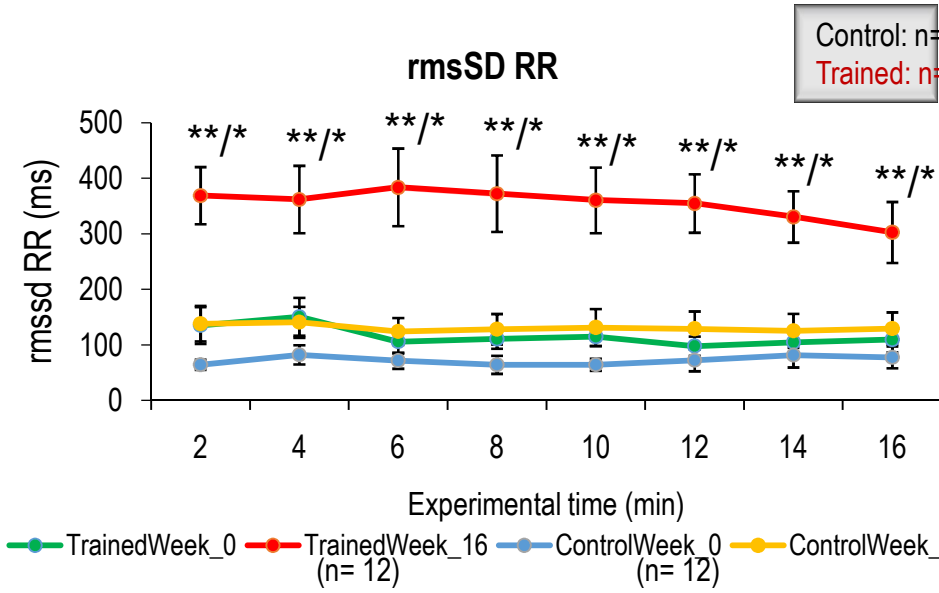




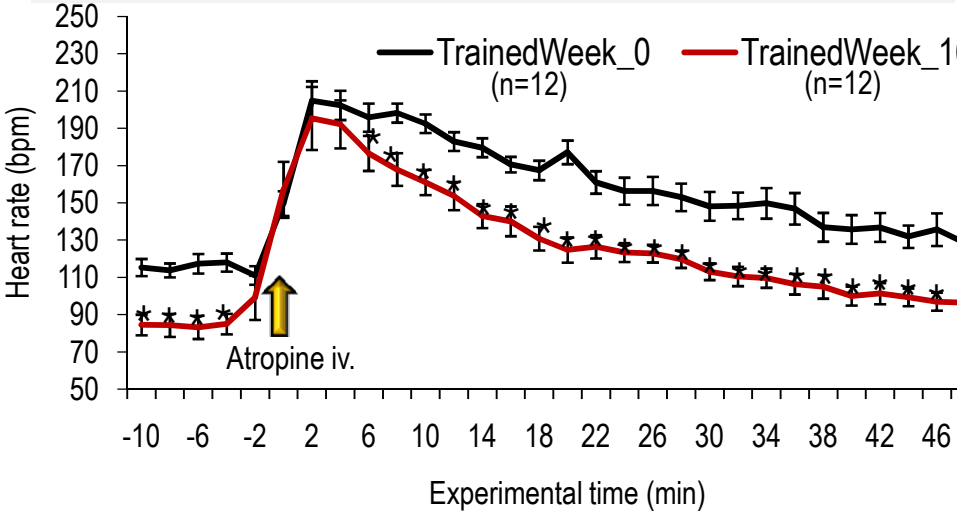
viations: ***rmsSD***, root mean square of the successive differences;

*Trained 16th week vs. Control 16th week; * * p<0.05 Trained 0th week vs. Trained 16th week*

B) Heart rate variability increase



C) Heart rate response to i.v. atropine (Dose: 0.04 mg/kg)



ECG: Repolarization changes and ectopic activity

A) Baseline (drug free) ECG measurements

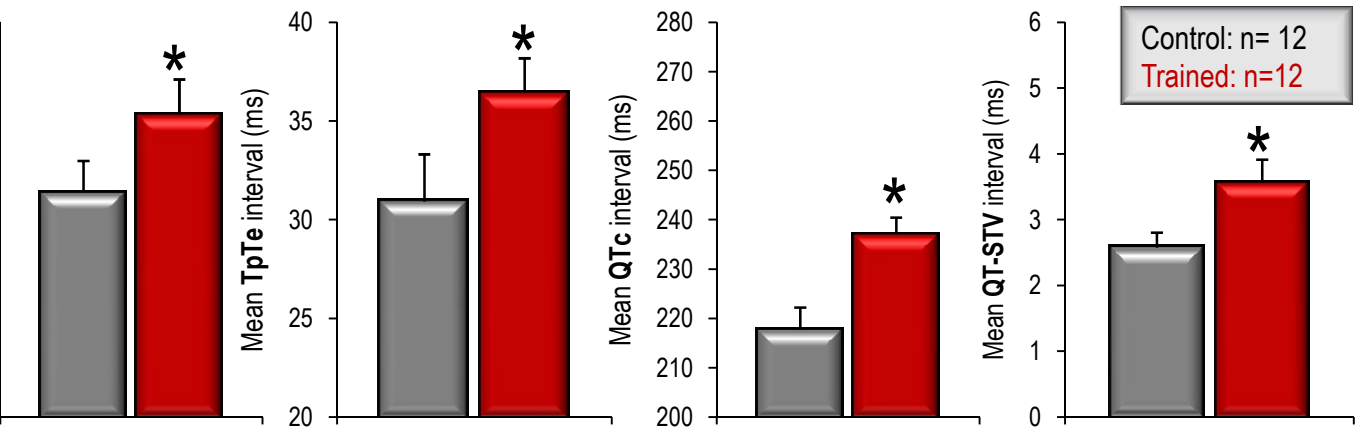
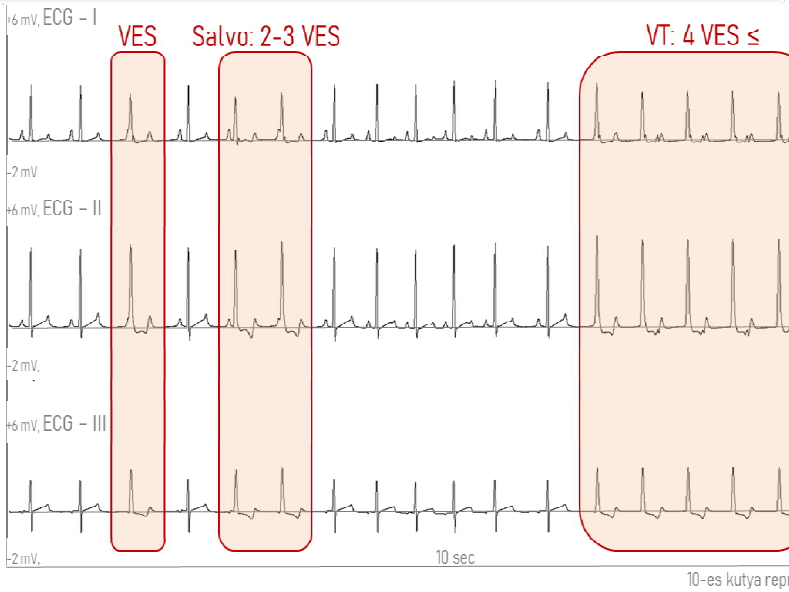


Illustration of ventricular arrhythmias in trained do



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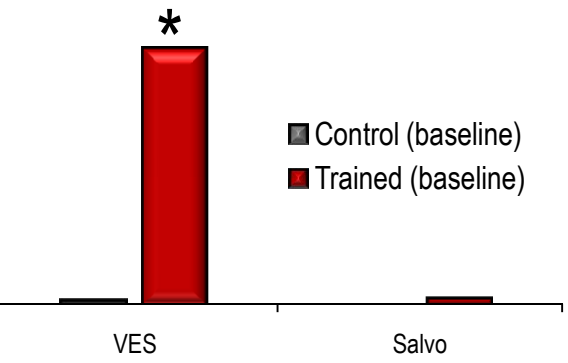
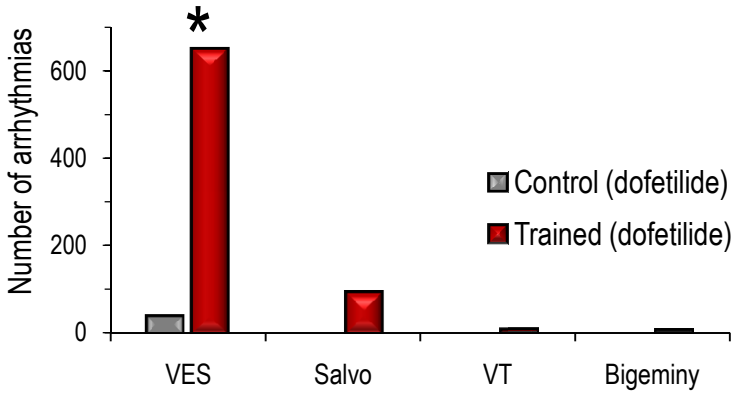
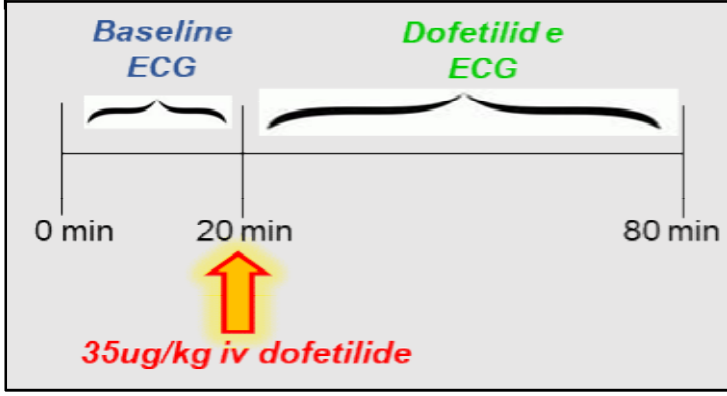
) Arrhythmias on baseline ECG (t=20 min)



B/2) Arrhythmias on dofetilide ECG (t=60 min)



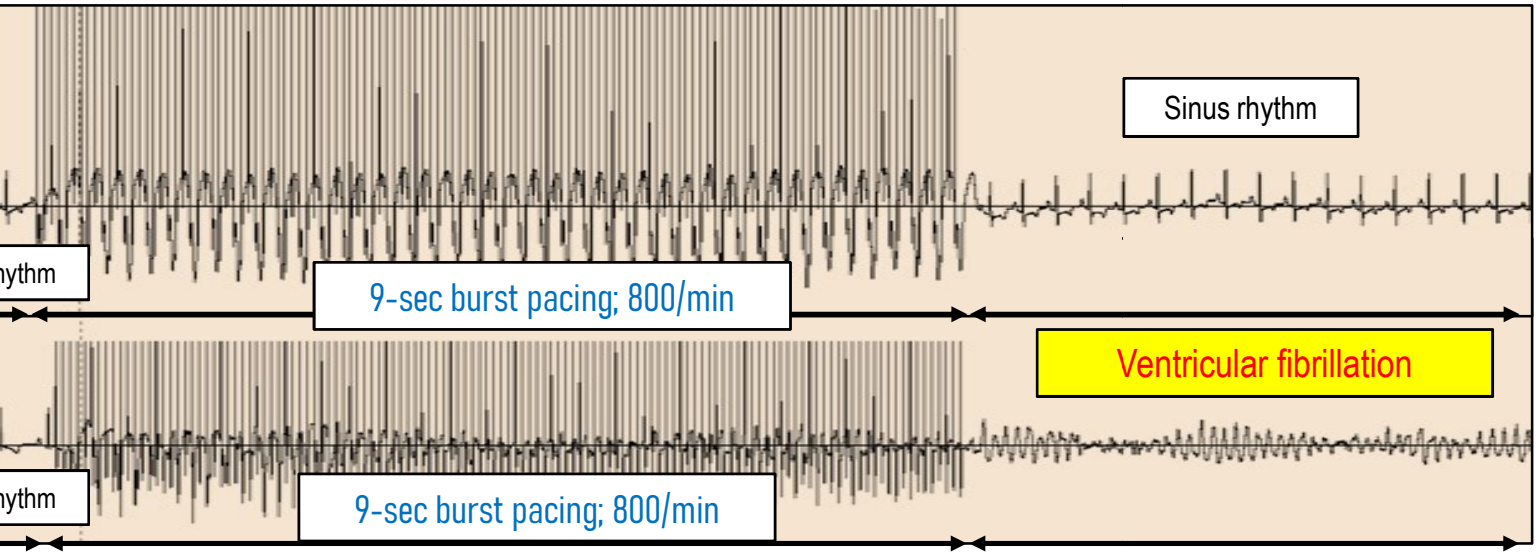
ECG recording protocol



iations: STV: Short **t**erm **v**ariability; QTc: QT **c**orrected for heart rate

