J Clin Exp Cardiolog 2017, 8:5 (Suppl)
http://dx.doi.org/10.4172/2155-9880-C1-069

Chronic CaMKII inhibition leads to a signaling switch to PKA for the regulation of heart function in response to cardiac stress

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Objective: CaMKII is regarded as a novel therapeutic target in heart failure (HF). Here, we studied the effect of instant and chronic CaMKII inhibition on cardiac function in response to β-adrenergic stimulation and workload in HF mice.

Methods & Results: Pressure overload HF was induced by severe thoracic aortic banding (sTAB), while cardiac function was monitored by murine echocardiography. CaMKII inhibitor KN93 was given intraperitoneally to HF mice daily for consecutive 7 days and heart function was measured 15min after KN93 injection and after 7 days injection to determine the instant and chronic effect, respectively. We found that instant and chronic CaMKII inhibition improved systolic function but exacerbated the diastolic function, with a greater reduction in diastolic function in mice with instant CaMKII inhibition. We have tested the effects of isoproterenol (ISO) injection or 10 min swimming on cardiac function before and after instant and chronic CaMKII inhibition. Results showed that instant CaMKII inhibition significantly reduced the exercise tolerance. Interestingly, chronic CaMKII inhibition significantly improved cardiac reserve to ISO or swimming. Western blot results showed an increase in β1-AR expression in HF mice with chronic CaMKII inhibition. In line with this change, phospholamban phosphorylation at PKA-dependent site Ser-16 was increased.

Conclusion: Although diastolic function is deteriorated, chronic inhibition of CaMKII improves systolic function and cardiac reserve to stress in HF mice, which is likely mediated by upregulation of β1-AR expression and a subsequent signaling switch from CaMKII to PKA.

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