Arrhythmogenic cardiac ventricular remodeling in a large animal model of chronic endurance exercise

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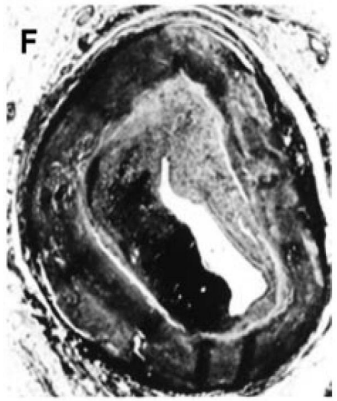
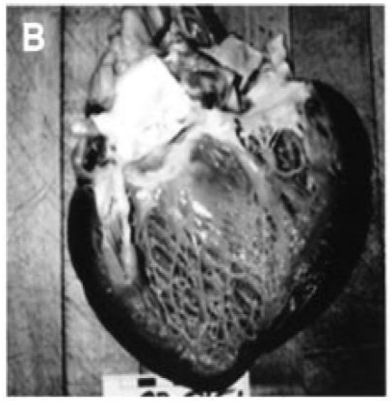
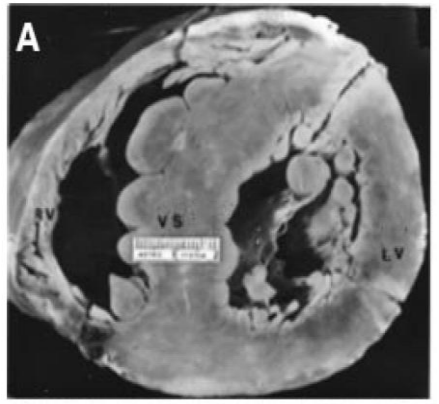
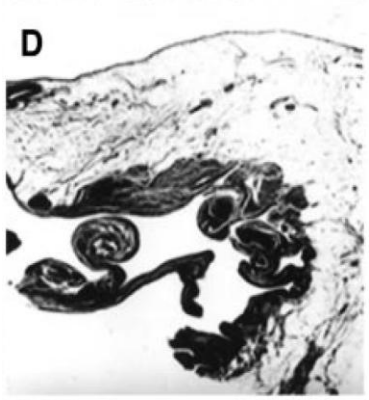
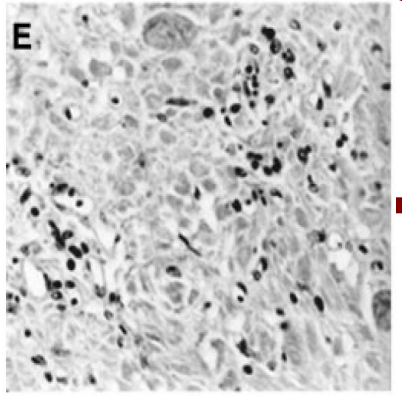
Autopsy findings in young athletes with SCD

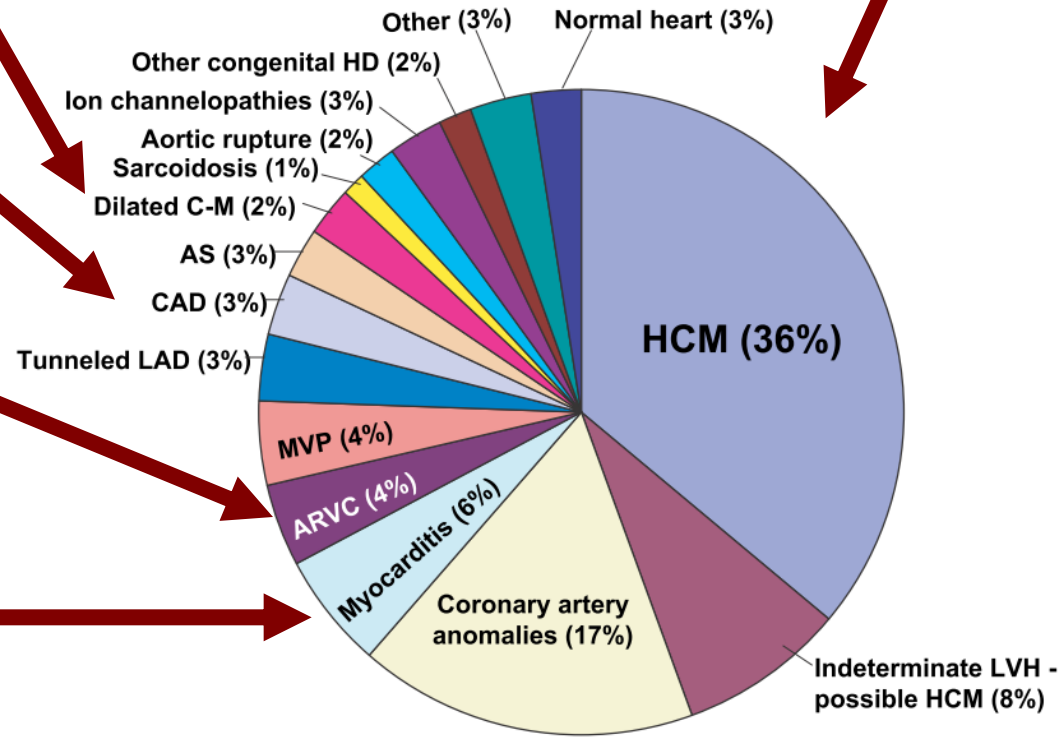








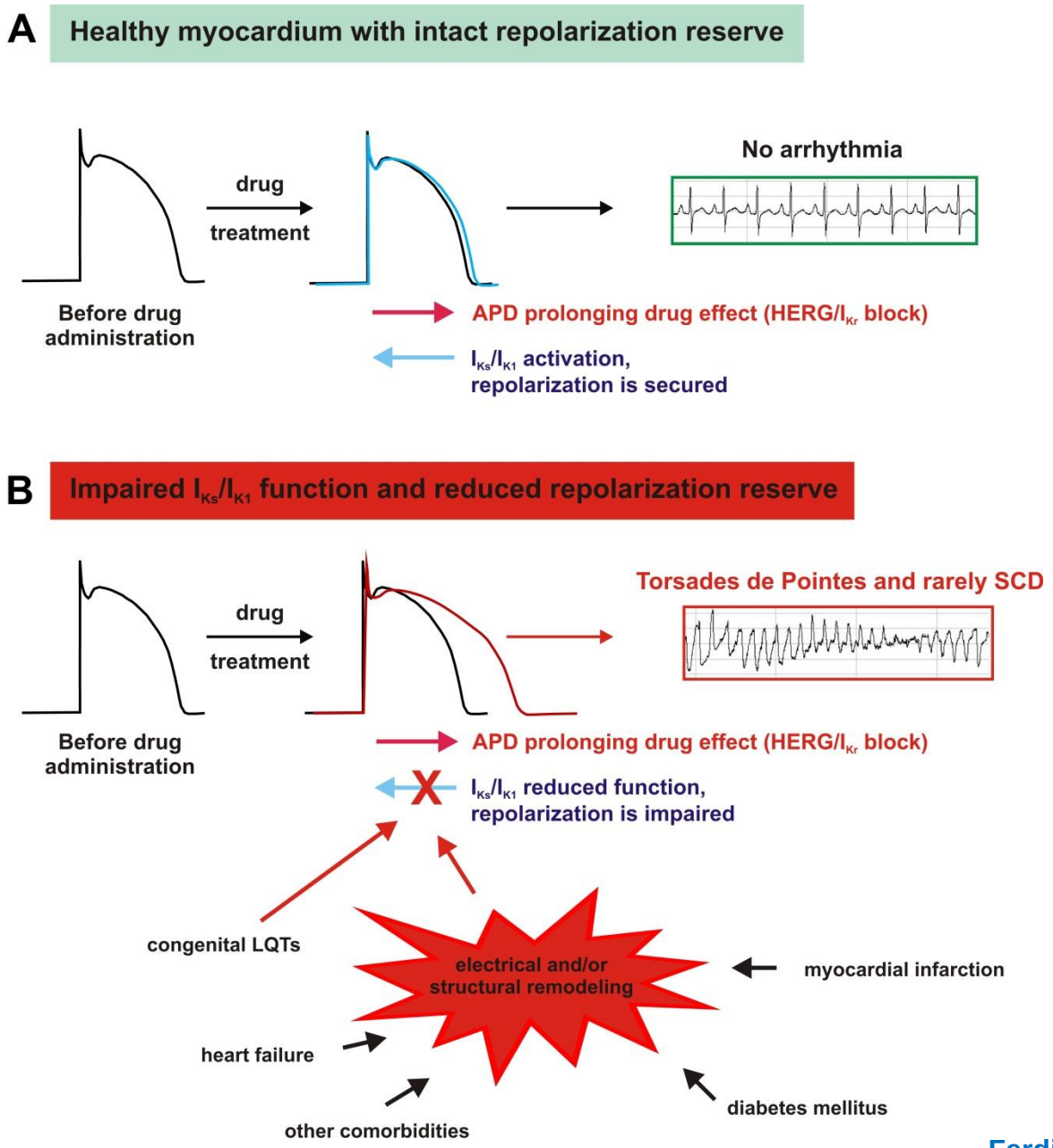




Maron and Pelliccia, *Circulation* 2006;114; 1633-1644

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

Cardiac repolarization reserve and the role of I_{Ks}



Ferdinandy, Baczkó *et al*., *European Heart J*, 2019

Research aims

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

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

Experimental groups

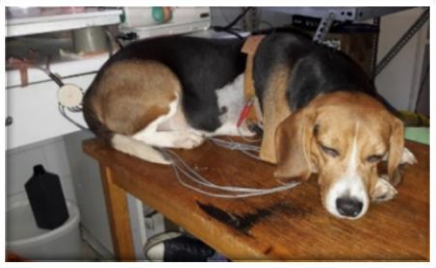
'Control' *(n=12)*

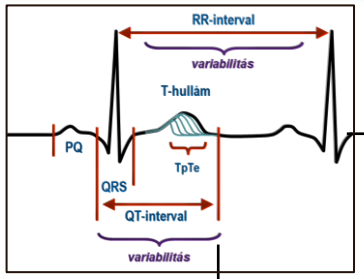
'Trained' *(n=12)*

Training program duration:	**16-week treadmill running**
No. of trainings:	5 times /week
Training sessions:	2x90 min long-distance running +
	2x50 min interval running
Inclination:	0% - 5% - 12%
Peak daily distance:	**80 km**
Peak running speed:	**22 km/h**