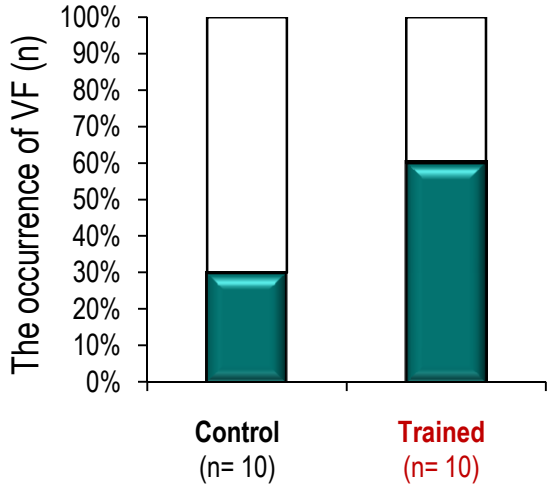
*p<0.05 Trained 16th week vs. Control

Arrhythmia (VF) susceptibility and LV fibrosis



ntrol dog (#20) burst pacing B) Trained dog (#13) burst pacing at 16th week

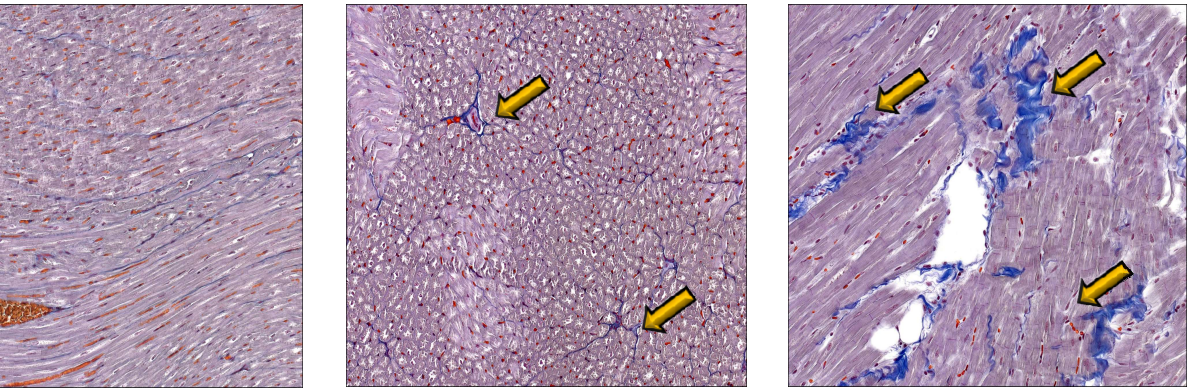
Ventricular fibrillation (VF) after burst pac



ore 0 = no fibrosis
Control dog

Score 1 = mild fibrosis
Exercised dog

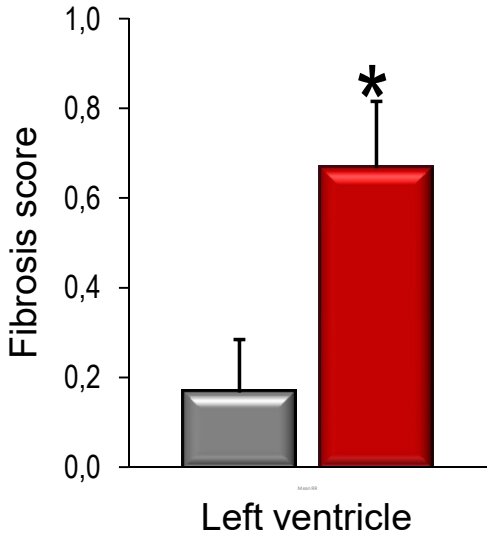
Score 2 = moderate fibrosis
Exercised dog

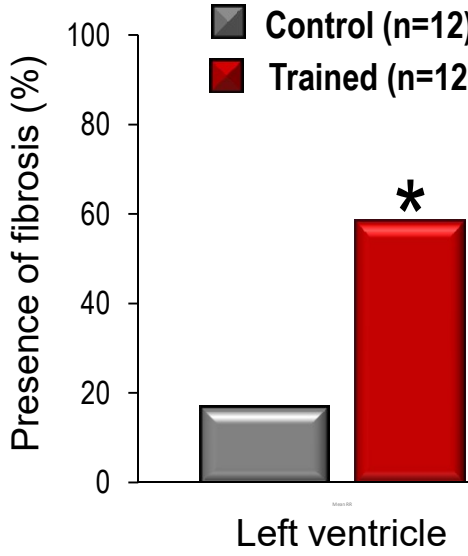


Crossmon's trichrome staining

.05 Trained 16th week vs. Control 16th week

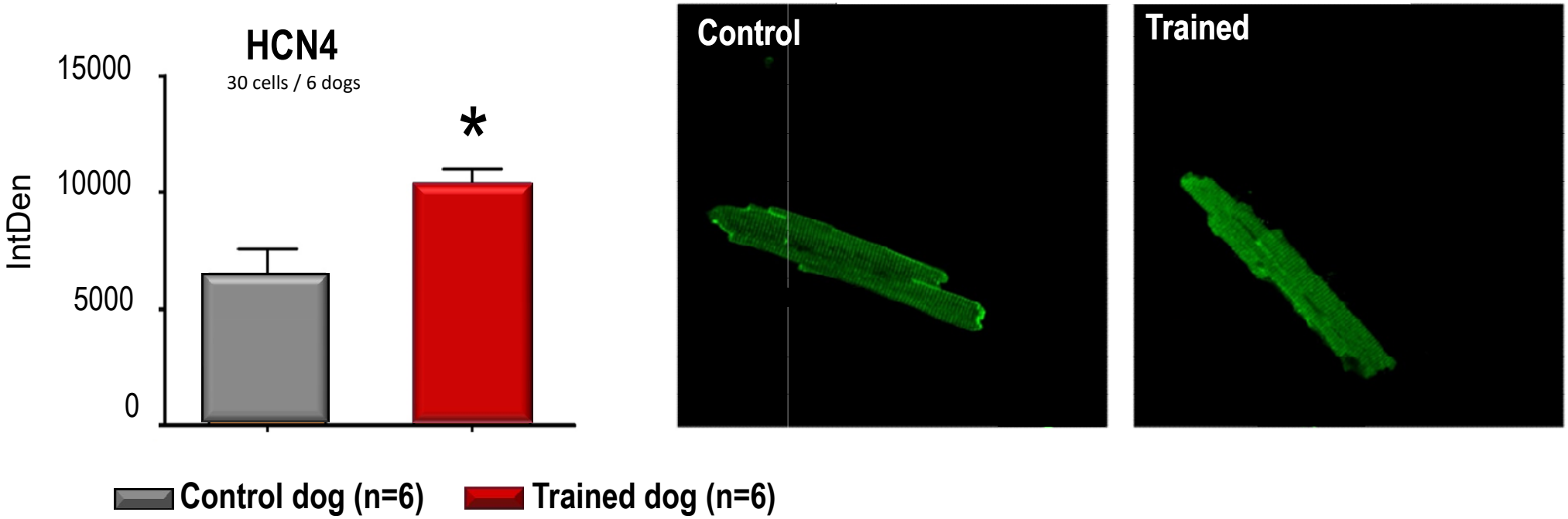
The extent of fibrosis in histological sections of the left vent

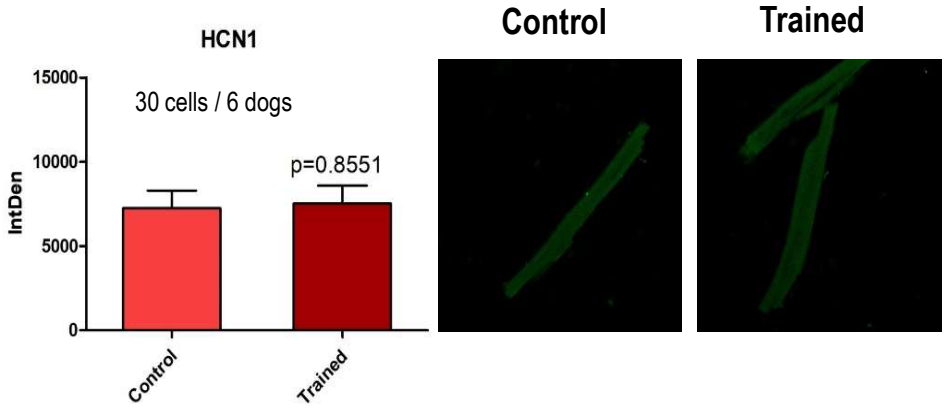


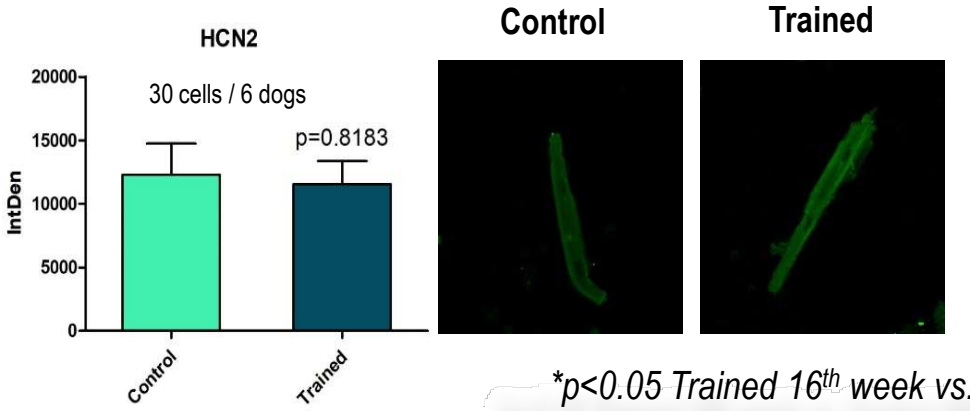


Pacemaker channel (I_f) protein density determination by immunochemistry in dog ventricular myocytes

