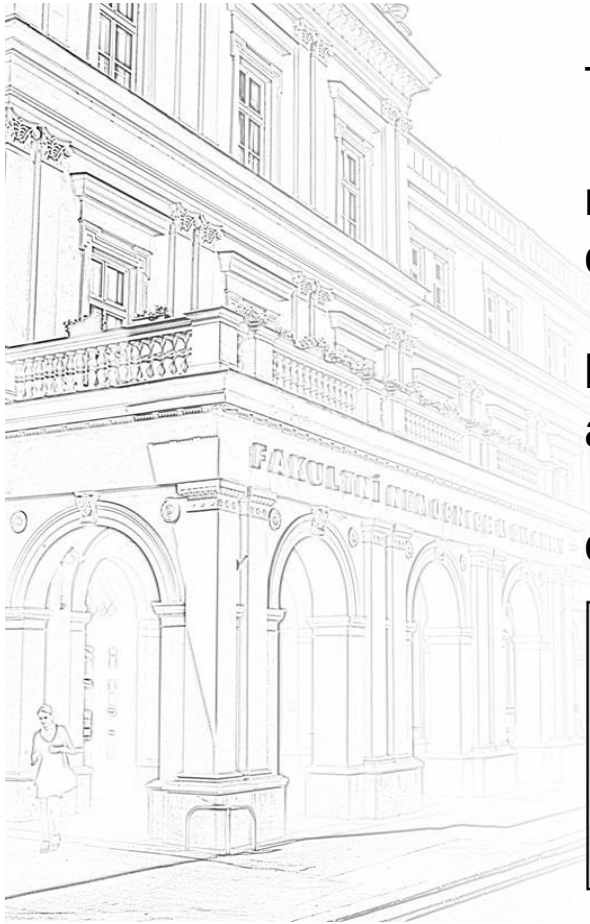
Aminophylline Induces Two Types of Arrhythmic Events in Human Pluripotent Stem Cell–Derived Cardiomyocytes

Simon Klimovic[1,2,3*], Martin Scurek[4,5*] Martin Pesl[2,6,7*], Deborah Beckerova[2, 6], Sarka Jelinkova[2], Tomas Urban[2, 7] Daniil Kabanov[1,2,3], Zdenek Starek[6,7], Marketa Bebarova[8], Jan Pribyl[1], Vladimir Rotrekl[2,6], Kristian Brat[4,5,6]

1 CEITEC, Masaryk University, Brno, Czechia.
2 Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czechia.
3 Department of Biochemistry, Faculty of Science, Masaryk University, Brno, Czechia.
4 Department of Respiratory Diseases, University Hospital Brno, Brno, Czechia.
5 Faculty of Medicine, Masaryk University, Brno, Czechia.
6 International Clinical Research Center, St. Anne's University Hospital, Brno, Czechia.
7 1st Department of Internal Medicine-Cardioangiology, Faculty of Medicine, St. Anne's Uni Hospital, MUNI, Brno, Cz
8 Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czechia.

Aminophilline

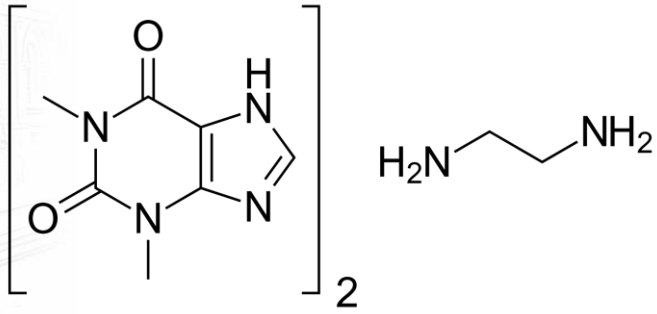


Theophylline with Ethylenediamine in 2:1 ratio

nonselective adenosine receptor antagonist
competitive nonselective phosphodiesterase inhibitor

bronchodilation adjunct to inhaled beta-2 selective agonists and systemically administered corticosteroids

