POSTER SESSION 2

Session held on 5 July 2014

doi:10.1093/cvr/cvu091

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Short-term ACE Inhibition upregulates cardiac expression of SERCA2a and protects against ventricular arrhythmias in healthy rats

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Introduction: Chronic angiotensin converting enzyme inhibitor (ACEIs) treatment can suppress arrhythmogenesis. To examine whether the effect is more immediate and independent of suppression of pathological remodelling, we tested the antiarrhythmic effect of short-term ACE inhibition in healthy normotensive rats.

Methods and results: Wistar rats were administered with enalaprilat (ENA, i.p., 5 mg/kg every 12 h) or vehicle (CON) for two weeks. Cellular shortening was measured in isolated, electrically paced cardiomyocytes. Standard 12-lead electrocardiography was performed and, hearts of anesthetized open-chest rats were subjected to 6-min ischemia followed by 10-minute reperfusion to examine susceptibility to ventricular arrhythmias. Expressions of calcium regulating proteins (SERCA2a, cardiac sarco/endoplasmic reticulum Ca2+-ATPase; CSQ, calsequestrin; TRD, triadin; PLB, phospholamban; FKBP12.6, FK506-binding protein) were measured by Western blot and mRNA levels of L-type calcium channel (Cacna1c), ryanodine receptor (Ryr2) and potassium channels Kcnh2 and Kcnq1 were measured by qRT-PCR. ENA decreased systolic as well as diastolic blood pressure (by 20%, and by 31%, respectively, for both $P<0.05$) but enhanced shortening of cardiomyocytes at basal conditions (by 34%, $P<0.05$) and under beta-adrenergic stimulation (by 73%, $P<0.05$). Enalaprilat shortened QTc interval duration (CON: 78 ± 1 ms vs. ENA: 72 ± 2 ms; $P<0.05$) and significantly decreased the total duration of ventricular fibrillations (VF) and the number of VF episodes ($P<0.05$). Reduction in arrhythmogenesis was associated with a pronounced upregulation of SERCA2a and increased Cacna1c mRNA levels.

Conclusion: Short-term ACEI treatment can provide protection against I/R injury-induced ventricular arrhythmias in healthy myocardium and this effect is associated with increased SERCA2a expression.

	CON	ENA
Calcium regulating proteins		
SERCA2a	100 ± 20	304 ± 13*
CSQ	100 ± 6	105 ± 7
TRD	100 ± 16	117 ± 10
PLB	100 ± 9	109 ± 16
FKBP12	100 ± 12	93 ± 7