Overexpression of HCN4 protein in dog left ventricular myocytes

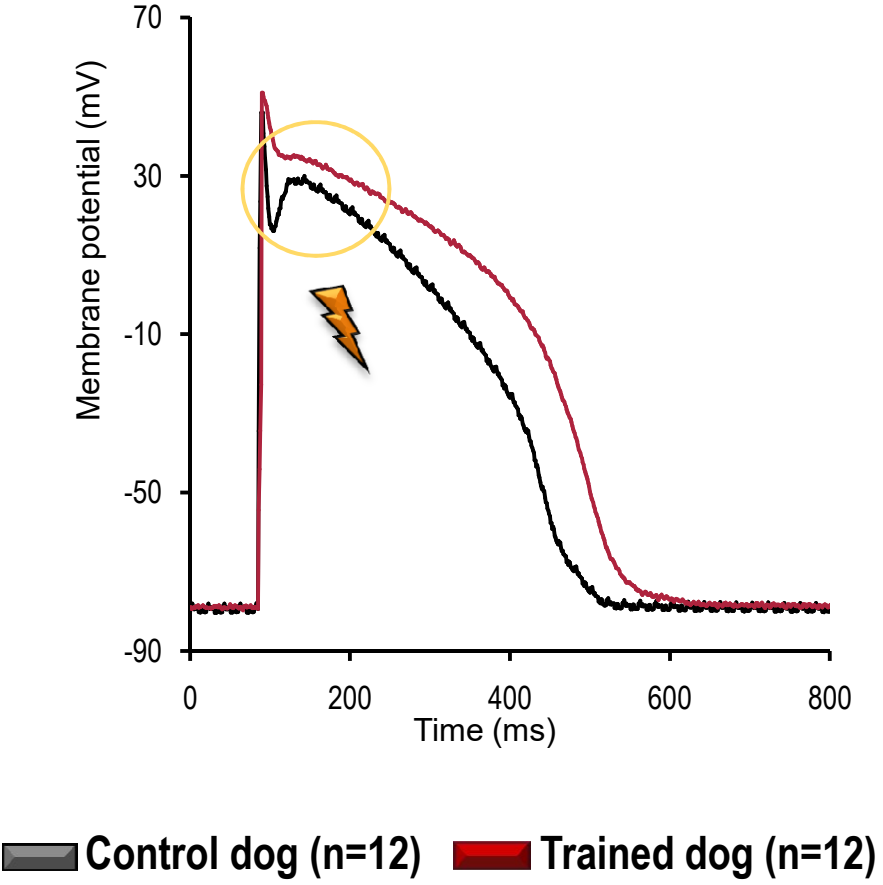




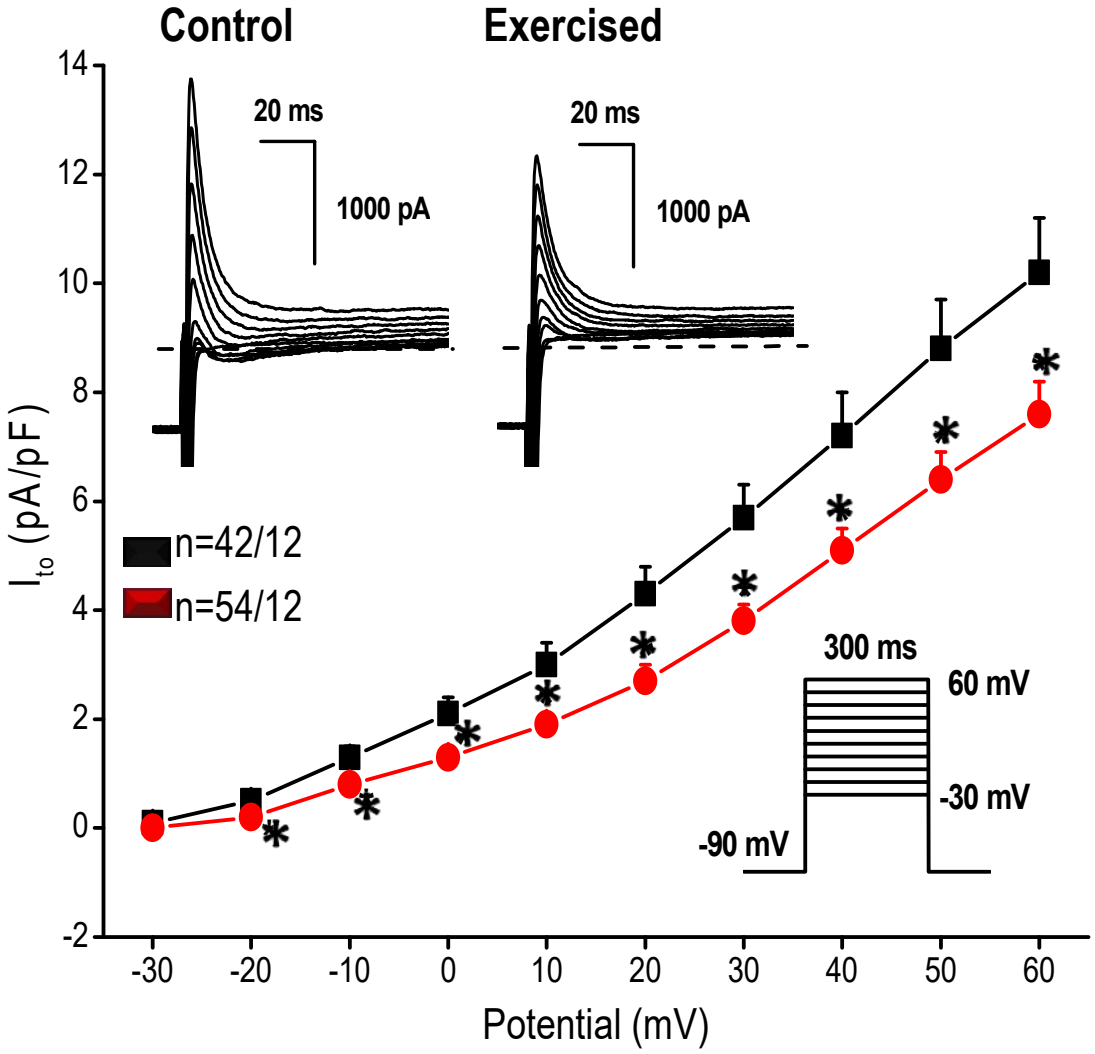


*p<0.05 Trained 16th week vs. Control 1

Transmembrane ionic current measurements in dog left ventricular myocyt



Magnitude of transient outward potassium current (I_{to})



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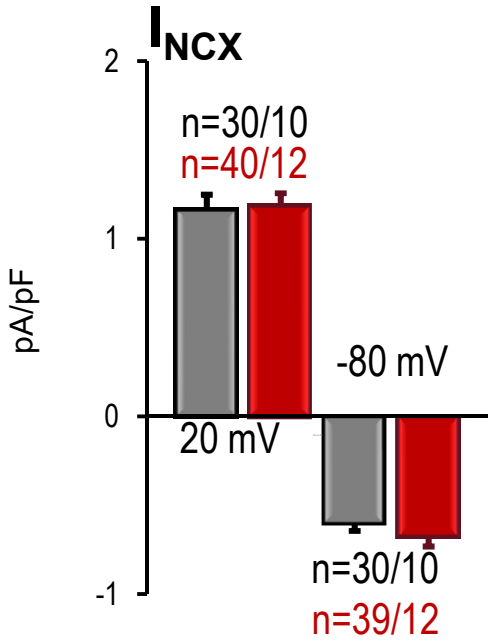
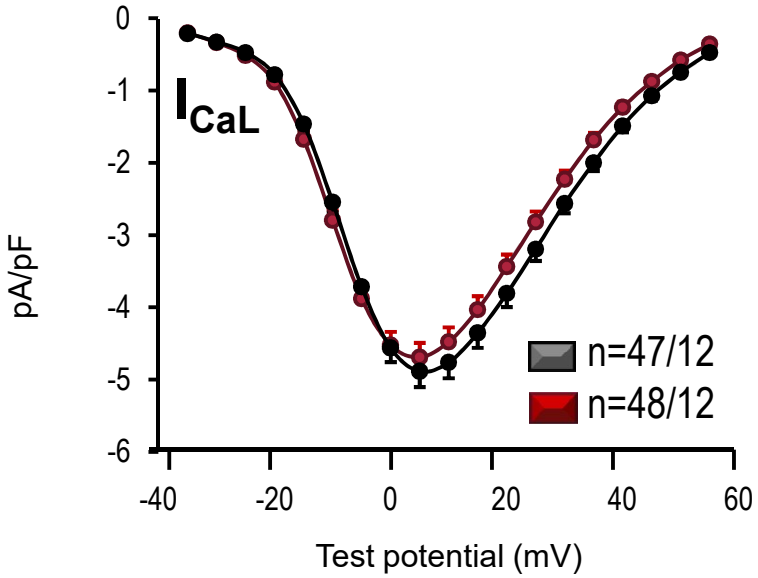
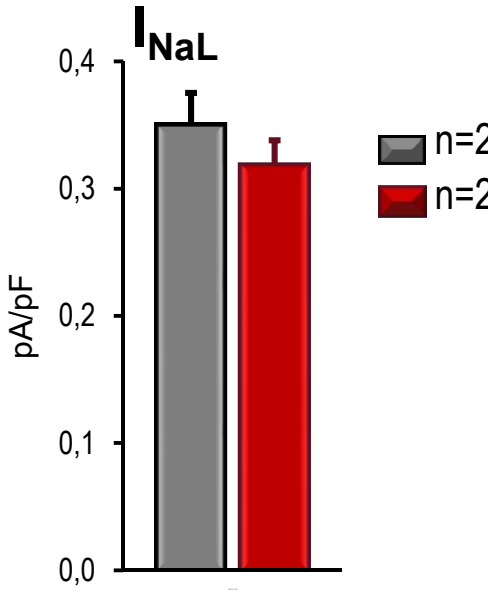
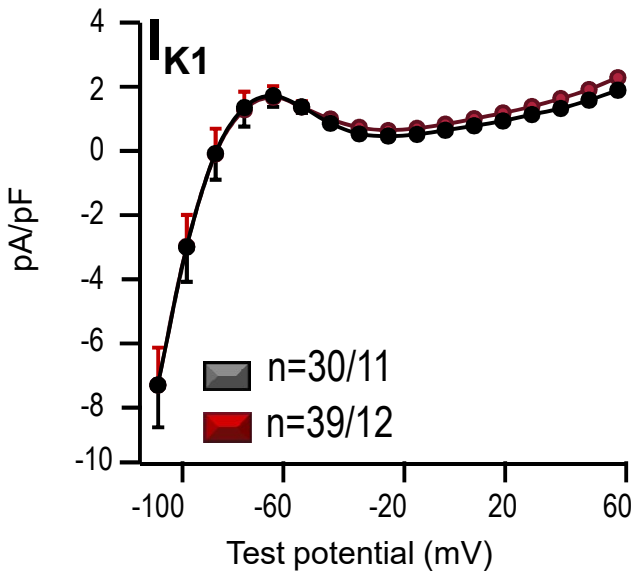
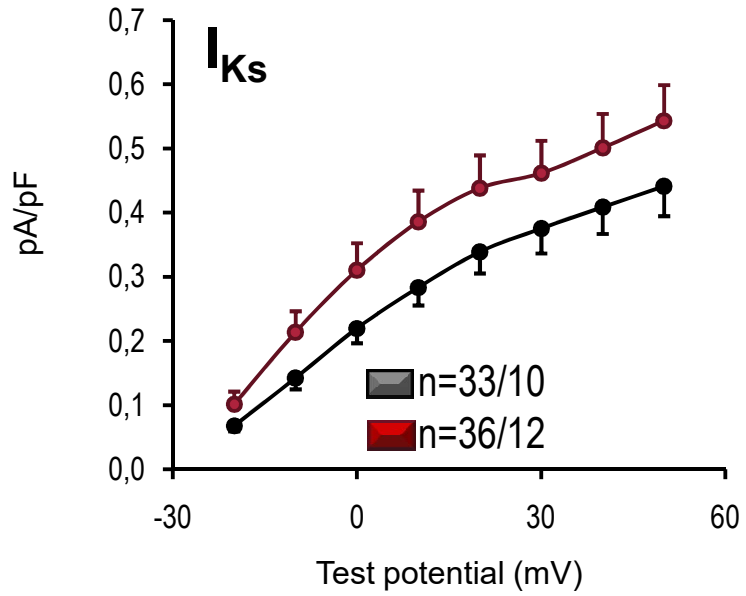
Transmembrane ionic current measurements in dog left ventricular myocyt

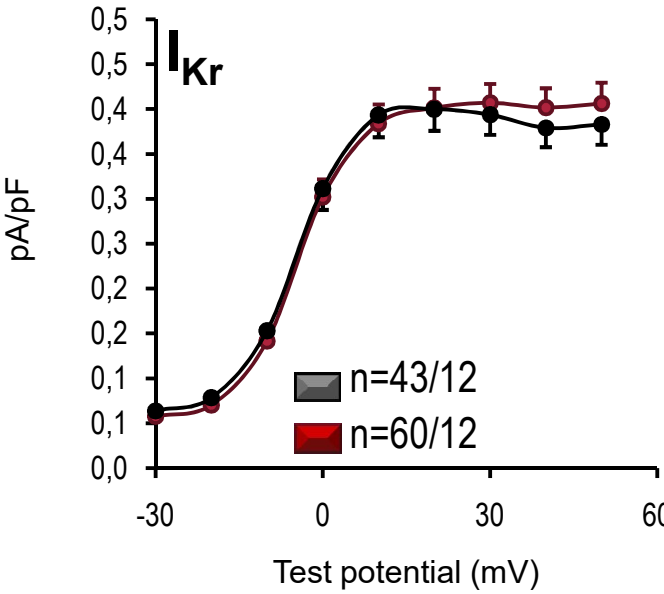












Control dog (n=12) Trained dog (n=12)

