**P13. Connective tissue growth factor (CTGF/CCN2) desensitizes myocardial β-adrenergic receptor signaling and inhibits isoproterenol induced hypertrophy.**

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**Background:** Under physiological conditions, expression of myocardial CTGF is repressed in the postnatal heart. However, in heart failure of various etiologies myocardial CTGF is dramatically induced. Since cross-talk between receptor tyrosine kinases and β-adrenergic signaling has previously been reported, the aim of this study was to investigate to what extent CTGF signaling affects efficacy β-adrenergic agonists, and if so, through what mechanisms.

**Methods and results:** Transgenic mice with cardiac-restricted overexpression of CTGF (Tg-CTGF) were employed and compared with nontransgenic littermate control mice (NLC). Stimulation of ventricular muscle strips with increasing concentrations of the β-adrenergic receptor agonist isoproterenol revealed substantial inhibition of maximal developed contractile force in muscle fibers from Tg-CTGF vs. NLC mice. Primary cultures of adult mouse cardiac myocytes also exhibited attenuated cAMP synthesis in response to isoproterenol in cardiac myocytes from Tg-CTGF versus NLC mice. Indeed, similar reduction of maximal efficacy of isoproterenol was observed in ventricular muscle trips and isolated cardiac myocytes. Furthermore, no differences in maximal contractile responses to the cAMP analog dibutyryl-cAMP was detected. Analysis of [¹²⁵I]-iodocyanopindolol binding did not disclose alternations in β-adrenergic receptor densities on cardiac myocytes from Tg-CTGF mice versus NLC mice. Chronic exposure to isoproterenol for 14 days delivered subcutaneously through mini-osmotic pumps revealed less myocardial hypertrophy and preserved cardiac function as compared to NLC mice. Our data provide evidence that β-adrenergic receptors on cardiac myocytes from Tg-CTGF mice are functionally desensitized. The mechanism of β-adrenergic receptor desensitization in Tg-CTGF heart are currently under investigation.

**Conclusion:** CTGF desensitizes β-adrenergic receptor signaling in the heart. Reduced responsiveness of β-adrenergic receptors on cardiac myocytes may contribute to cardioprotection and prevention of heart failure.