clinically relevant concentrations 20-110 µmol/l



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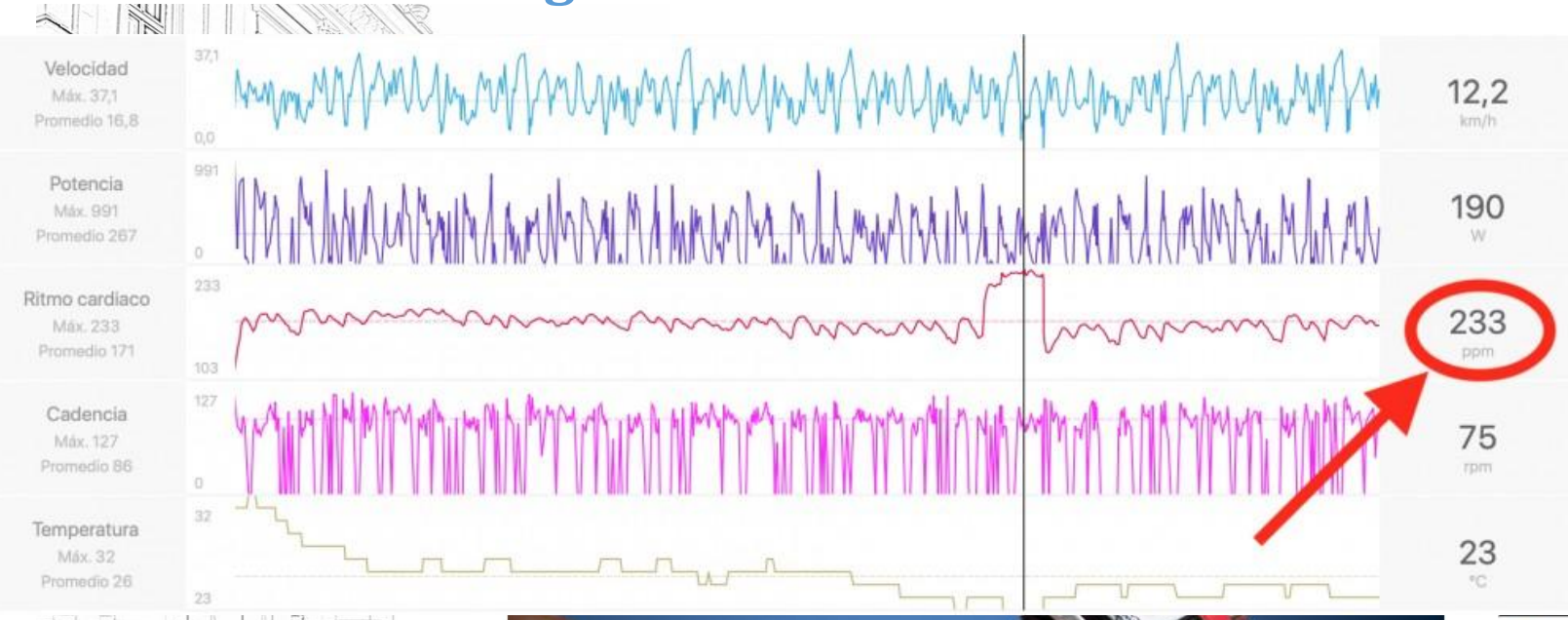
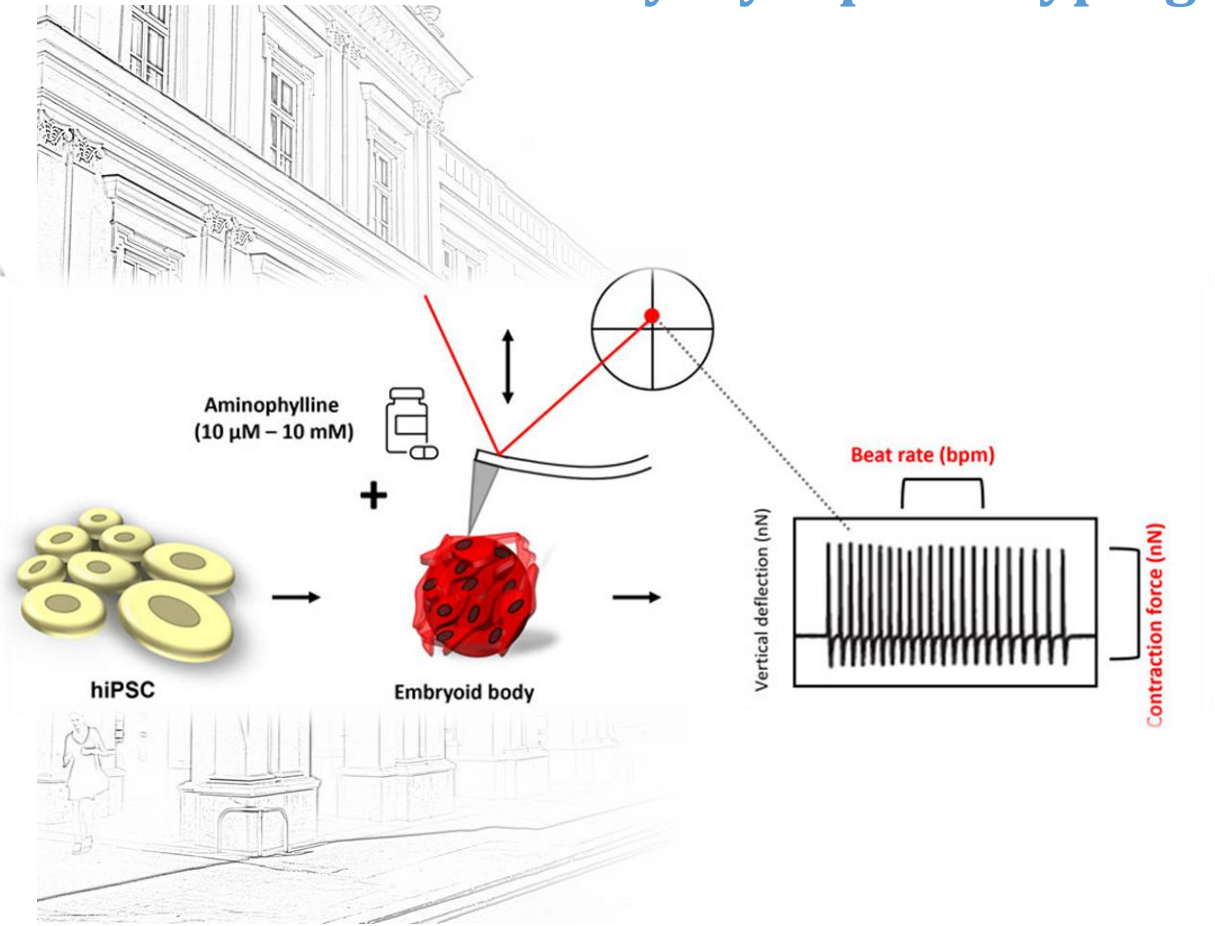
Drug related adverse effects