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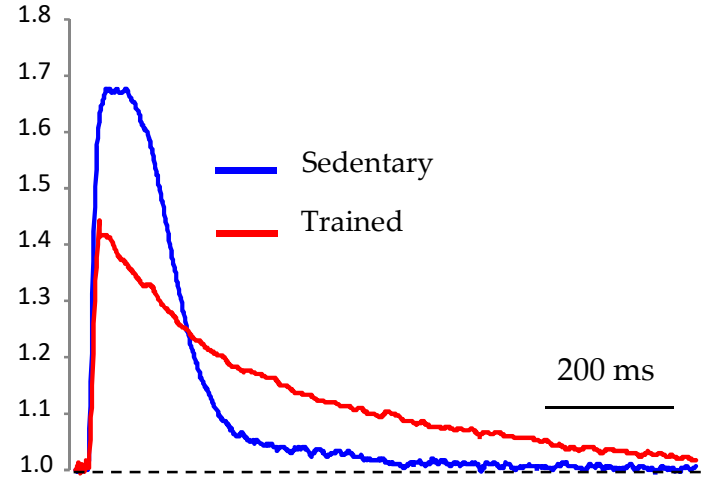
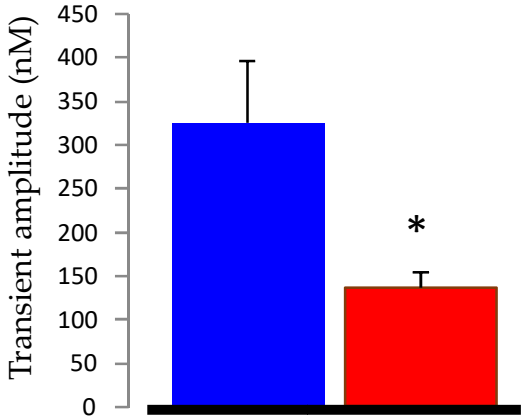
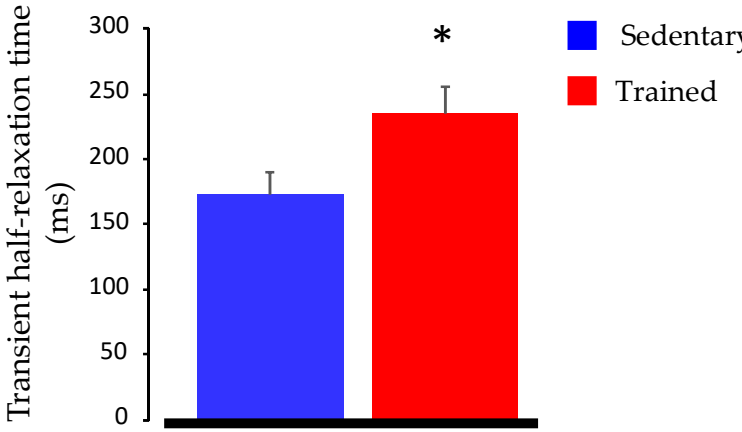
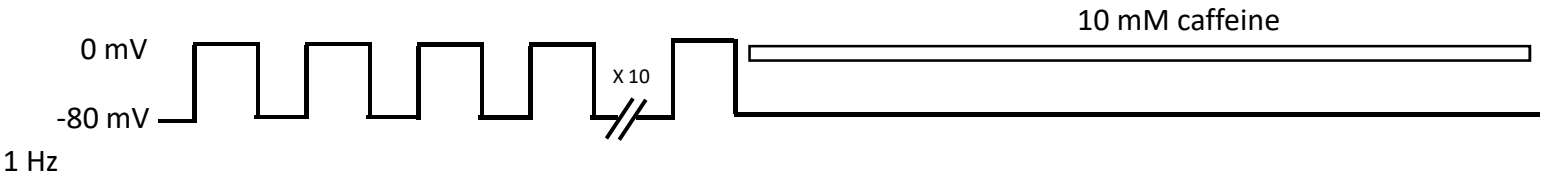
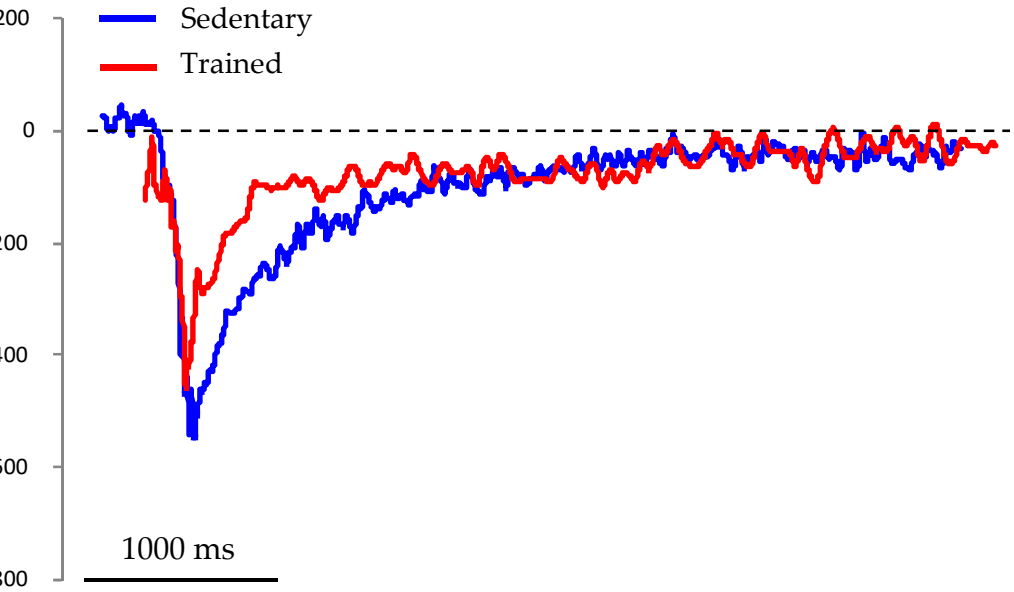
Intracellular Ca2+ handling in sedentary and trained dogs

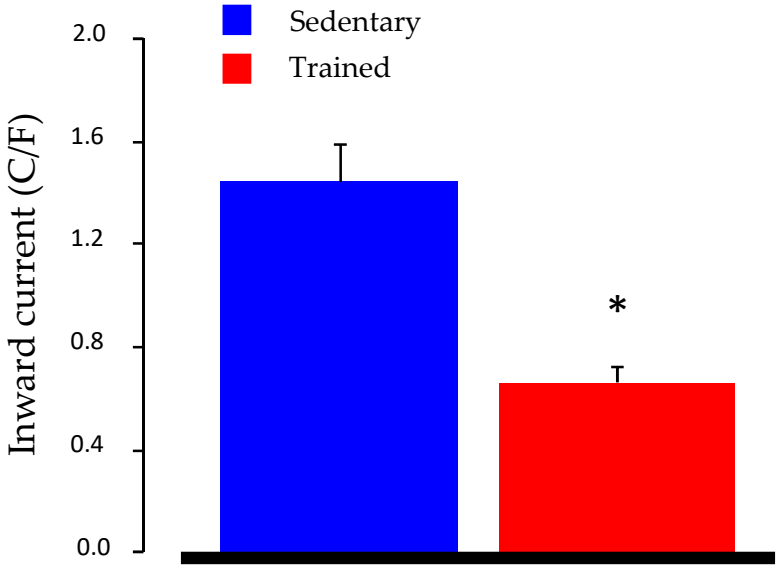




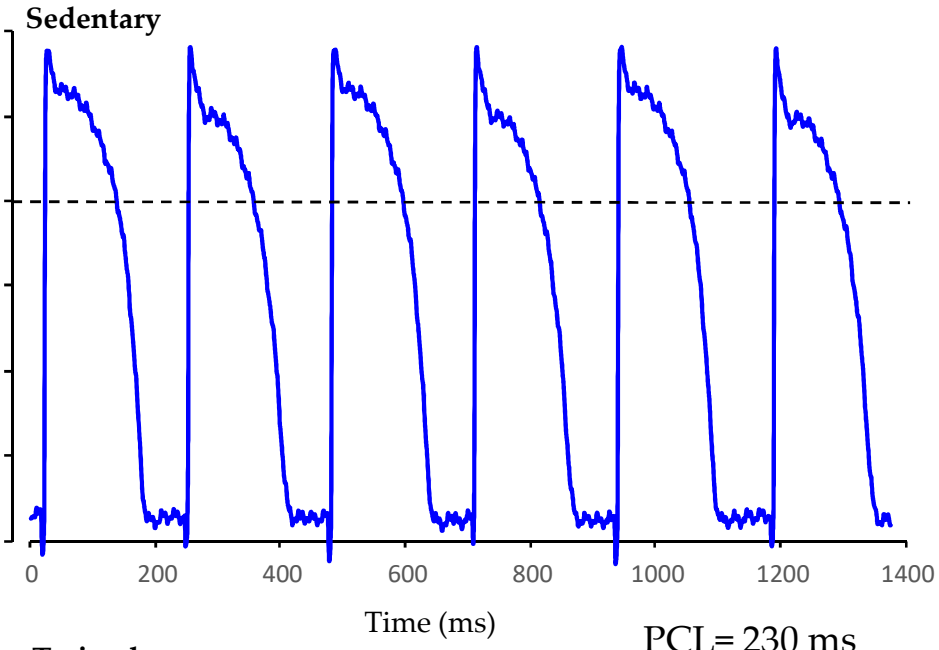




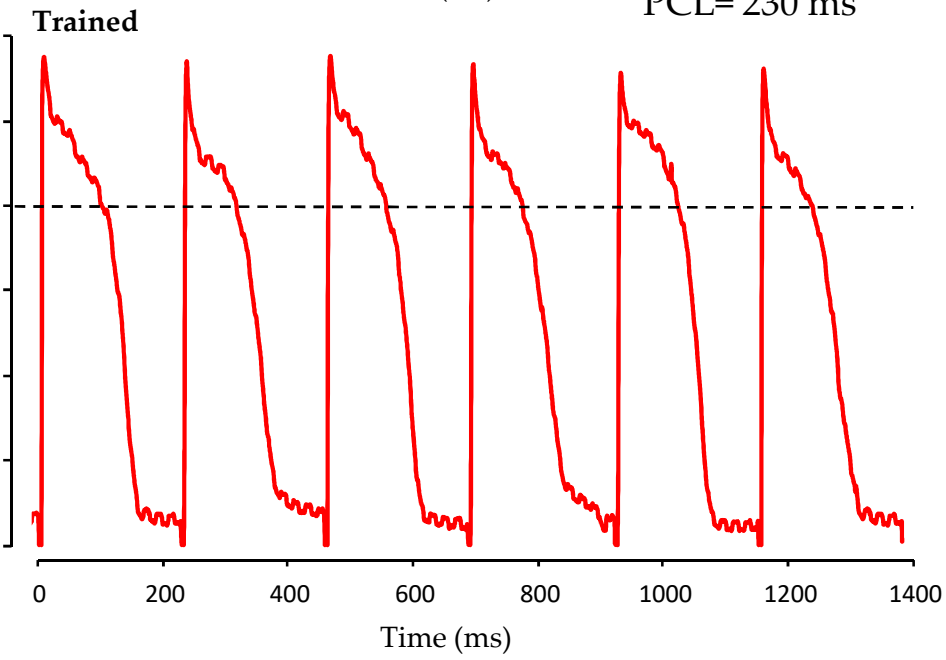




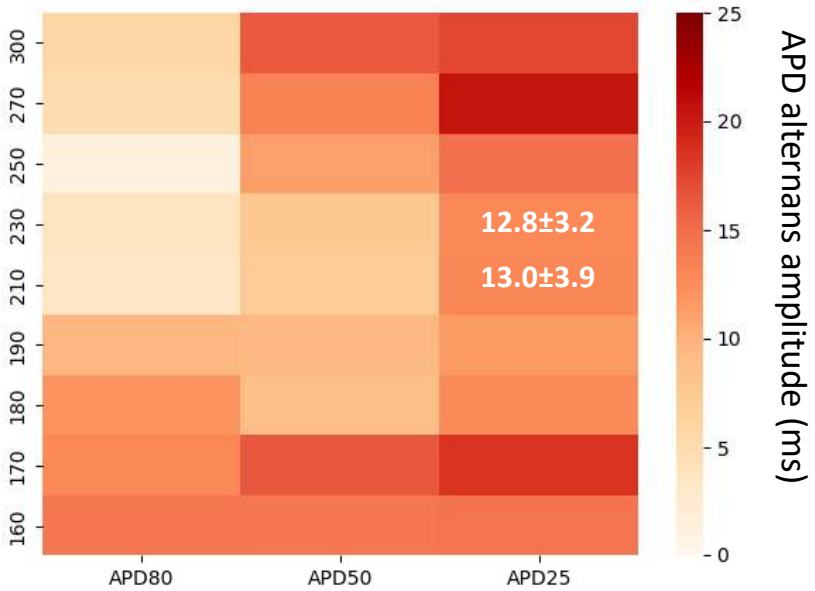
APD alternans in sedentary and trained dogs