Sex ratio

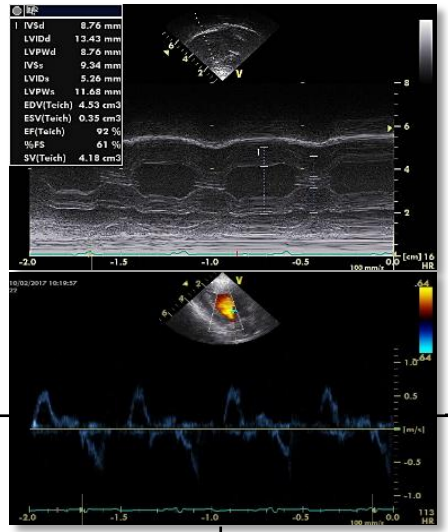
Methods





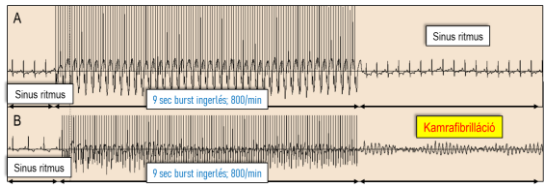
ECG characteristics

- 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



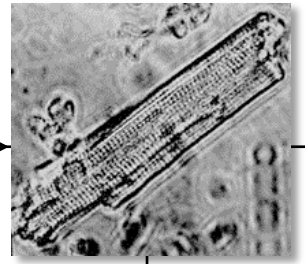
Burst stimulation

- 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

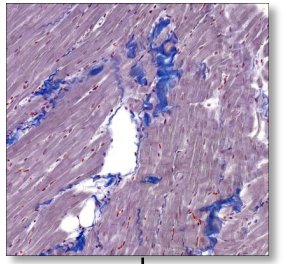
- Patch-clamp technique
- Perforated patch
- Current-clamp, 37 °C

Transmembrane ionic current measurements

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

Biological markers

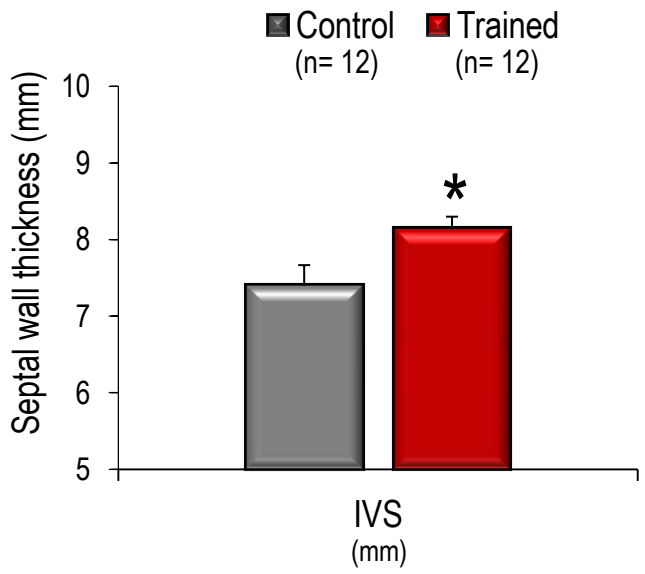
- Immunocytochemistry

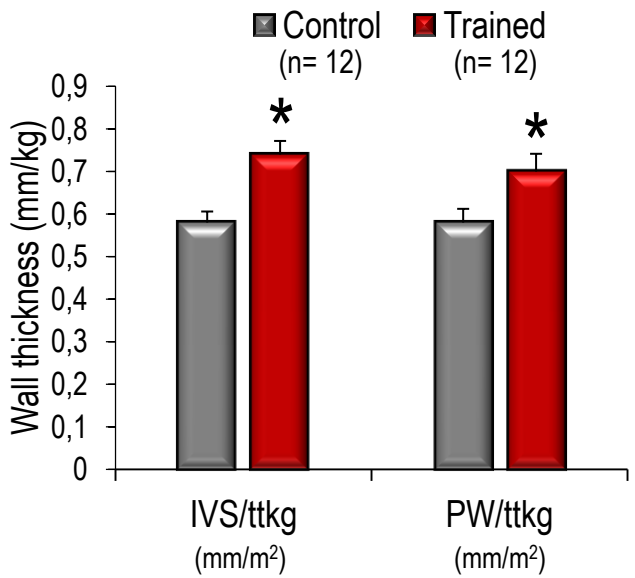


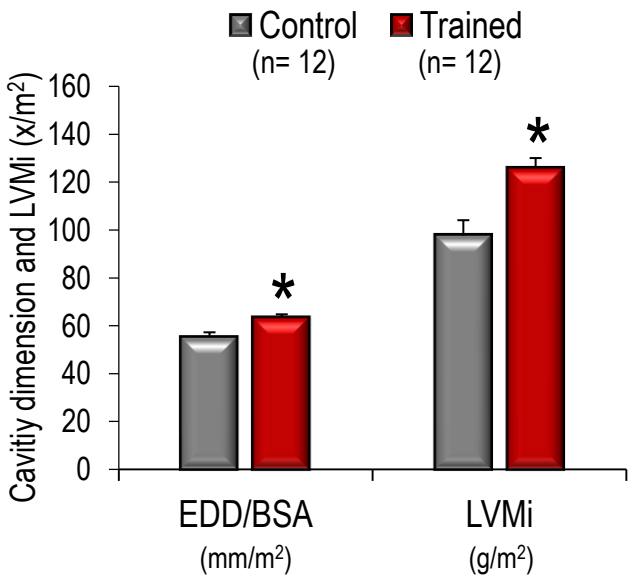
Presence of fibrosis

- Crossmon's trichrome staining
- Semi-quantitative analysis

Echocardiography: Left ventricular hypertrophy







Abbreviations:

IVS, Interventricular septal wall thickness

PW, Left ventricular posterior wall thickness

EDD, Left ventricular end diastolic diameter

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

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

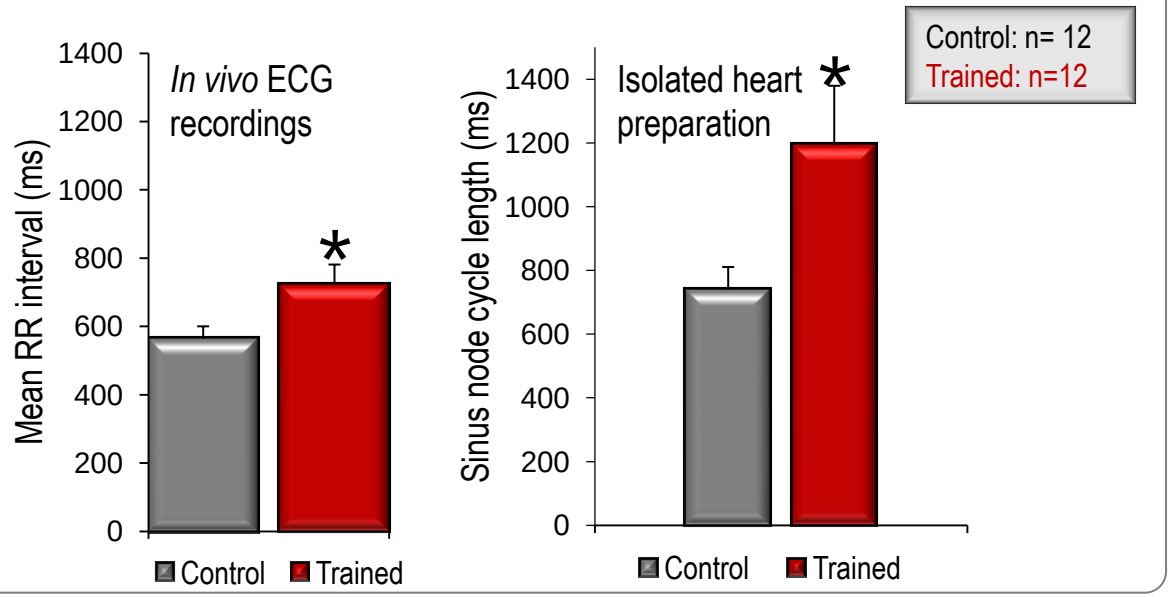
LVMi, Left ventricular mass index: LVM/BSA (g/m^2)