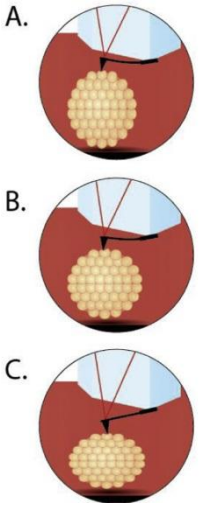


arrhythmia

Cardiomyocyte phenotyping by AFM



Atomic force microscopy +
stem cell derived CMs cluster



contraction rate

relaxation time

displacement / deflection

computed contraction force

Pesl et al. Biosens. Bioelectron 2016
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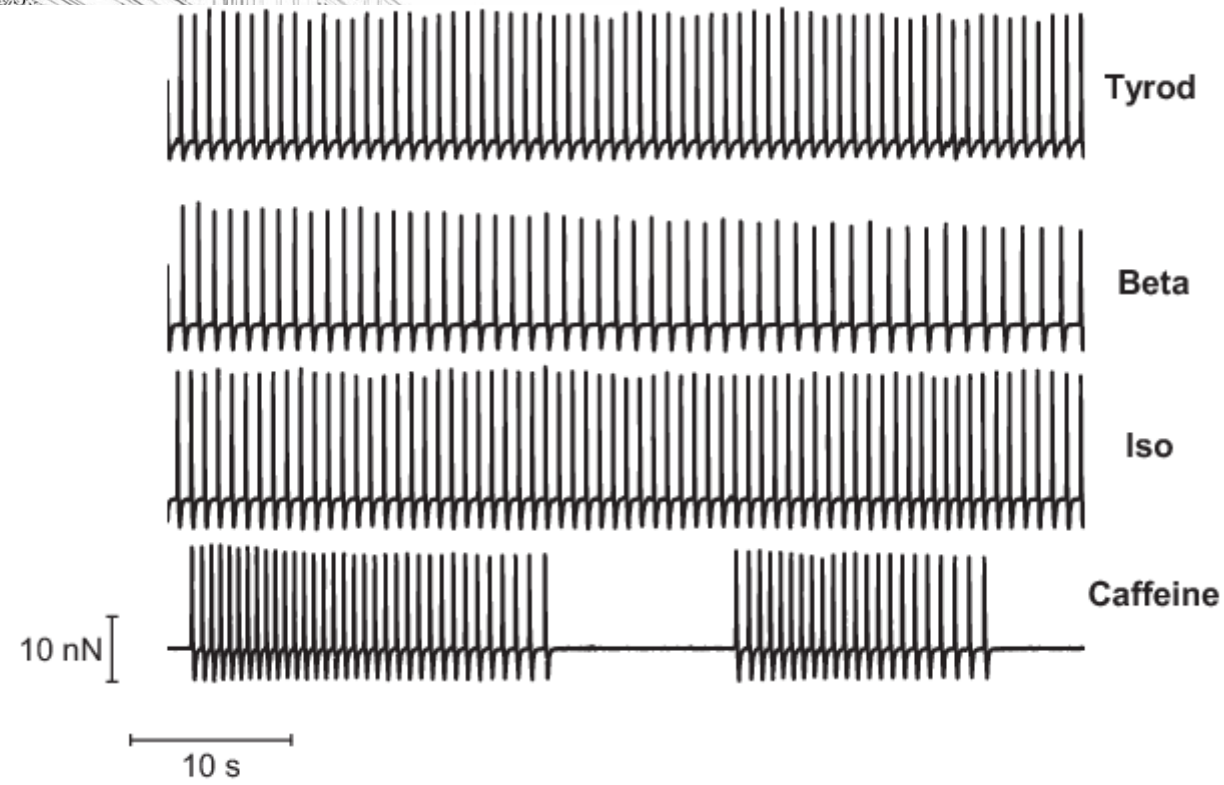