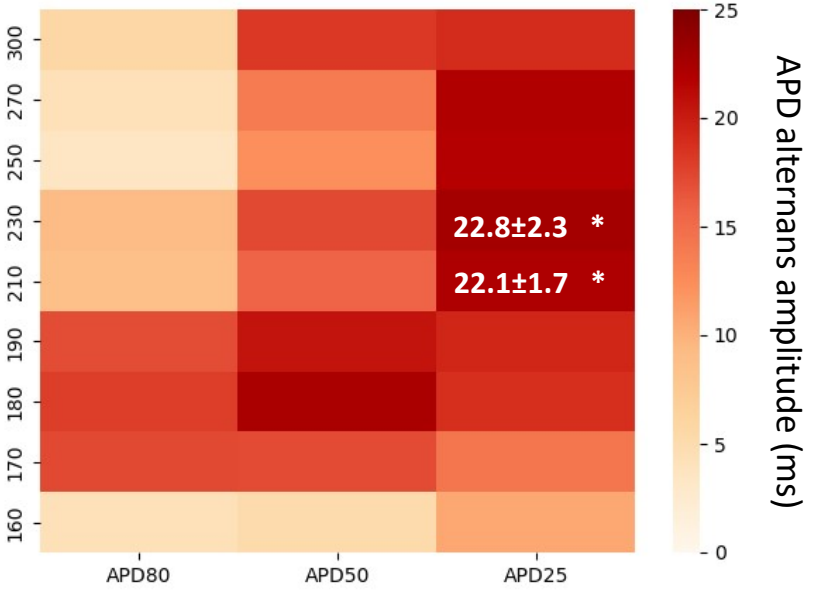
PCL= 230 ms



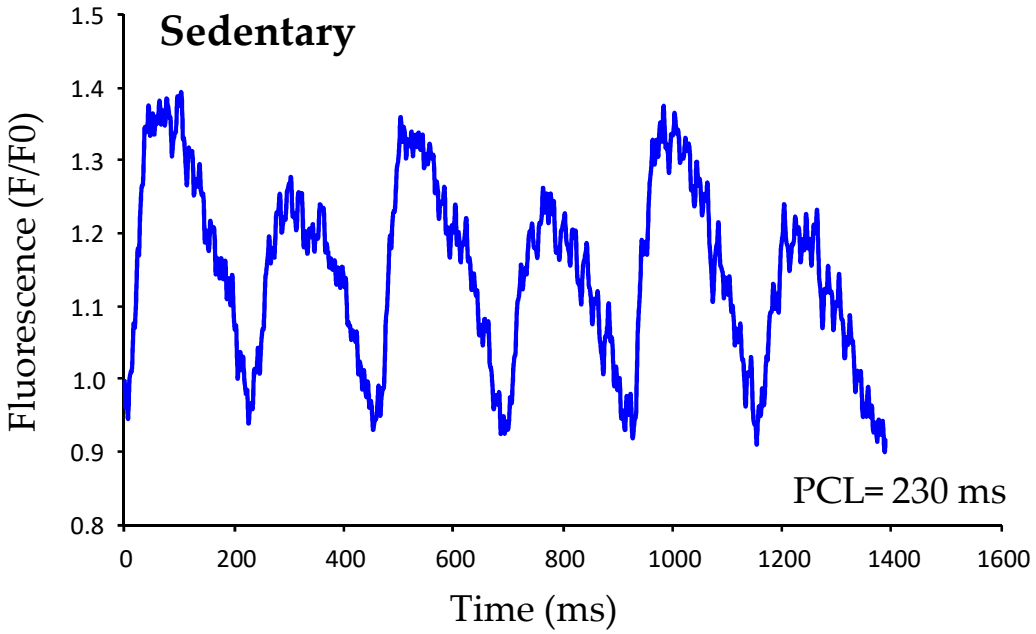
Sedentary

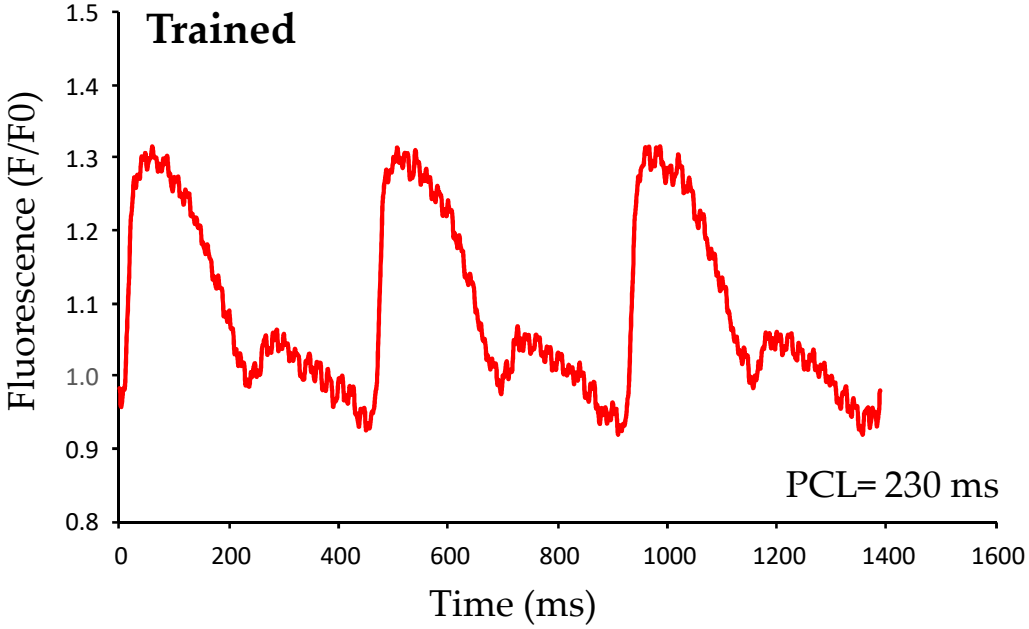


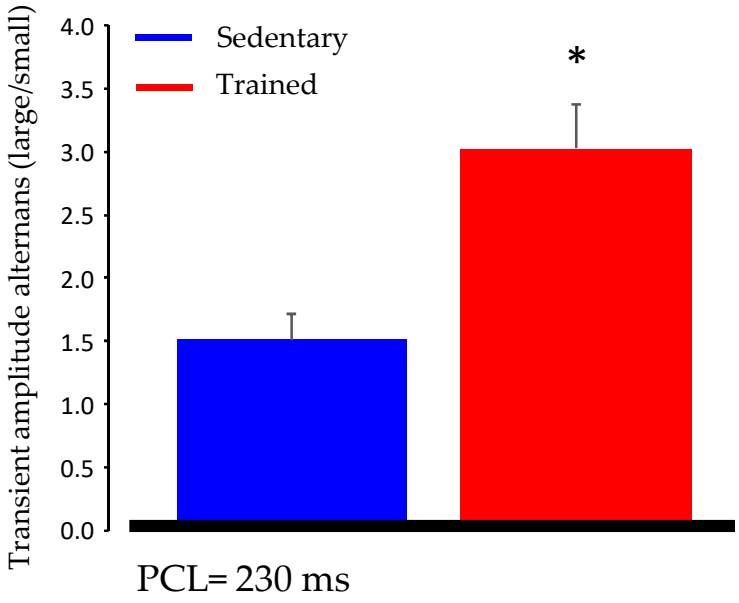
Trained



Ca2+ transient alternans in sedentary and trained dogs







Unpublished ob

clusions 16 weeks of continuous intensive endurance training

- ✓ Left ventricular **hypertrophy** → physiological morphological adaptation
- ✓ Training induced **bradycardia** with **increased heart rate variabiliy** → vagal enhancement
- ✓ Moderate response to atropine *in vivo* and **decreased sinus node cycle length** → intrinsic changes in the sinus node?

- ✓ Increased **ventricular ectopic activity**
- ✓ Burst stimulation: increased incidence of **ventricular fibrillation**
- ✓ **Overexpression of HCN4 protein** in left ventricular myocytes

Arrhythmia Trigger

- ✓ Moderate left ventricular **fibrosis**
- ✓ **Prolonged repolarisation and increased repolarisation inhomogeneity** on the ECG (**↑QTc, ↑STV QT, ↑TpTe**)
- ✓ **Prolonged action potential duration and increased APD variability** in left ventricular myocytes
- ✓ **Decreased I_{to}-current magnitude** in left ventricular myocytes

Arrhythmia Substrate

Morphological/ functional remodeling **+ / -**  **And / or extreme bad luck?** → **Sudden Cardiac Death**

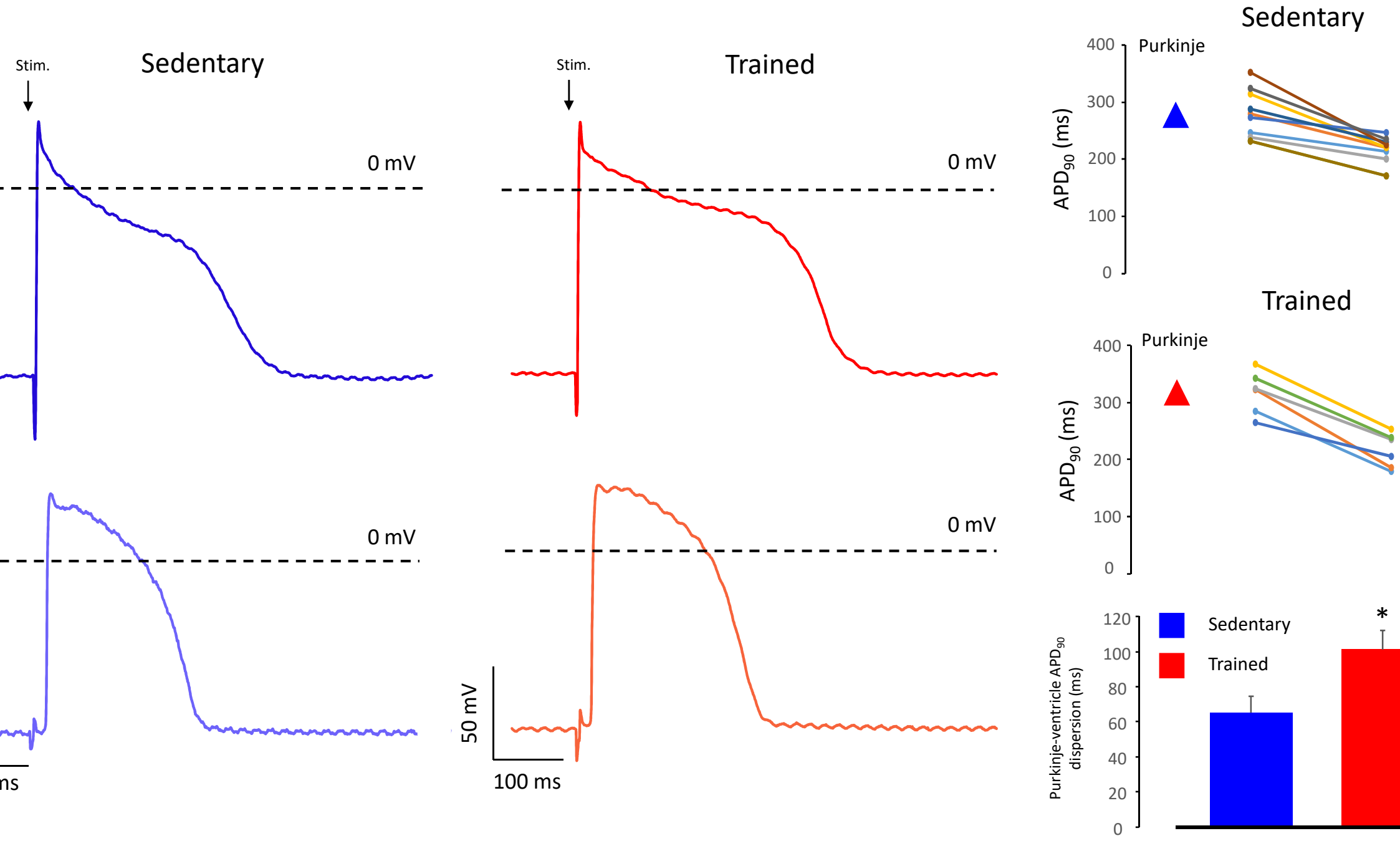
Polyák et al, *eLife* 2023

exandra POLYÁK

ván BACZKÓ
ila FARKAS
émi ZOMBORI-TÓTH
la TOPAL
émi TÓTH
os PROROK
ter GAZDAG
efina SZLOVÁK
más ZOMBORI
rgely ÁGOSTON
lvia DÉRI
tán HUSTI
szló VIRÁG
rbert NAGY
ária KOSZTKA
elinda MOLNÁR
bor GIRST
bor DOBAI