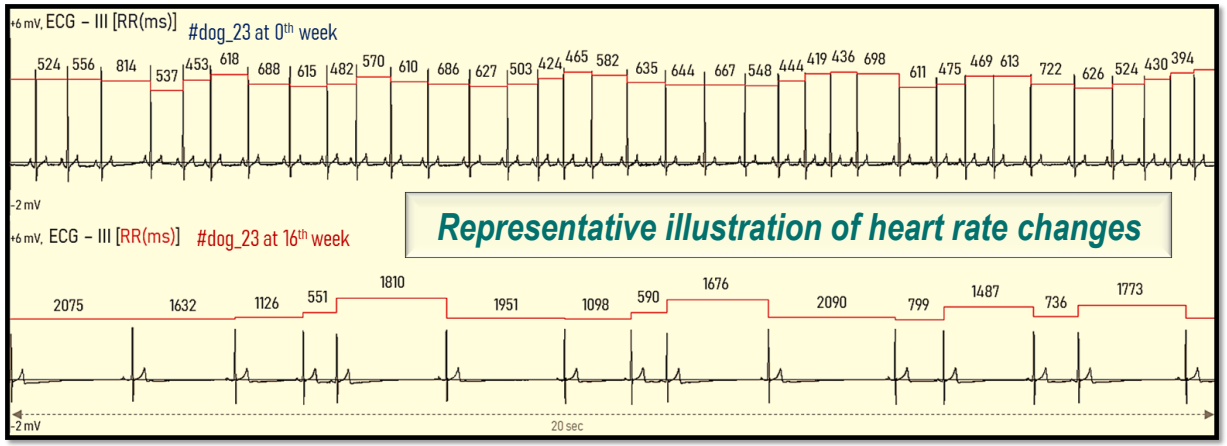
**p<0.05 Trained 16th week vs. Control 16th week*

[1] Wey et al. Allometric Scaling of M-Mode Cardiac Measurements in Normal Adult Dogs
[2] Troy et al. Measurement of left ventricular wall thickness and mass by echocardiography

Bradycardia and increased heart rate variability

A) Bradycardia

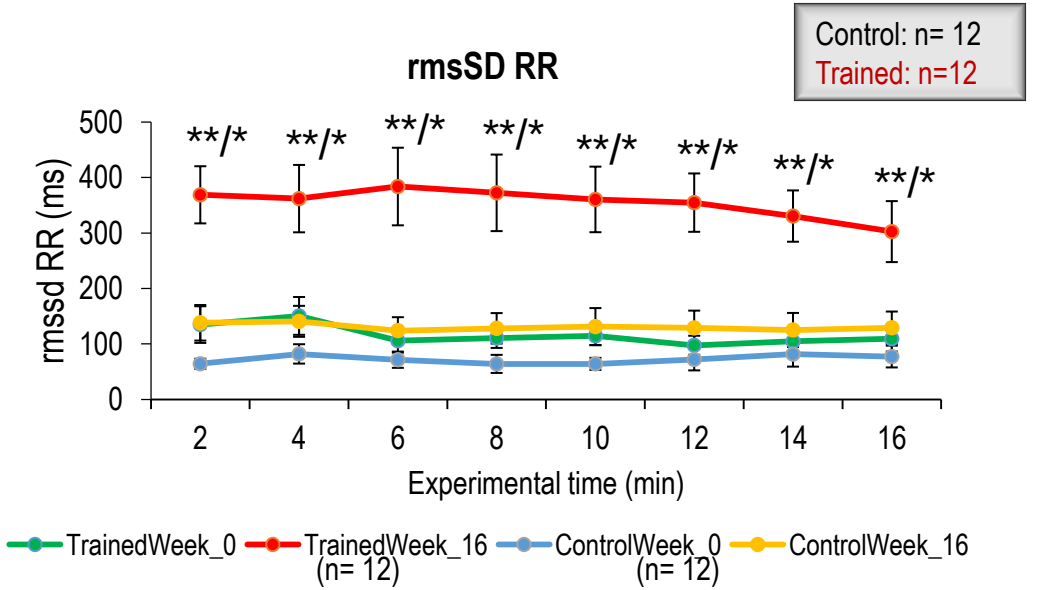




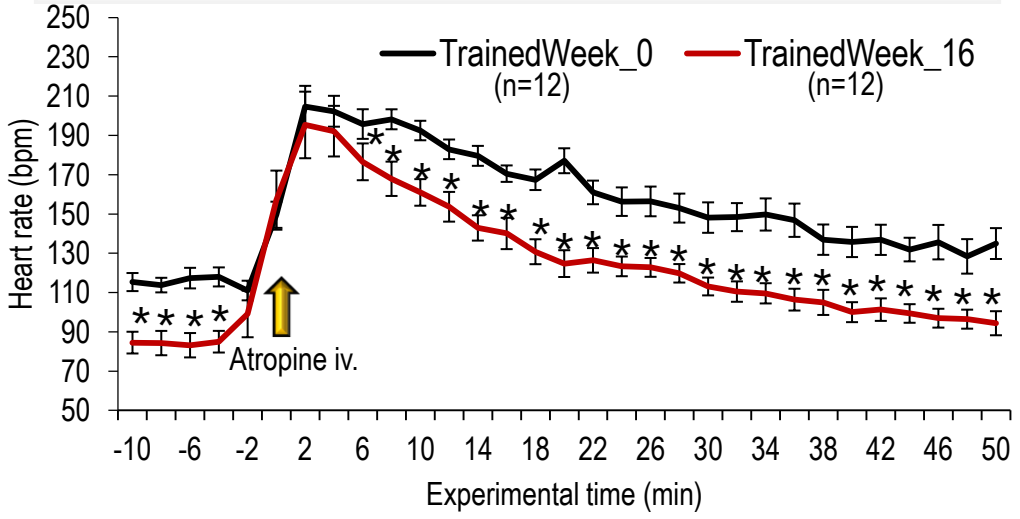
Abbreviations: ***rmsSD***, root mean square of the successive differences;

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

B) Heart rate variability increase

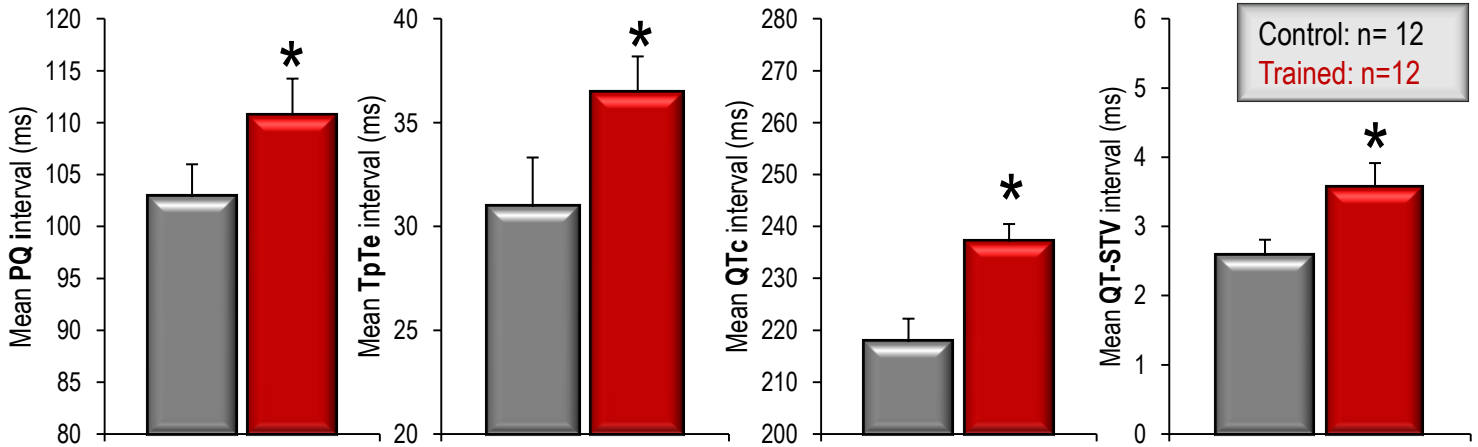


C) Heart rate response to i.v. atropine (Dose: 0.04 mg/kg)

