

regeneration occurs. The potential of somatic cell reprogramming has been recently advanced to the direct cardiac programming of murine and human fibroblasts as an alternative to address the loss of heart muscle. Interestingly, this process has shown to be more effective in the *in vivo* tissue context as compared to *in vitro* reprogramming suggesting that the three-dimensional environment of the heart is important for this process. We hypothesize that reprogrammed fibroblasts subjected an engineered tissue environment would show enhanced cardiac trans-differentiation.

Methods and results: We subject human foreskin fibroblasts to virus-free DNA reprogramming with the transcription factors GATA4, HAND2, MEF2C, TBX5 and MYOCD, and subsequently supported their self-organization in a three-dimensional collagen hydrogel. After 2 weeks of tissue assembly we observe induction of gene expression for NKX2-5, and MYL7 that is not present when reprogramming is performed solely under monolayer culture conditions (2226 ± 1107 and 7.51 ± 5.7 -fold; $n=3-5$), however, no beating tissues have so far been observed.

Conclusion: Mechanical signaling provided to fibroblasts via three-dimensional culture might be involved in potentiating the activation of specific programs needed to induce cardiac reprogramming of somatic cells initiated by the introduction of specific transcription factors.

Funding: DHZK (German center for Cardiovascular Research), partner site Göttingen, Germany

doi:[10.1016/j.yjmcc.2018.05.034](https://doi.org/10.1016/j.yjmcc.2018.05.034)

Poster session 1

Name of presenter: Attila Oláh

Abstract # 19

Sex-specific electrophysiological differences of exercise-induced cardiac hypertrophy in a rodent model of athlete's heart

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Background: Although regular exercise training is associated with cardiovascular benefits, cardiac remodeling induced by long-term, intense exercise training is also related to increased risk of arrhythmia. We aimed at providing electrophysiologic investigation of exercise-induced myocardial hypertrophy in a rat model of athlete's heart and determining sex-specific differences.

Methods and results: Age-matched young adult rats were divided into female exercised (FEx), female control (FCo), male exercised (MEx) and male control (MCo) groups. After exercised animals completed a 12-week-long swim training protocol, echocardiography was used to confirm exercise-induced hypertrophy. *In vivo* electrophysiologic characterization was performed by programmed stimulation with an octapolar catheter inserted into the right atrium.

Myocardial hypertrophy was verified by left ventricular mass (echocardiography) and post-mortem heart weight data in both exercised groups. We found signs of atrial remodeling in female exercised rats, increased P-wave duration and amplitude. We also observed increased T-wave amplitude and QT interval in female swim-trained rats. Hearts of male exercised rats were primarily

associated with increased RR duration and Wenkebach cycle length (WCL 109.8 ± 4.7 ms MEx vs. 97.3 ± 2.1 ms MCo, $p < 0.05$) compared to control ones.

Exercise training was related to increased R wave amplitude and QRS duration and altered right atrial refractory period (RAERP) in both genders and we could induce non-sustained atrial flutter in two exercised animals (one male and one female) by double extrastimulation.

Conclusion: Our data suggests that exercise-induced cardiac hypertrophy might hold an increased risk of arrhythmia. In male individuals elevated parasympathetic tone, while in female ones marks of atrial remodeling could be the characteristic alterations.

Funding: This project was supported by a grant from the National Research, Development and Innovation Office (NKFIH) of Hungary (K 120277); by the scholarship of Ministry of Human Capacities of Hungary (New National Excellence Program) to A.O. (ÚNKP-17-4-I-SE-78).

doi:[10.1016/j.yjmcc.2018.05.035](https://doi.org/10.1016/j.yjmcc.2018.05.035)

Poster session 1

Name of presenter: Marine Gandon-Renard

Abstract # 20

FKBP12.6 overexpression protects the cardiac myocyte from β -adrenergic stimulated proarrhythmogenic Ca^{2+} release in mice cardiomyocytes

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Background: The Ca^{2+} release channels (ryanodine receptors, RyR2) are essential in cardiac excitation-contraction coupling and are regulated, among others, by FK506 binding proteins (FKBP), FKBP12 and FKBP12.6. FKBP12.6 has higher affinity for RyR2 but is less abundant in cardiomyocytes than FKBP12. In heart failure (HF), FKBP expression decreases which has been proposed to participate in arrhythmia development. Cardiac FKBP12.6 overexpression protects the heart against β -adrenergic-triggered arrhythmias, but the mechanism of this protection remains elusive.

Methods and results: Here, we developed 2 transgenic mouse lines with cardiac-specific low- (TG1) and high-overexpression (TG2) levels of FKBP12.6 to analyze Ca^{2+} handling and β -adrenergic signaling. Surprisingly, our first results showed that TG1 and TG2 mice developed mild and marked cardiac hypertrophy, respectively. $[\text{Ca}^{2+}]_i$ transients amplitude, measured by confocal microscopy in electrically stimulated cardiomyocytes, was higher in TG1 mice than in wild type (WT) mice, without a significant difference in the SR Ca^{2+} load. β -adrenergic stimulation (50 nM isoproterenol) had lower effect in TG1 mice, limiting the appearance of pro-arrhythmogenic Ca^{2+} release events. However, TG2 mice showed Ca^{2+} handling characteristics similar to HF, with slower $[\text{Ca}^{2+}]_i$ transients relaxations. Interestingly, and contrary to HF, pro-arrhythmogenic Ca^{2+} release events were also depressed.

Conclusion: These results indicate distinct effects on Ca^{2+} -cycling and its response to β -adrenergic stimulation depending on the level of FKBP12.6 overexpression.

doi:[10.1016/j.yjmcc.2018.05.036](https://doi.org/10.1016/j.yjmcc.2018.05.036)