Nemzeti Kutatási, Fejlesztési és Innovációs Hivatal NKFIH K-128851 Ministry of Human Capacities EFOP-3.6.2-16-2017-00

Purkinje-ventricle dispersion of sedentary and trained dogs



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

OPEN ACCESS Freely available online

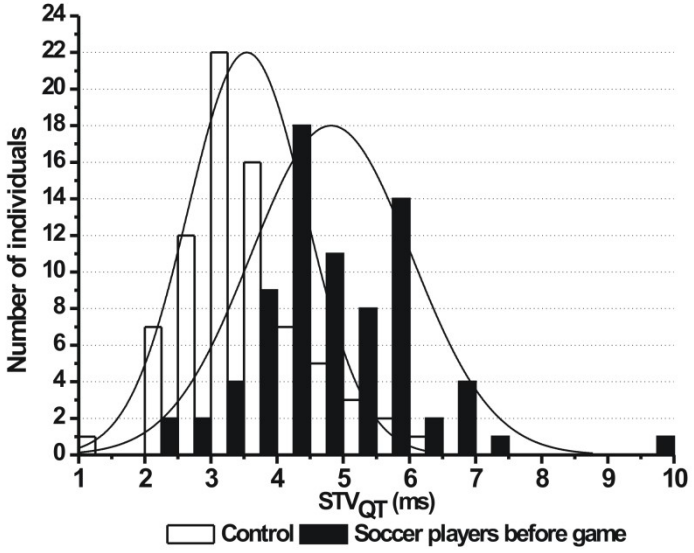
PLoS one

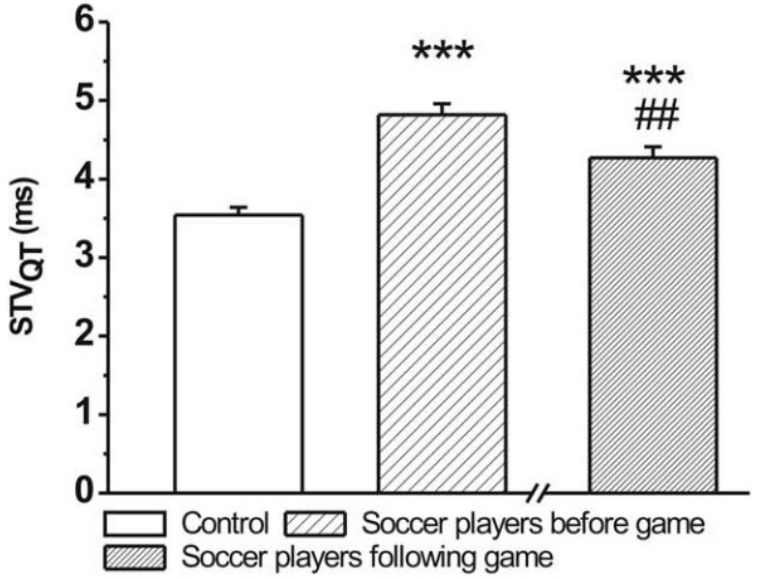
Increased Short-Term Variability of the QT Interval in Professional Soccer Players: Possible Implications for Arrhythmia Prediction

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})

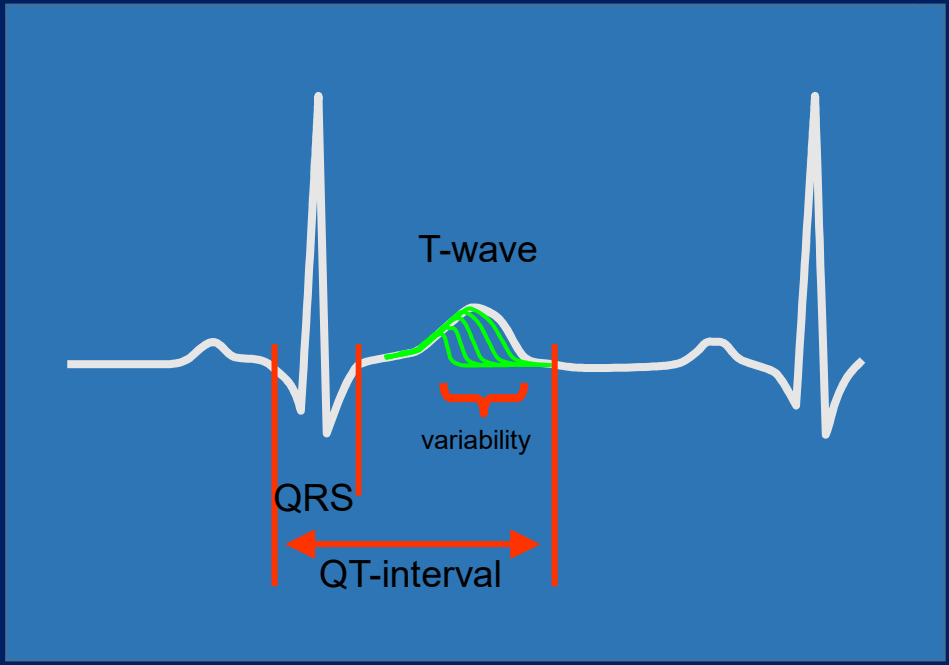


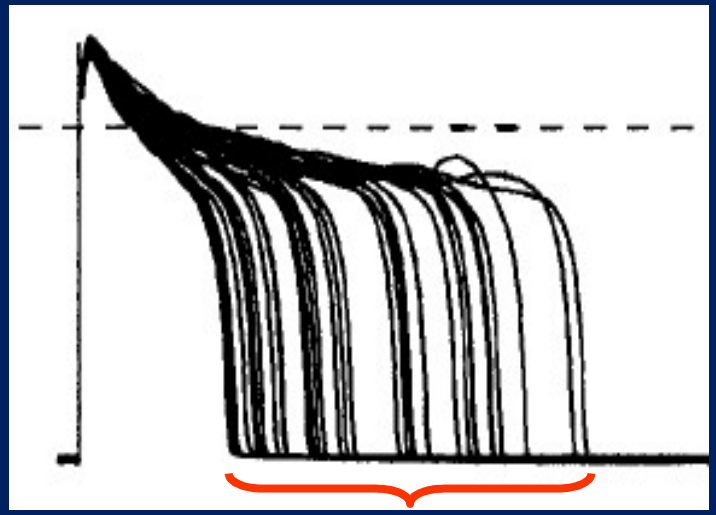


Short-term variability (STV) of repolarization as a parameter for repolarization reserve

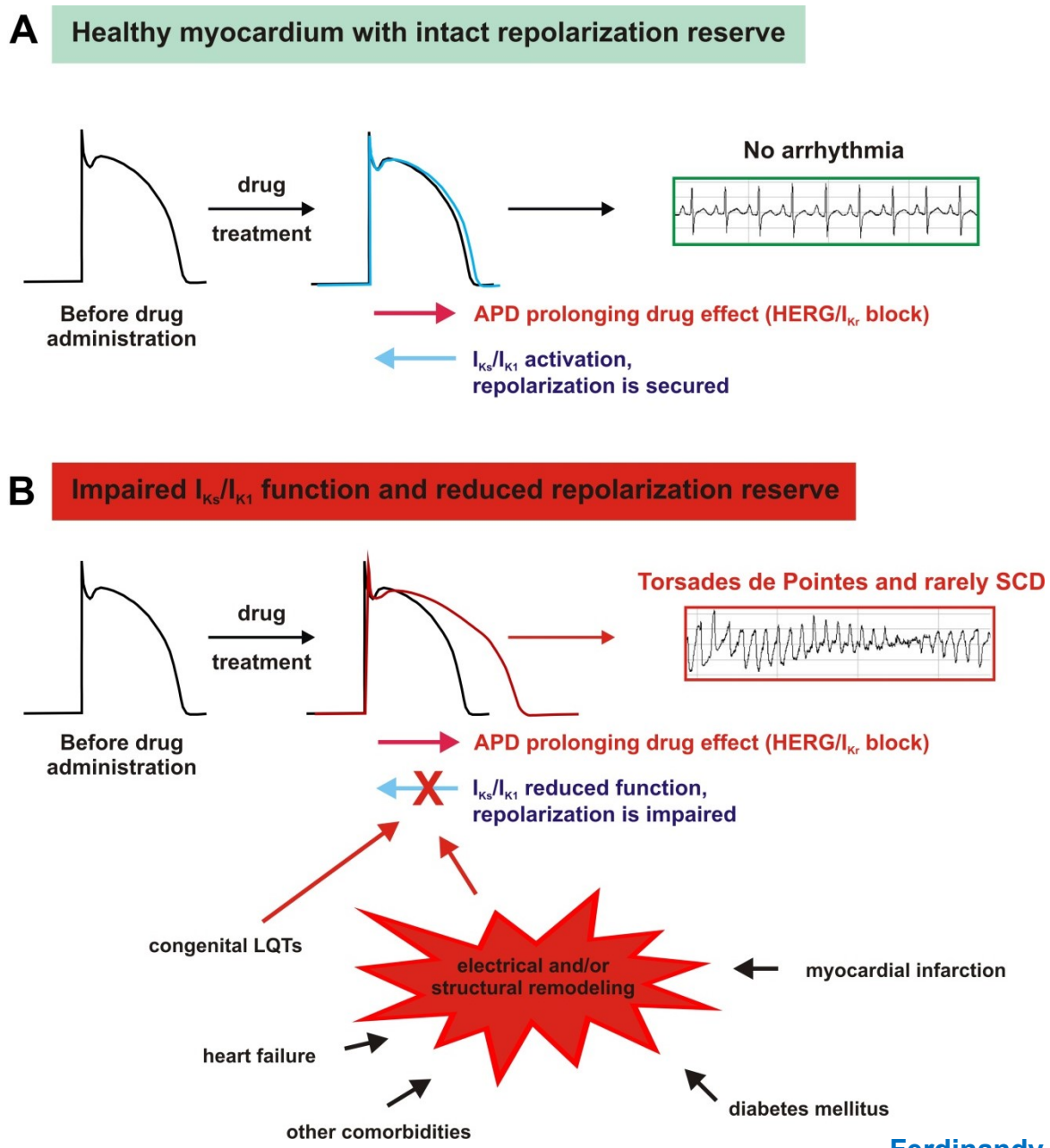
In vivo, clinical (ECG)

Cellular (action potential)