Drug effects and related adverse events

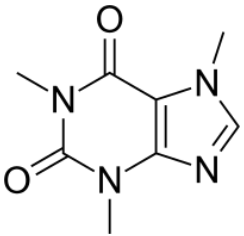


standard pharmacological indicators of different phenotypic features

beta adrenergic blocking
Metoprolol

beta adrenergic stimulation
Isoproterenol / Adrenalin

Methylxanthie
Caffeine



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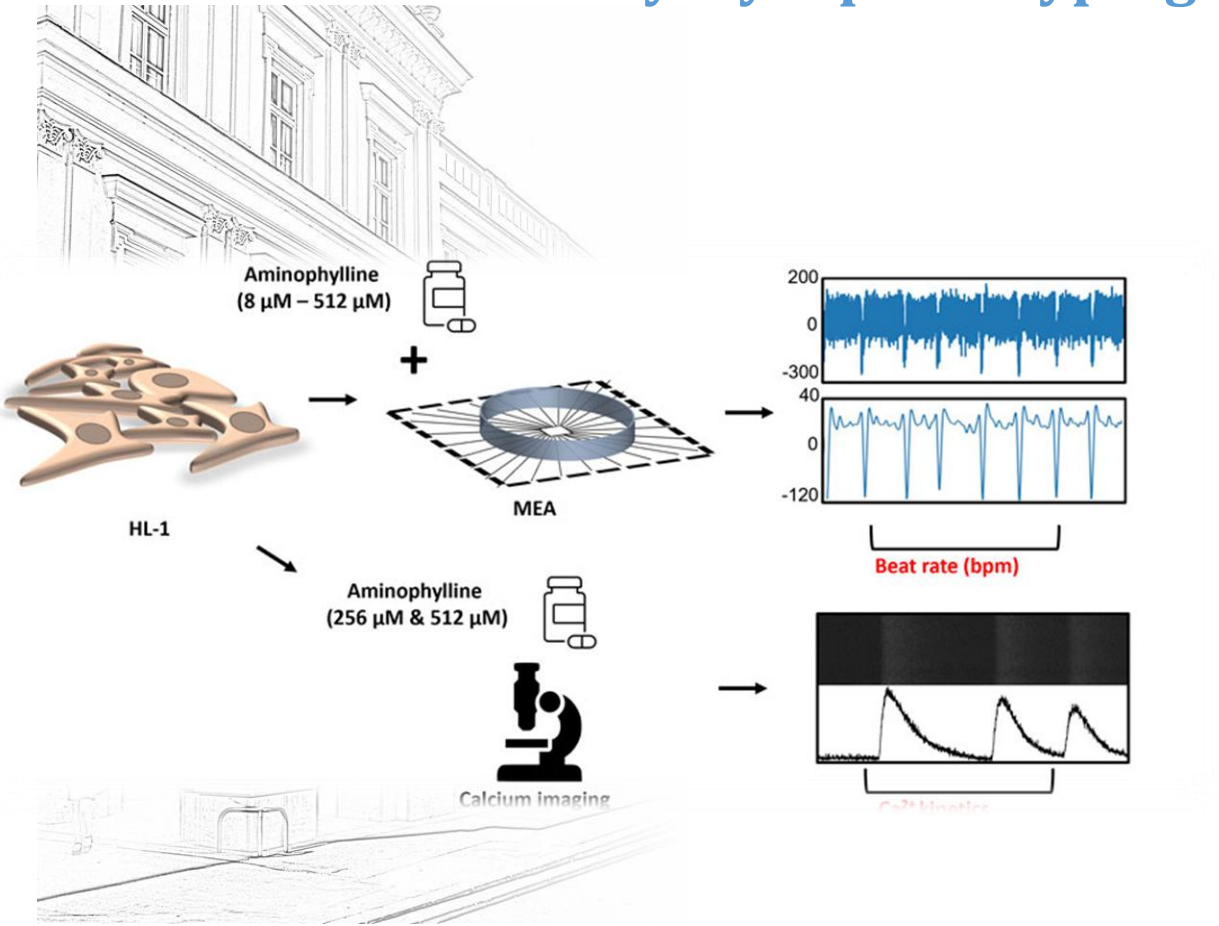
Cardiomyocyte phenotyping