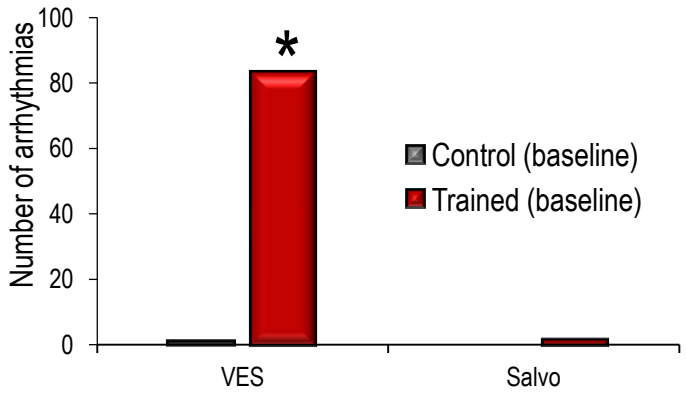


ECG: Repolarization changes and ectopic activity

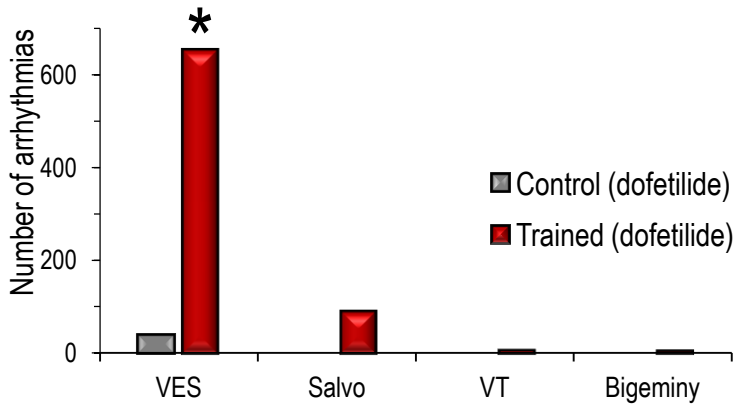
A) Baseline (drug free) ECG measurements



B/1) Arrhythmias on baseline ECG (t=20 min)

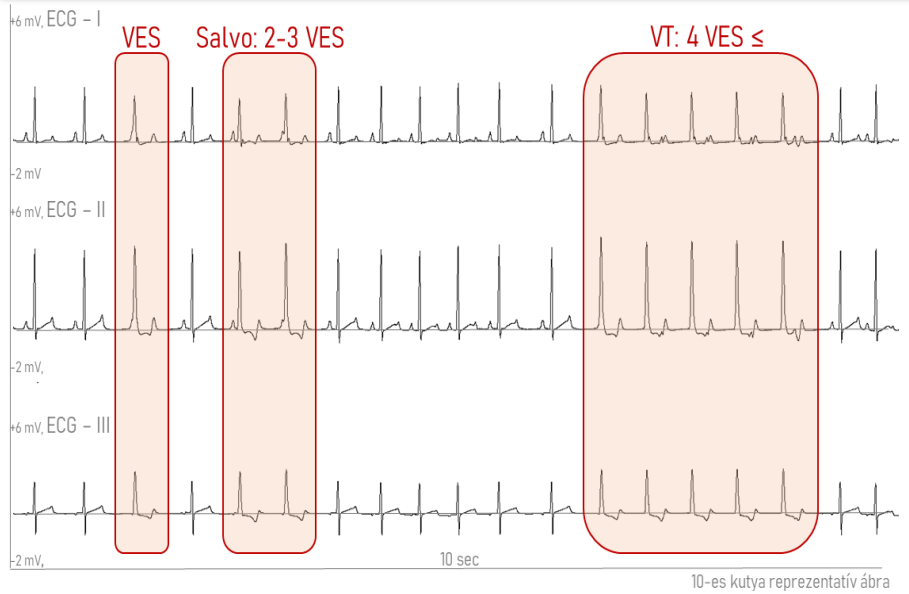


B/2) Arrhythmias on dofetilide ECG (t=60 min)



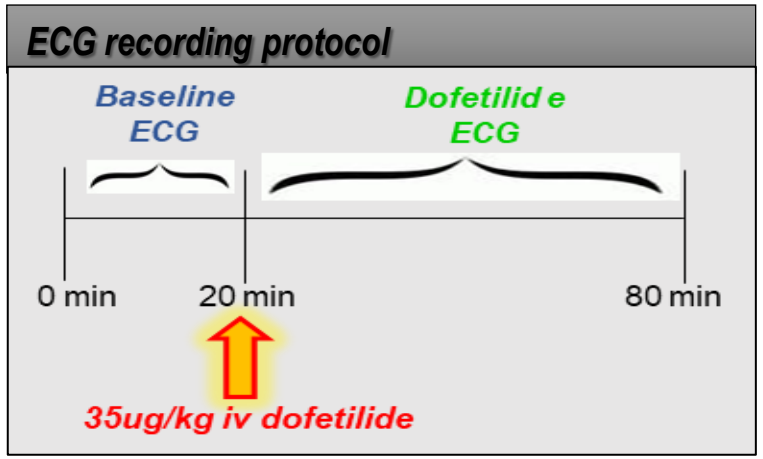
Abbreviations: STV: Short term variability; QTc: QT corrected for heart rate

Illustration of ventricular arrhythmias in trained dogs



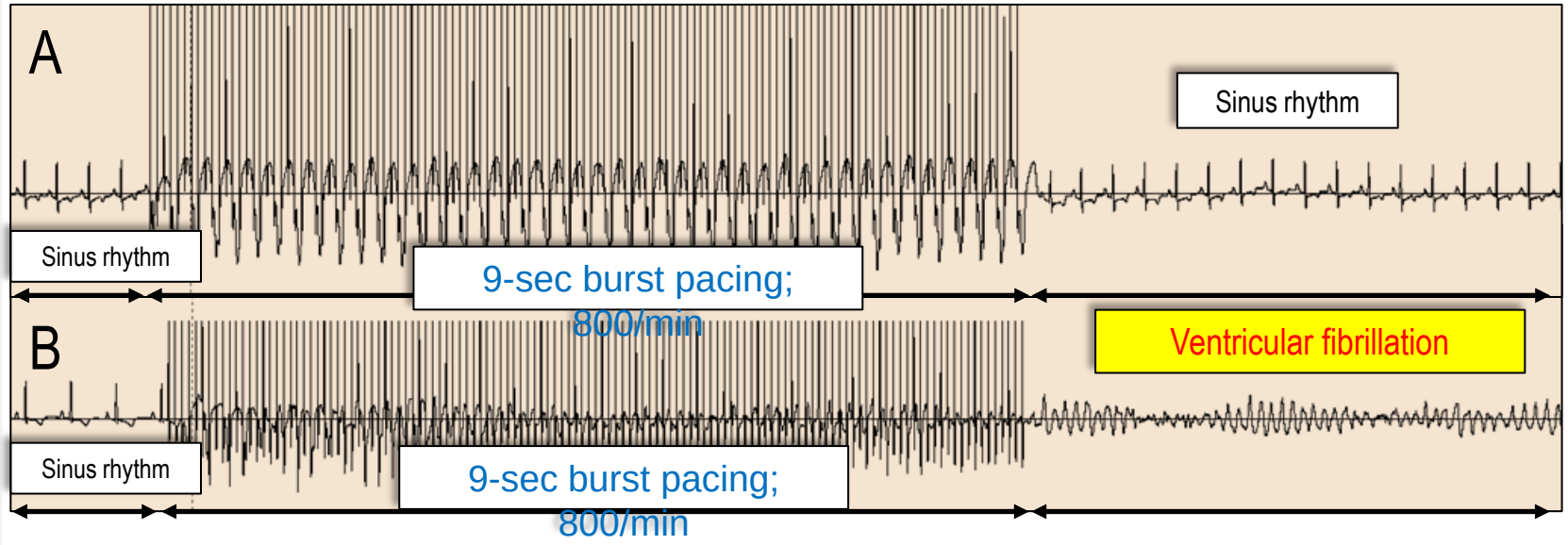
Curtis et al. Lambeth conventions (II)

ECG recording protocol



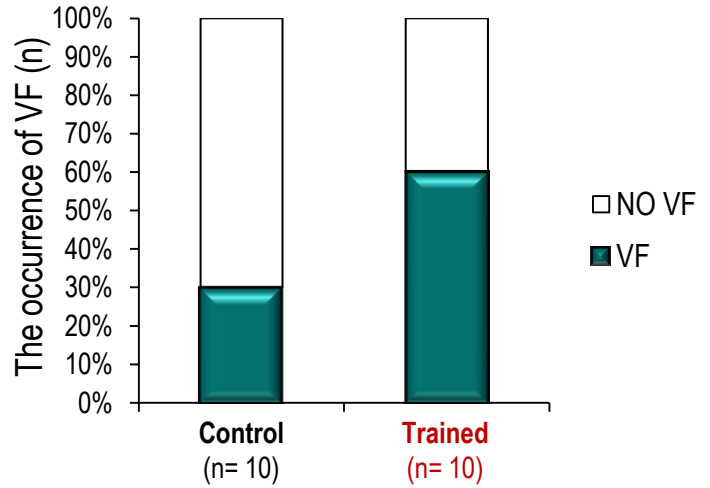
*p<0.05 Trained 16th week vs. Control 16th week