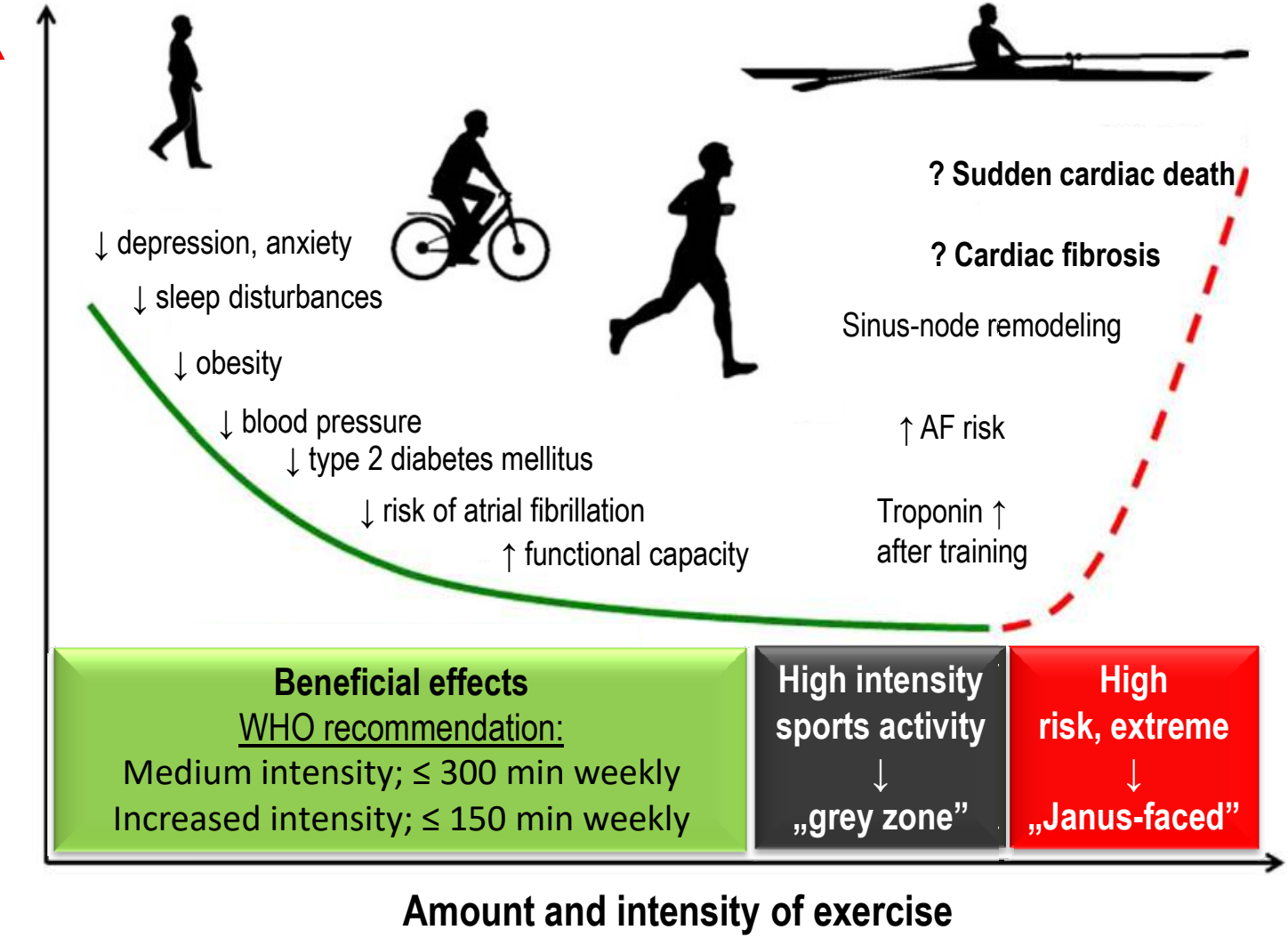


Cardiac repolarization reserve and the role of I_{Ks}



Ferdinandy, Baczkó Varró *et al.*, *European Heart*

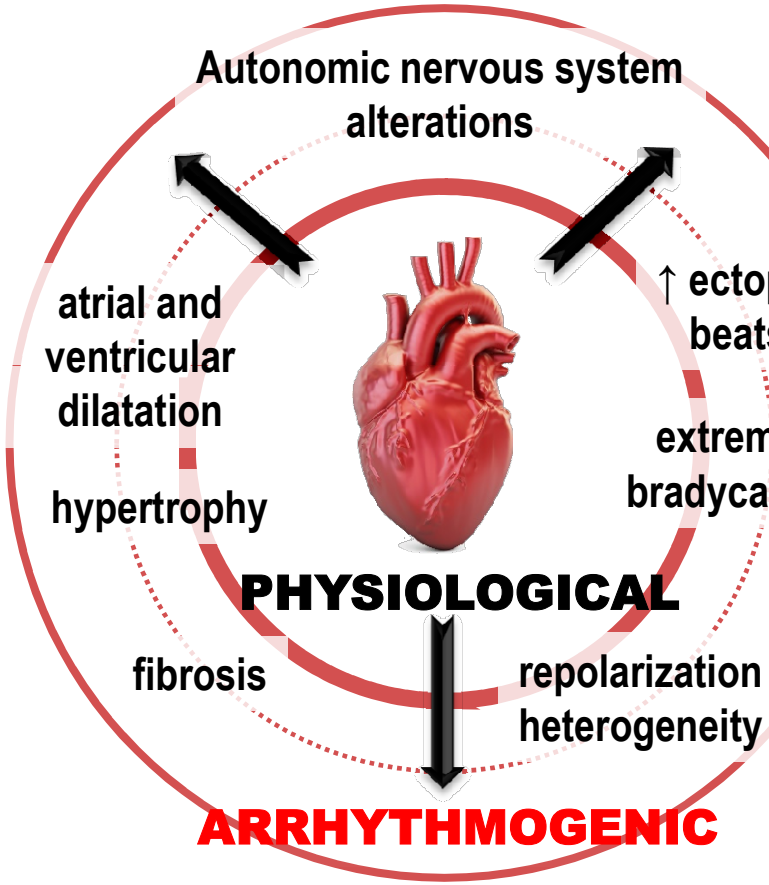
Beneficial & harmful effects of sports activities



EXTREME PHYSICAL ACTIVITY

↓

MALADAPTATION



+

Doping agents

018) The athlete's heart is a proarrhythmic heart, and what that means for clinical decision making. EP Europace

l (2018) The Extreme Exercise Hypothesis: Recent Findings and Cardiovascular Health Implications. Curr Treat Opt Card Med

(2016) The U-shaped relationship between exercise and cardiac morbidity. Trends Cardiovasc Med

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Europace (2018) **20**, 1401–1411
doi:10.1093/europace/eux294

REVIEW

athlete's heart is a proarrhythmic heart, what that means for clinical decision ing

eidbuchel*

Cardiology, Antwerp University and University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium

TRENDS IN CARDIOVASCULAR MEDICINE 26 (2016) 232–240

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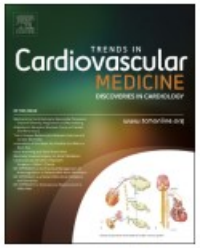


U-shaped relationship between exercise and liac morbidity

CrossMark

ed Merghani, MRCP, Aneil Malhotra, MRCP, and
y Sharma, MRCP, FESC*

ent of Cardiovascular Sciences, St George's, University of London, Cranmer Terrace, London, UK

(2018) The athlete's heart is a proarrhythmic heart, and what that means for clinical decision making. EP Europace

t al (2018) The Extreme Exercise Hypothesis: Recent Findings and Cardiovascular Health Implications. Curr Treat Opt Card Med

al (2016) The U-shaped relationship between exercise and cardiac morbidity. Trends Cardiovasc Med

Curr Treat Options Cardio Med (2018) 20: 84
DOI 10.1007/s11936-018-0674-3

Sports Cardiology (M Papadakis, Section Editor)

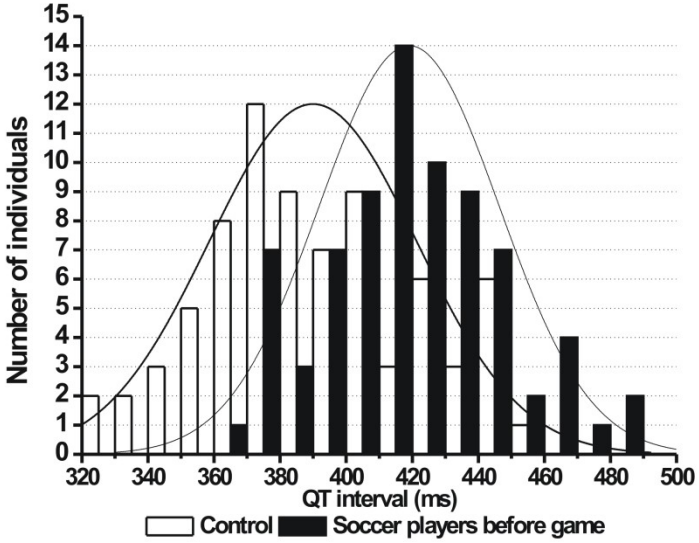
The "Extreme Exercise Hypothesis": Recent Findin and Cardiovascular Health Implications

Thijs M. H. Eijsvogels, PhD[1,*]
Paul D. Thompson, MD[2]
Barry A. Franklin, PhD[3]

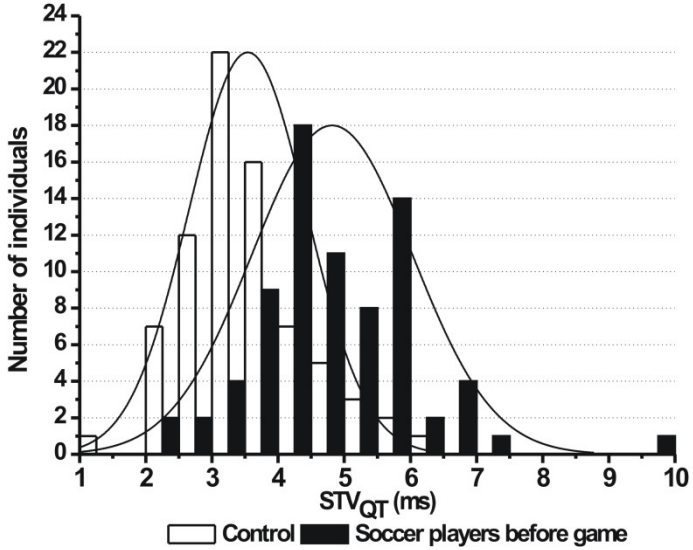
Address
[*,1]Radboud Institute for Health Sciences, Department of Physiology (392), Radboud University Medical Center, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands
Email: Thijs.Eijsvogels@radboudumc.nl
[2]Division of Cardiology, Hartford Hospital, Hartford, CT, USA
[3]Department of Cardiovascular Medicine, William Beaumont Hospital, Royal Oak, MI, USA

Short-term QT variability in soccer players

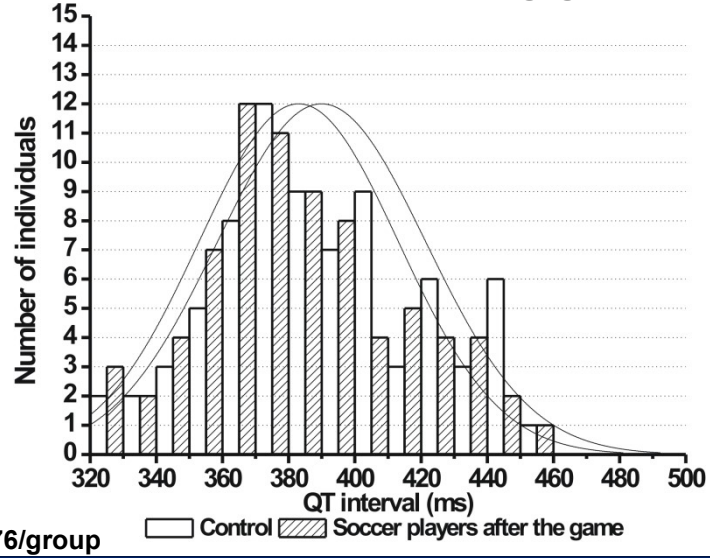
QT interval before game



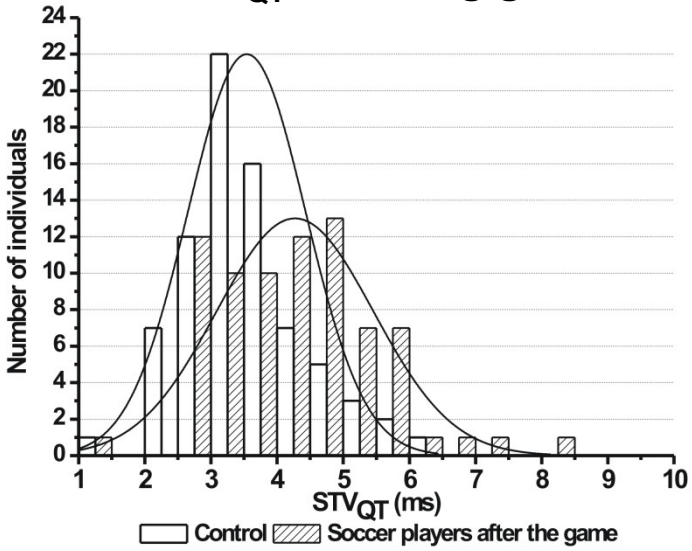
STV_{QT} before game



QT interval following game



STV_{QT} following game



n = 76/group

Lengyel et al., *PLoS ONE*, 2011

Increased short-term variability (STV) of repolarization in animal experimental models

ardiol 100: 279 – 287 (2005)
7/s00395-005-0519-6

ORIGINAL CONTRIBUTION

B. Thomsen
Truin
M. van Opstal
I. Beekman
A. Volders
tengl
. Vos

Sudden cardiac death in dogs with remodeled hearts is associated with larger beat-to-beat variability of repolarization

he American College of Cardiology
the American College of Cardiology Foundation
y Elsevier Inc.