Microelectrode array setup
HL1 immortalized line CMs

Field potential of monolayer

Calcium Imaging
intrinsic Ca^{2+} kinetics

Fluo-8 AM, a calcium-binding
- to further confirm eventual arrhythmogenic effect

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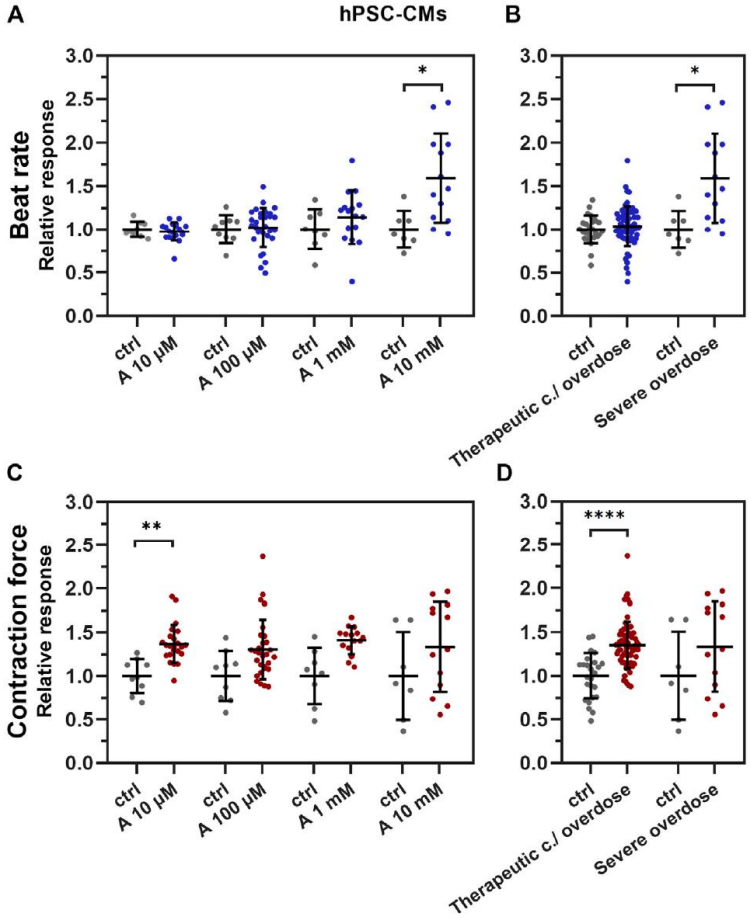
Results Inotropy/Chronotropy