Arrhythmia (VF) susceptibility and LV fibrosis



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

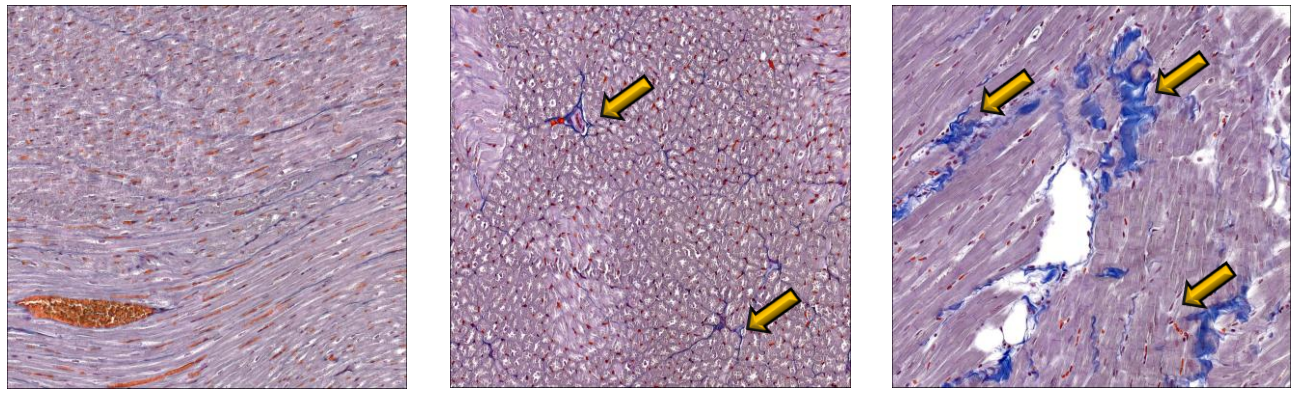
Ventricular fibrillation (VF) after burst pacing



Score 0 = no fibrosis
Control dog

Score 1 = mild fibrosis
Exercised dog

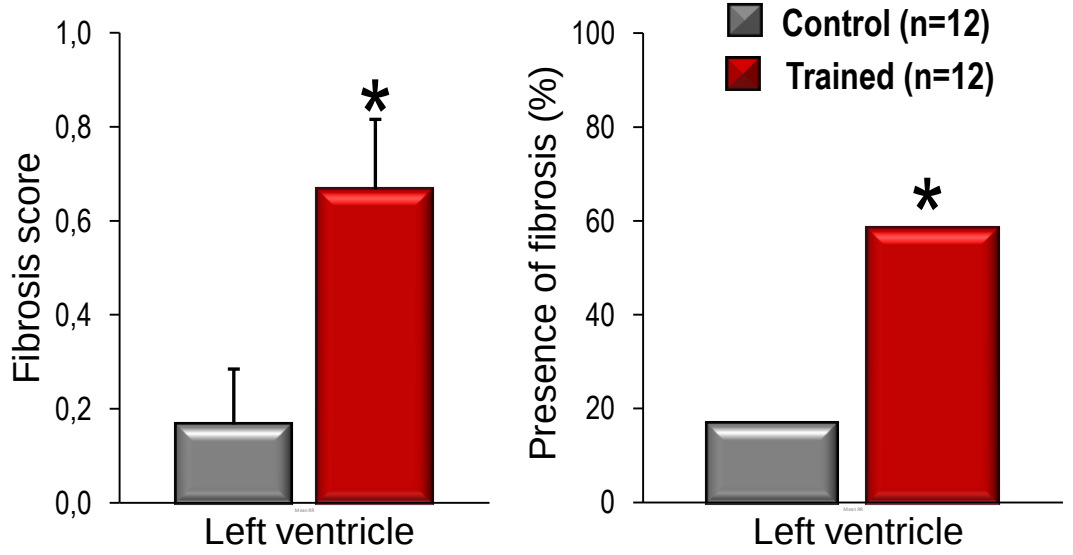
Score 2 = moderate fibrosis
Exercised dog



Crossmon's trichrome staining

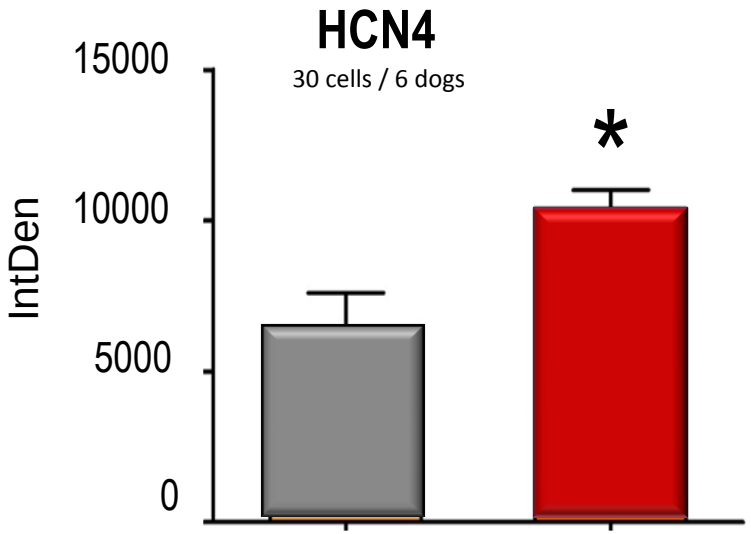
**p<0.05 Trained 16th week vs. Control 16th week*

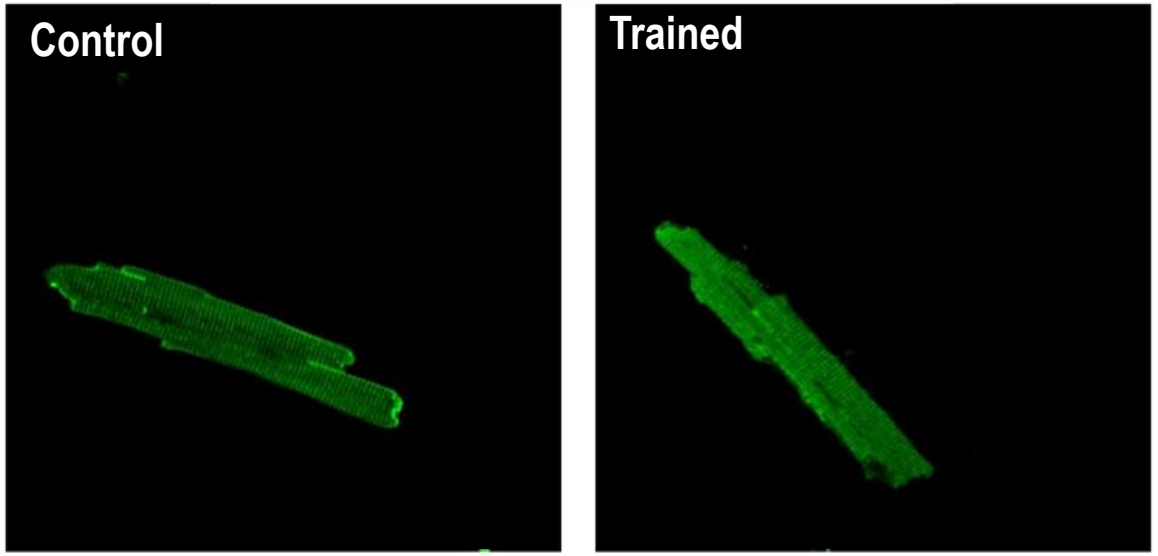
The extent of fibrosis in histological sections of the left ventricle



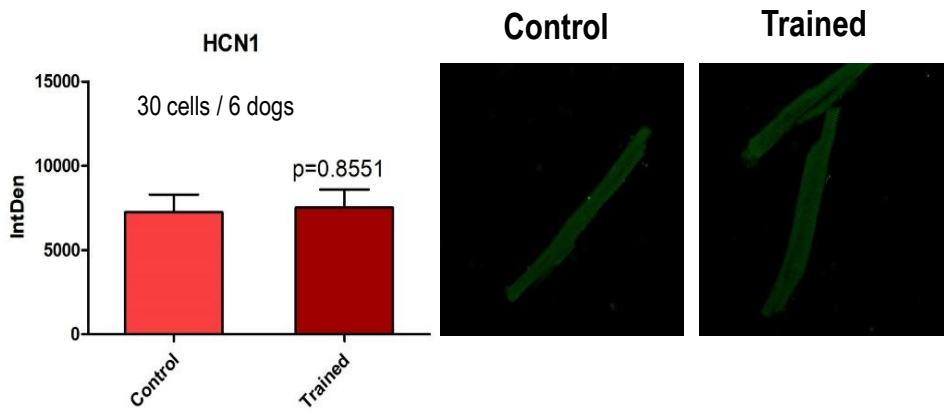
Pacemaker channel (I_f) protein density determination by immunochemistry in dog ventricular myocytes

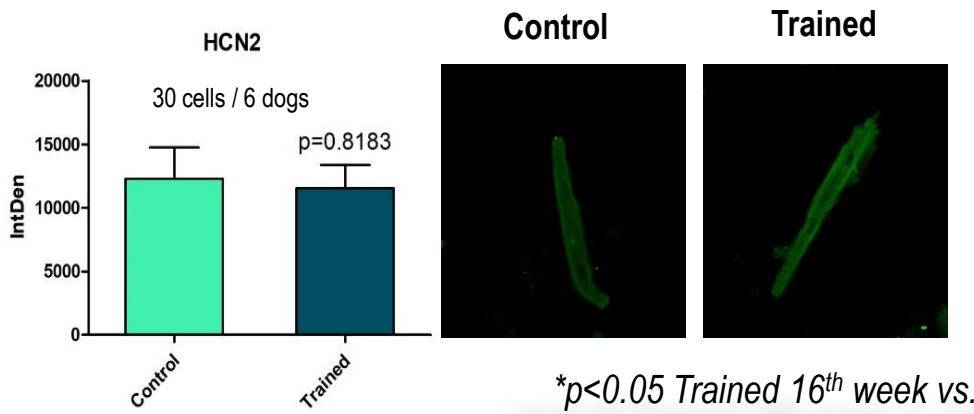
Overexpression of HCN4 protein in dog left ventricular myocytes