Vol. 48, No. 6, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.048

LINICAL STUDY

t-to-Beat Variability of Repolarization ermines Proarrhythmic Outcome in Dogs eptible to Drug-Induced Torsades de Pointes

B. Thomsen, PHD,*† Paul G. A. Volders, MD, PHD,† Jet D. M. Beekman,* Jørgen Matz, PHD,‡
. Vos, PHD*
and Maastricht, the Netherlands; and Copenhagen, Denmark

British Journal of Pharmacology (2007) 151, 941–951

0007–1188/07 $30.00
www.brjpharmacol.org

RESEARCH PAPER

Combined pharmacological block of I_{Kr} and I_{Ks} increases short-term QT interval variability and provokes torsades de pointes

C Lengyel[1,2], A Varró[1,3], K Tábori[1], JG Papp[1,3] and I Baczkó[1]

[1]*Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Albert Szent-Györgyi Medical Centre, University of Szeged, Szeged, Hungary;* [2]*1st Department of Internal Medicine, Faculty of Medicine, Albert Szent-Györgyi Medical Centre, University of Szeged, Szeged, Hungary and* [3]*Research Unit for Cardiovascular Pharmacology, Hungarian Academy of Sciences, Szeged, Hungary*

BJP British Journal of Pharmacology

British Journal of Pharmacology (2016) **173** 2046–2061 2046

RESEARCH PAPER

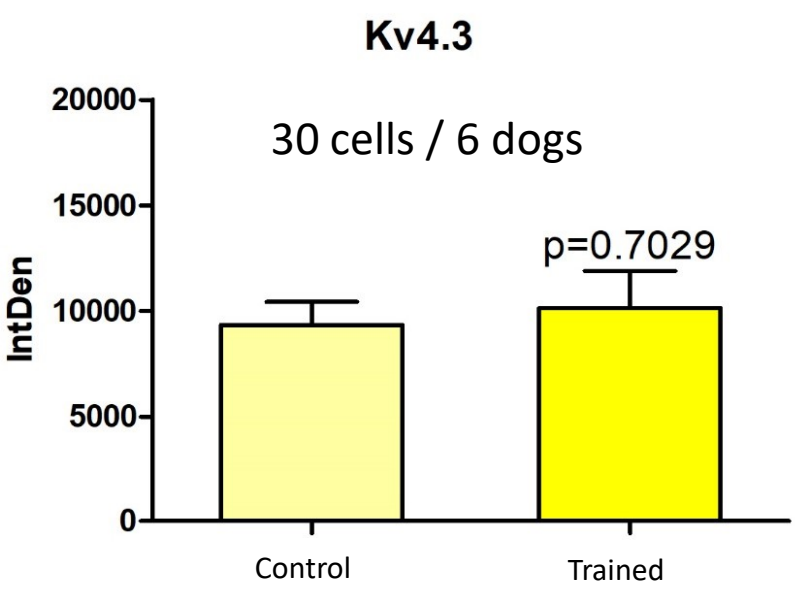
A novel transgenic rabbit model with reduced repolarization reserve: long QT syndrome caused by a dominant-negative mutation of the *KCNE1* gene

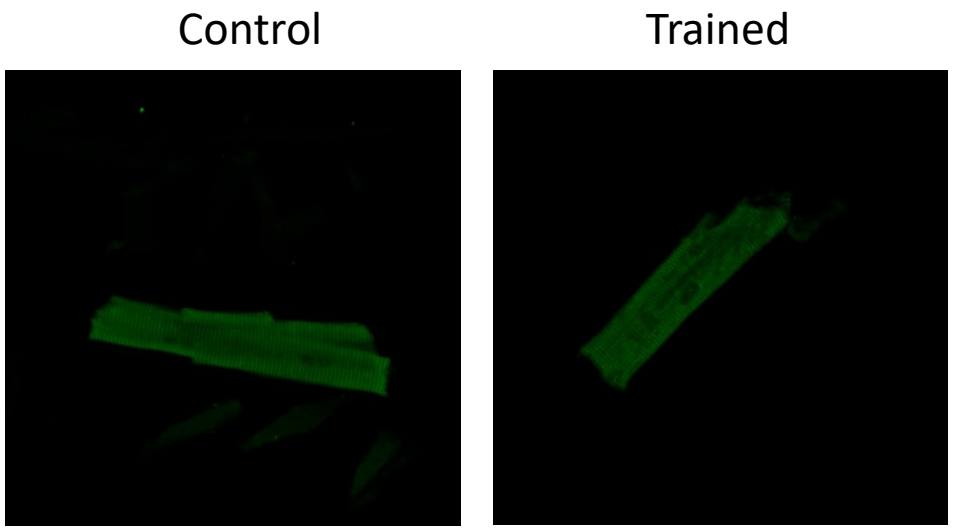
Correspondence Dr Zsuzsanna Bősze, Rabbit Genome and Biomodel Group, Animal Biotechnology Department of NARIC – Agricultura Biotechnology Institute, H-2100 Gödöllő, Hungary. E-mail: bosze@abc.hu

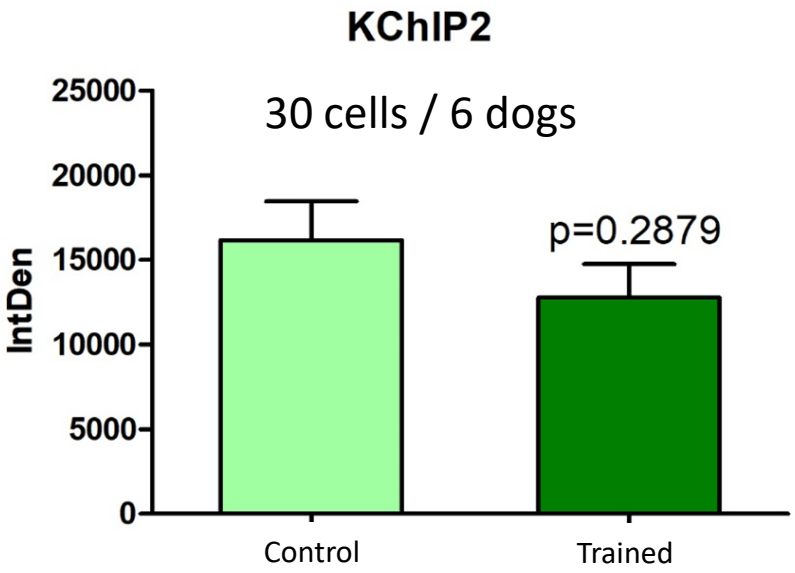
Received 24 September 2015; **Revised** 25 March 2016; **Accepted** 1 April 2016

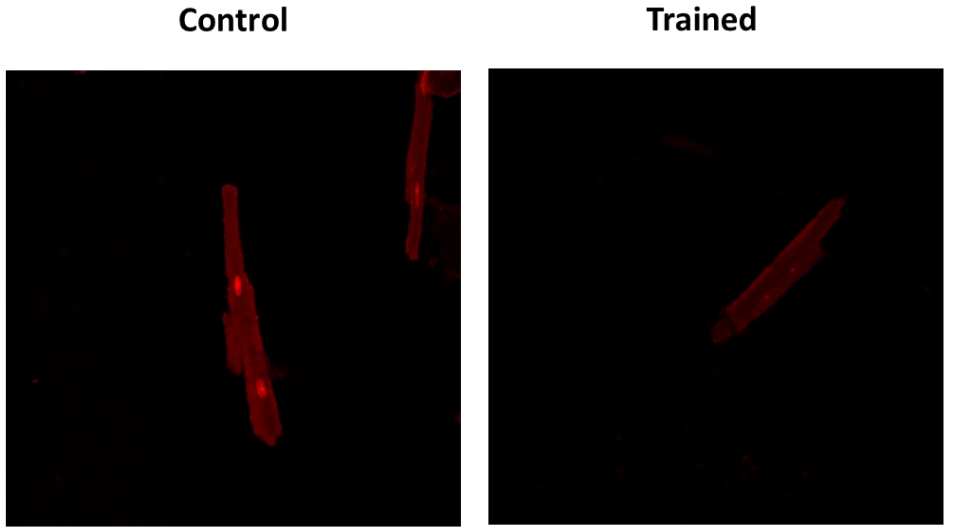
Péter Major[1]*, István Baczkó[2]*, László Hiripi[1], Katja E. Odening[3], Viktor Juhász[2], Zsófia Kohajda[2], András Horváth[2], György Seprényi[4], Mária Kovács[2], László Virág[2], Norbert Jost[2,5], János Prorok[2], Balázs Ördög[2], Zoltán Doleschall[6], Stanley Nattel[7,8,9], András Varró[2,5†] and Zsuzsanna Bősze[1,†]

Transient outward „channel” (I_{to}) protein densities determination by immonochemistry in dog ventricular myocytes









Increased short-term variability (STV) of repolarization in human pathological settings

European Heart Journal (2008) **29**, 185–190
doi:10.1093/eurheartj/ehm586

CLINICAL RESEARCH
Arrhythmia/electrophysiology

at-to-beat variability of QT intervals is reased in patients with drug-induced long-QT drome: a case control pilot study

n Hinterseer[1]*, Morten B. Thomsen[2], Britt-Maria Beckmann[1], Arne Pfeufer[3,4], r Schimpf[5], H.-Erich Wichmann[3,6], Gerhard Steinbeck[1], A. Vos[2], and Stefan Kaab[1]

nt of Medicine I, Klinikum Grosshadern, Ludwig Maximilians University Munich, Marchioninistrasse 15, D-81366 Munich, Germany; [2]Department of Medical Physiology, Centre Utrecht, Utrecht, The Netherlands; [3]Institute of Human Genetics and Epidemiology, GSF National Research Center for Environment and Health, Neuherberg, Institute of Human Genetics, Technical University Munich, Munich, Germany; [5]1st Department of Medicine, Cardiology, University Hospital of Mannheim, Mannheim, Institute of Epidemiology, GSF, National Research Center, Neuherberg, Germany

LOS | ONE

Usefulness of Short-Term Variability of QT Intervals as a Predictor for Electrical Remodeling and Proarrhythmia in Pa With Nonischemic Heart Failure

Martin Hinterseer, MD[a,*], Britt-Maria Beckmann, MD[a], Morten B. Thomsen, PhD[f], Arne Pfeufer, MD, BSc[b], Michael Ulbrich, MD[a], Moritz F. Sinner, MD[a], Siegfried Perz, H.-Erich Wichmann, MD, PhD[c], Csaba Lengyel, MD, PhD[g], Rainer Schimpf, MD, PhD Sebastian K.G. Maier, MD, PhD[e], András Varró, MD, PhD[g], Marc A. Vos, PhD[h], Gerhard Steinbeck, MD, PhD[a], and Stefan Kääb, MD, PhD[a]

Am J Cardiol 2010;106:216

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

ART

Short-term beat-to-beat variability of the QT interval is increased and correlates with parameters of left ventricu hypertrophy in patients with hypertrophic cardiomyopa

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

Transient outward „channel” (I_{to}) protein densities determination by Western blot in dog ventricular tissue