- linear concentration-dependent positive chronotropic effect of aminophylline significant in the 10 mM (severe overdose)
- increased inotropy (contraction force of Ebs) already in lower concentrations of aminophylline
- washout decrease efects during the washout period = suggesting that the chronotropic and inotropic effects is likely due to the effect of aminophylline and not due to irreversible cellular damage

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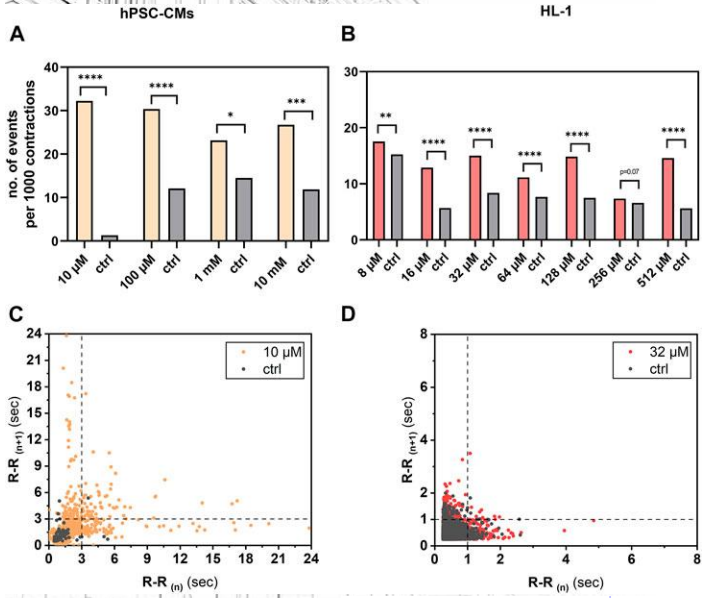
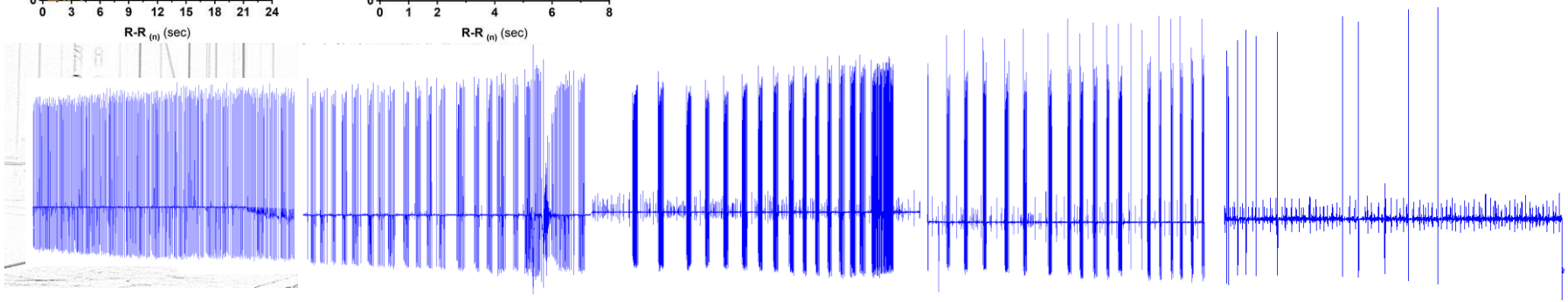
Results Stop&go effect



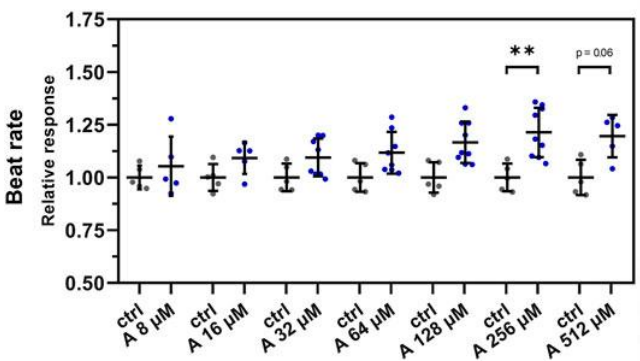
- assessed the number of R-R intervals over 3 s or 1 s, respectively.
- different cutoff R-R values tested