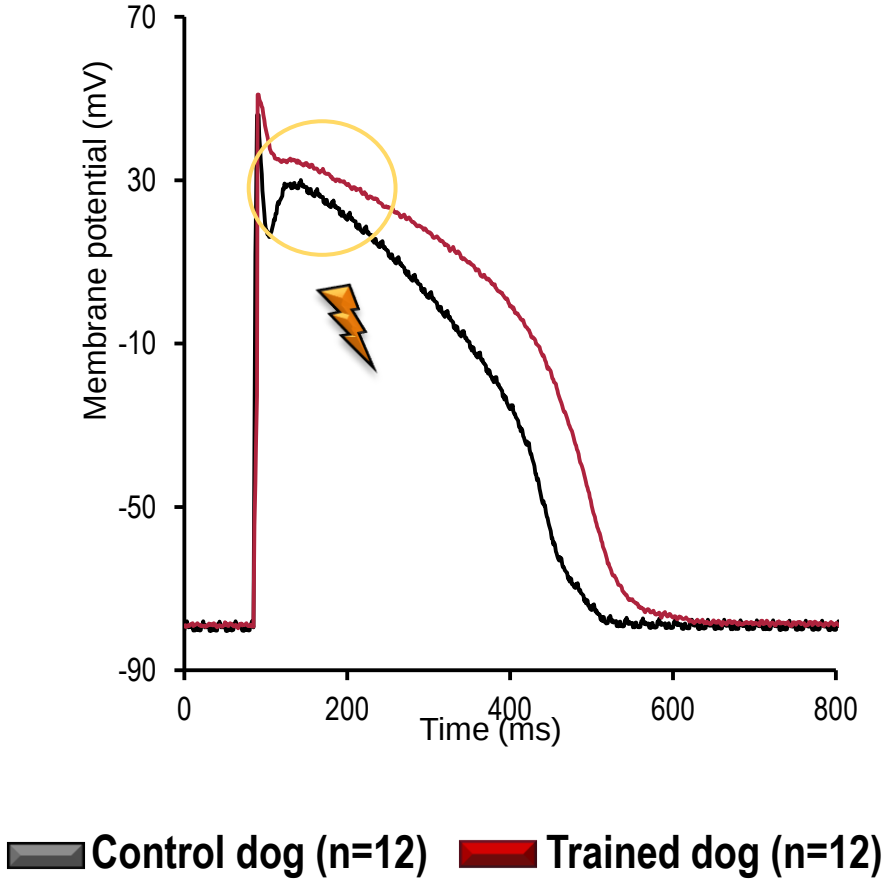
Control dog (n=6) Trained dog (n=6)



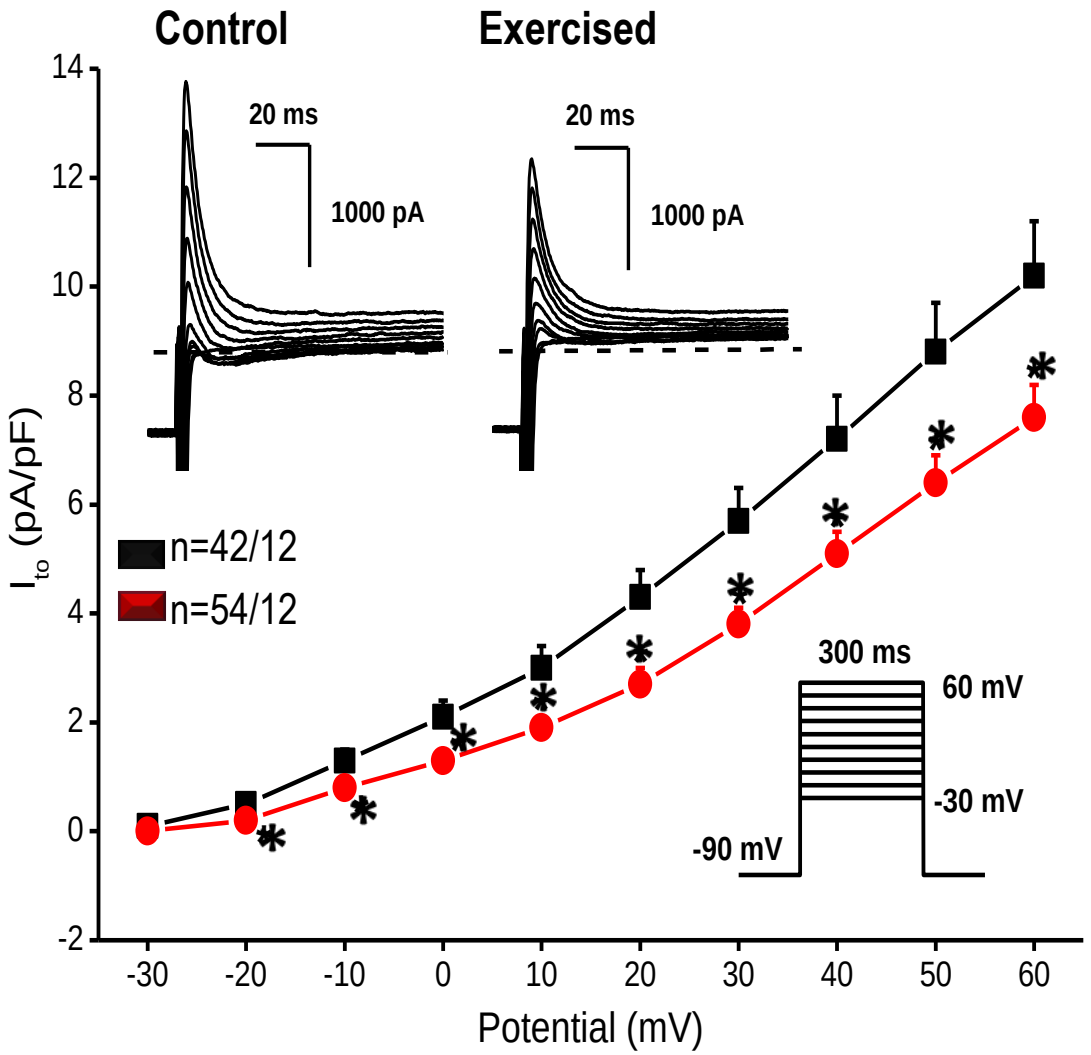


*$p<0.05$ Trained 16^{th} week vs. Control 16^{th} week

Transmembrane ionic current measurements in dog left ventricular myocytes



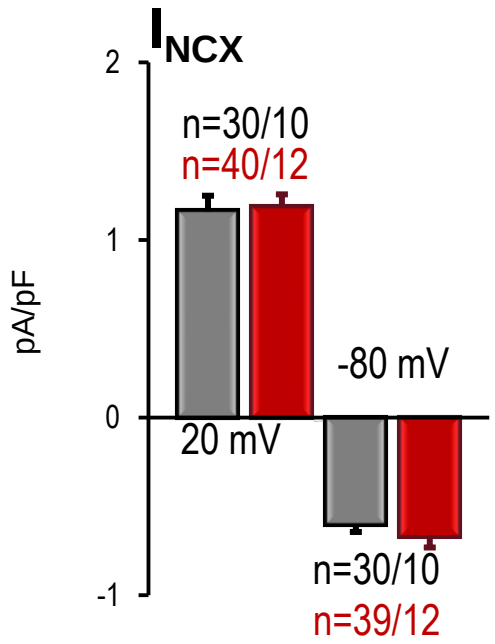
Magnitude of transient outward potassium current (I_{to})

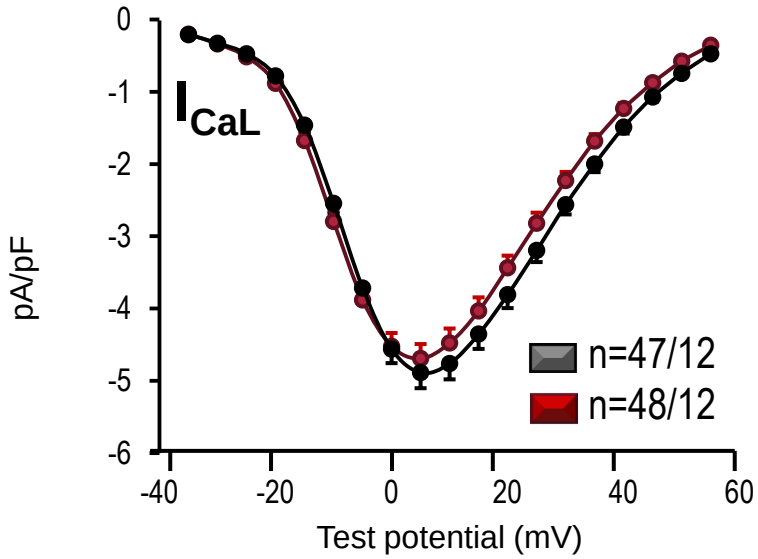


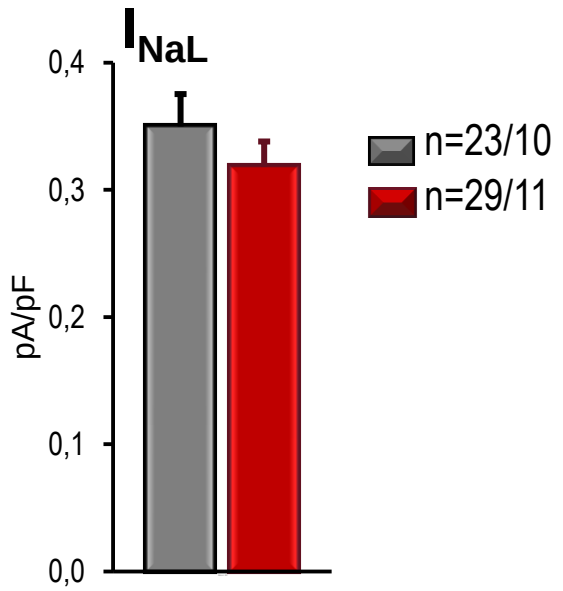
Polyák et al, *eLife* 2023

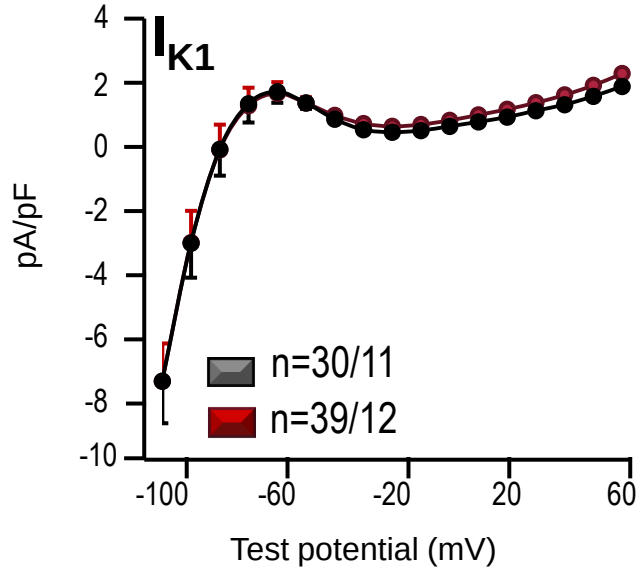
**p<0.05 Trained 16th week vs. Control 16th week*

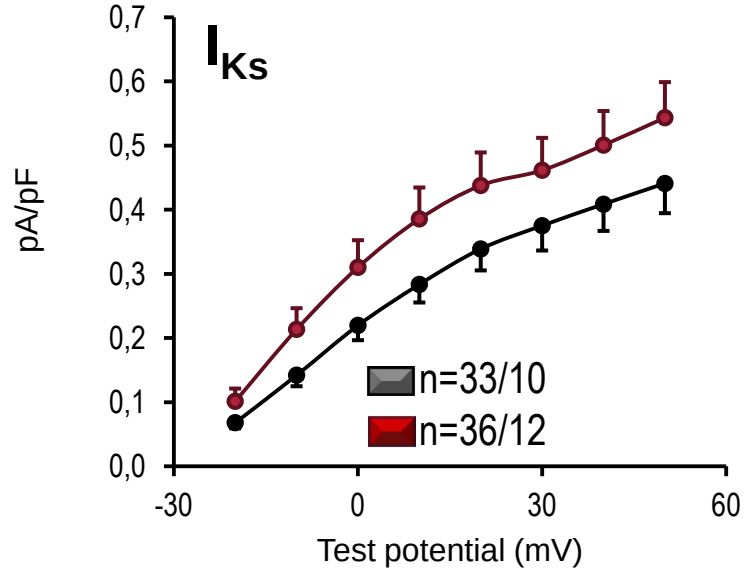
Transmembrane ionic current measurements in dog left ventricular myocytes

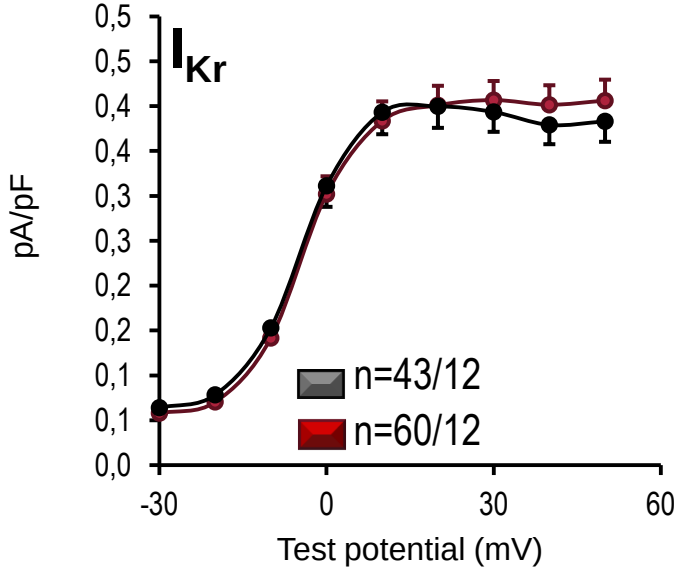












Control dog (n=12) Trained dog (n=12)

Polyák et al, *eLife* 2023

Conclusions

16 weeks of continuous intensive endurance training

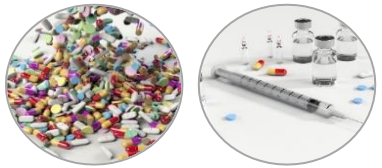
- ✓ Left ventricular **hypertrophy** → physiological morphological adaptation
- ✓ Training induced **bradycardia** with **increased heart rate variabiliy** → vagal enhancement
- ✓ Moderate response to atropine *in vivo* and **decreased sinus node cycle length** → intrinsic changes in the sinus node?

- ✓ 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

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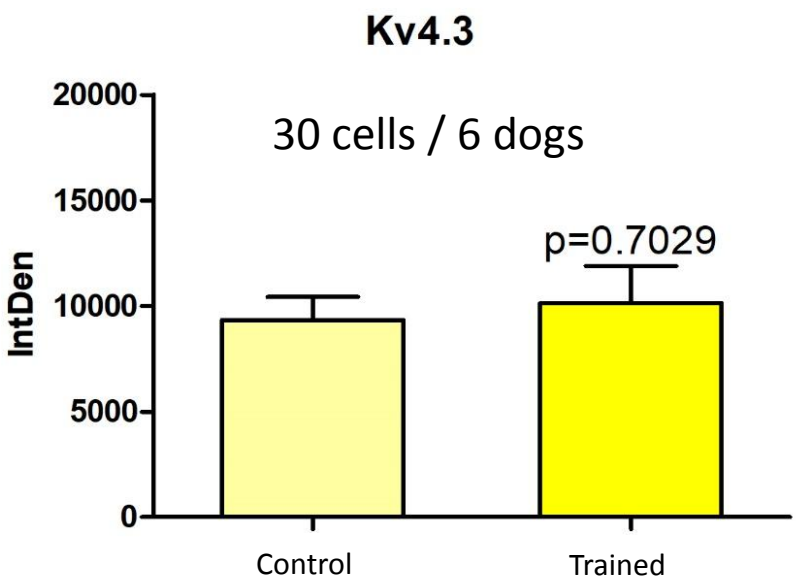
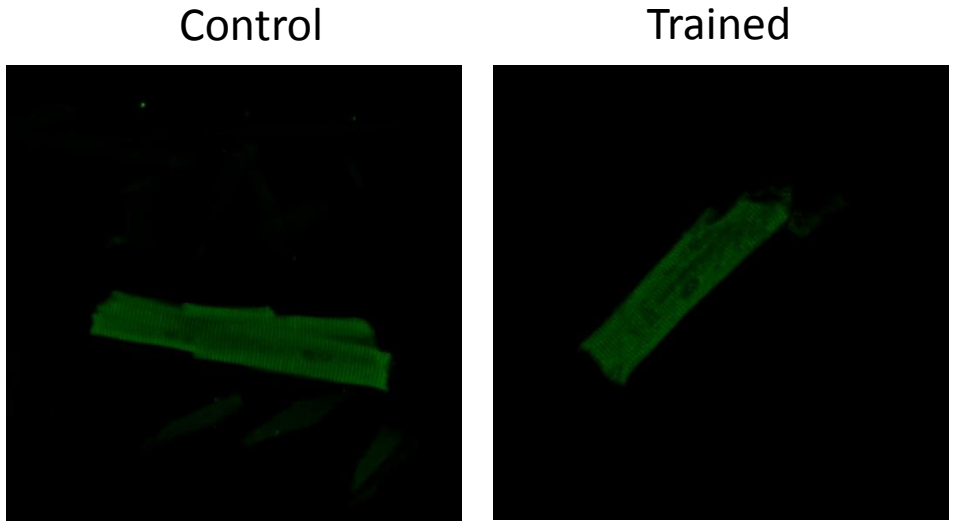
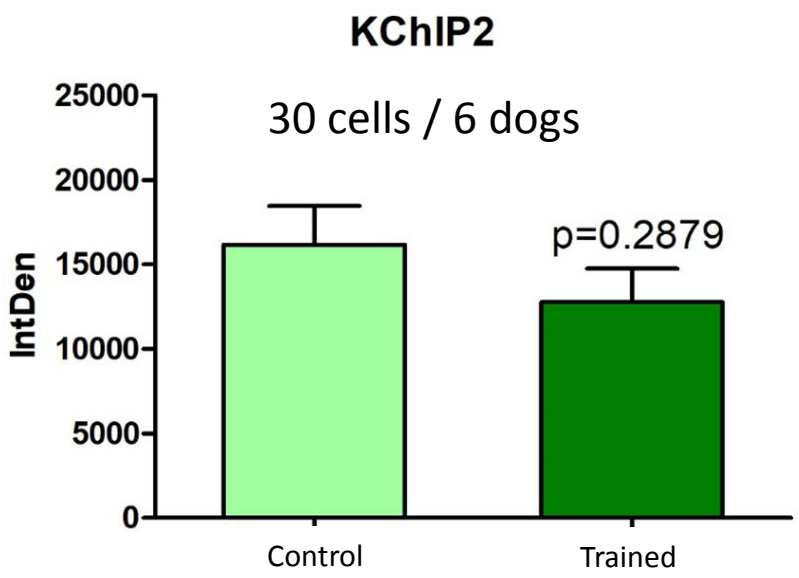
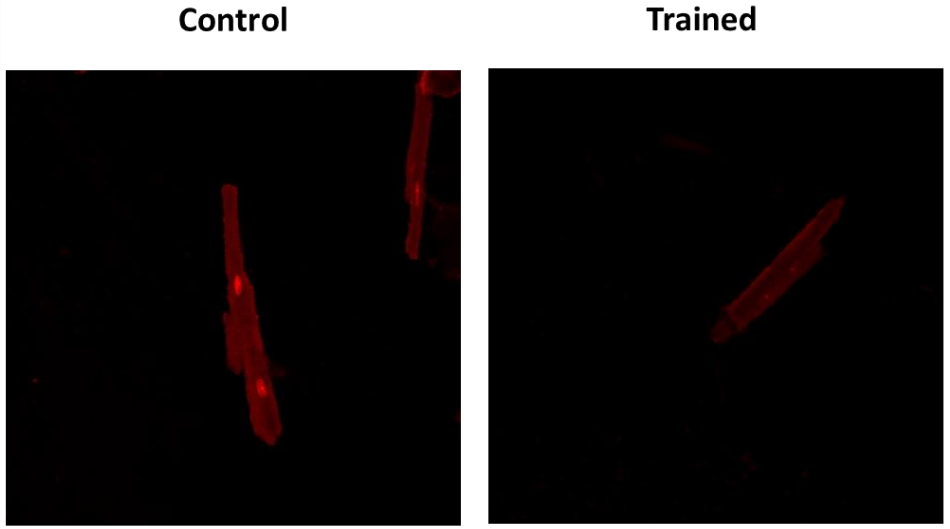
Ministry of Human Capacities EFOP-3.6.2-16-2017-00006