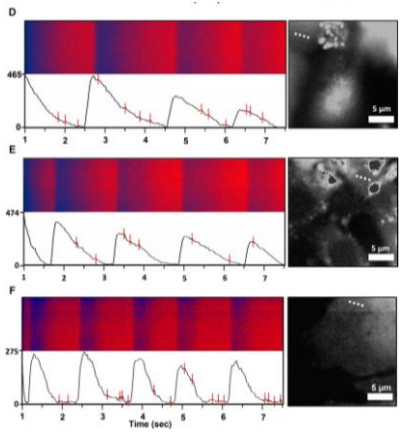
- higher occurence than that in non-treated controls in both cutoff models

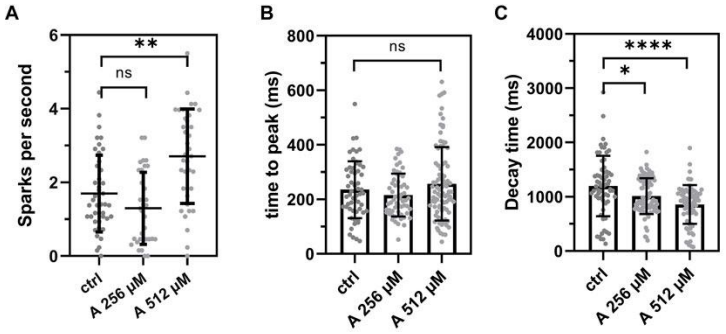


Results Calcium measurements

HL-1







- positive chronotropy with increasing concentration of aminophylline
- linear contraction rate increase in the cells treated with 256 µM aminophylline, similar non-significant trend at 512-µM treatment

- intracellular cytosolic Ca^{2+} in HL-1 cells
- higher concentrations of aminophylline calcium leakage (sparks), shorter decay time = arrhythmic events

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CONCLUSIONS

Aminophylline had two parallel arrhythmogenic mechanisms of action on clusters of cardiomyocytes

- concentration-dependent (“deterministic”) effect, presenting with an increased beat rate
(potential clinical correlate: sinus tachycardia),

- concentration-independent (“stochastic”) effect, characterized by tachycardia-like episodes alternating with long pauses
(potential clinical correlate: atrial fibrillation).

New parameters for cardiotoxicity vs. safety testing of various molecules or drugs.

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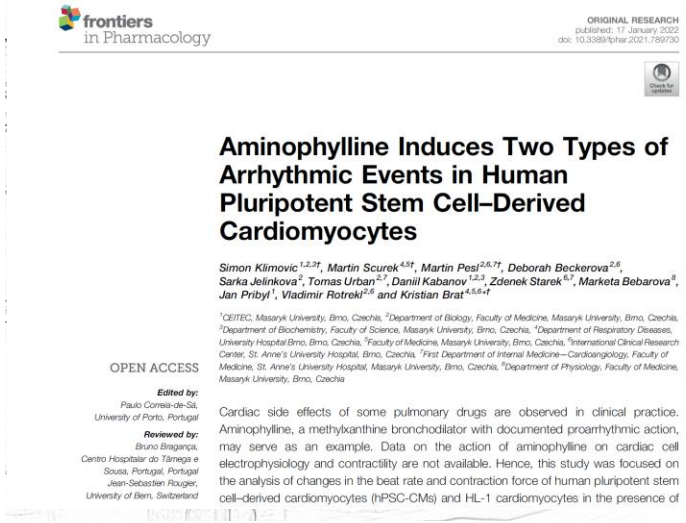

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[1]CEITEC, Masaryk University, Brno, Czechia, [2]Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czechia, [3]Department of Biochemistry, Faculty of Science, Masaryk University, Brno, Czechia, [4]Department of Respiratory Diseases, University Hospital Brno, Brno, Czechia, [5]Faculty of Medicine, Masaryk University, Brno, Czechia, [6]International Clinical Research Center, St. Anne's University Hospital, Brno, Czechia, [7]First Department of Internal Medicine—Cardioangiology, Faculty of Medicine, St. Anne's University Hospital, Masaryk University, Brno, Czechia, [8]Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czechia

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Cardiac side effects of some pulmonary drugs are observed in clinical practice. Aminophylline, a methylxanthine bronchodilator with documented proarrhythmic action, may serve as an example. Data on the action of aminophylline on cardiac cell electrophysiology and contractility are not available. Hence, this study was focused on the analysis of changes in the beat rate and contraction force of human pluripotent stem cell–derived cardiomyocytes (hPSC-CMs) and HL-1 cardiomyocytes in the presence of

Thanks for your interest!

contact: pesl@fnusa.cz

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