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

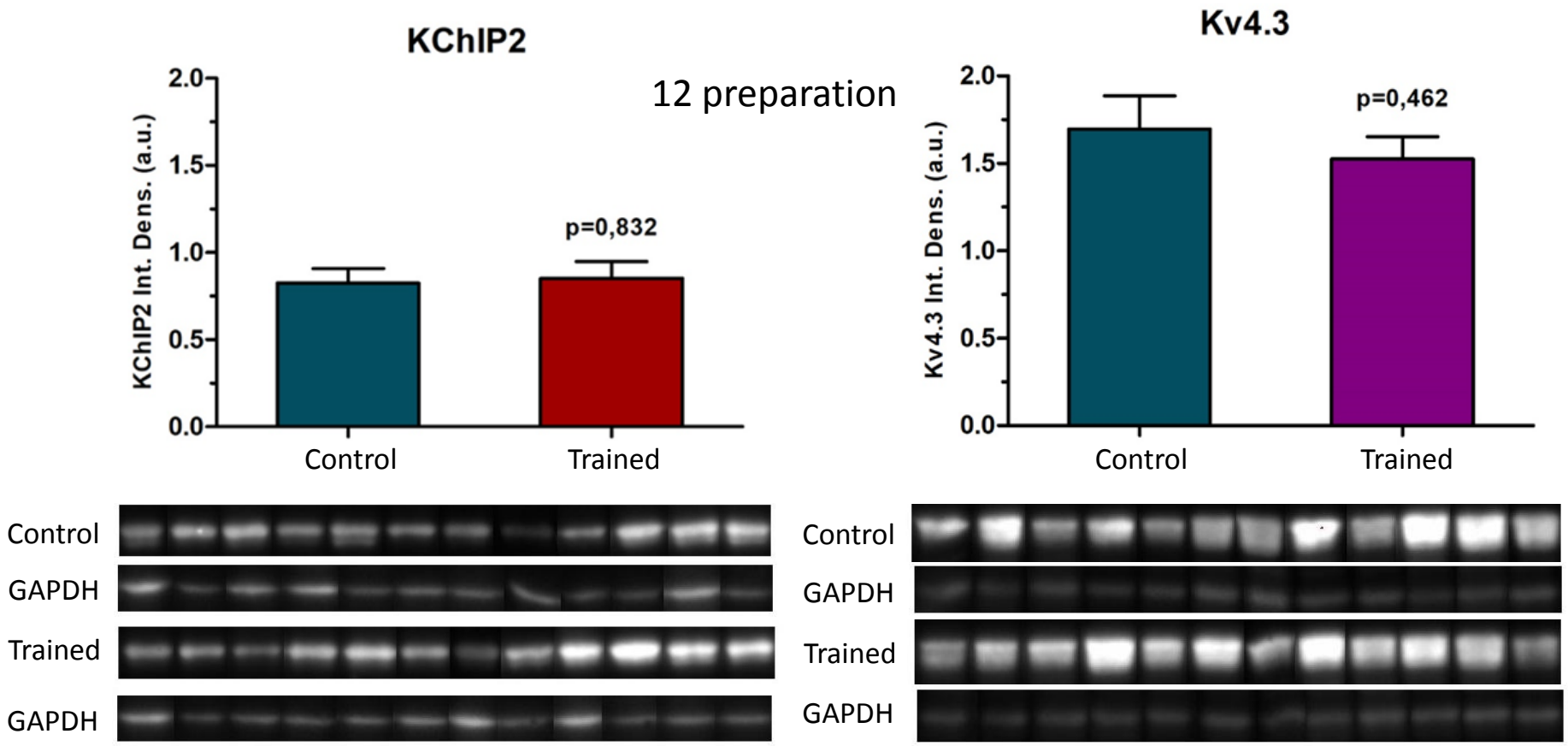








Transient outward „channel” (I_{to}) protein densities determination by Western blot in dog ventricular tissue



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

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PLoS one

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

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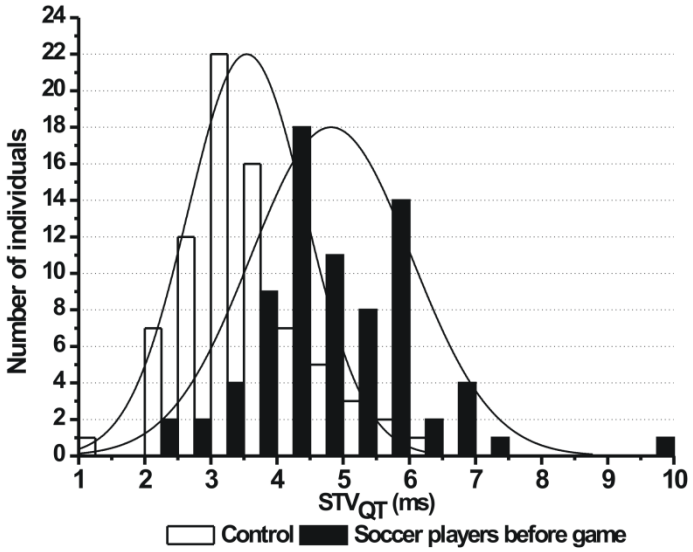
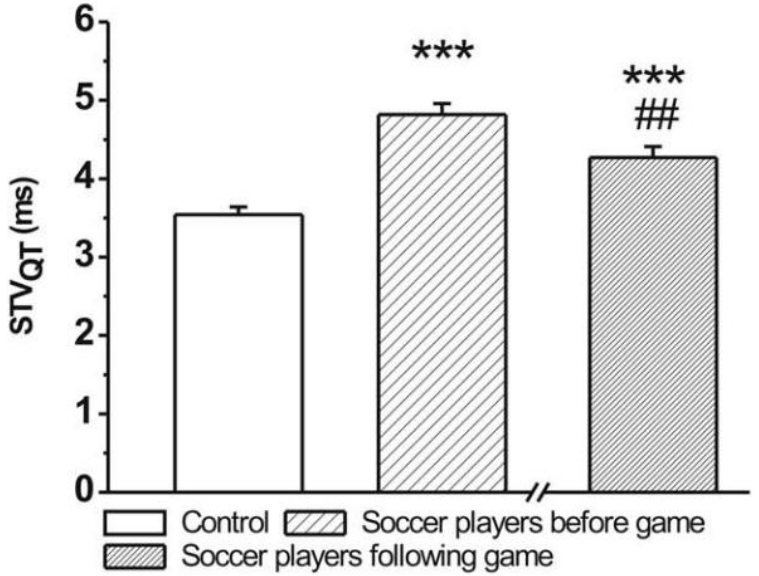
Short-term variability of the QT interval (STV_{QT})





Lengyel, … Baczkó, PLoS ONE, 2011