**Background:** Myocardial expression of connective tissue growth factor (CTGF) is dramatically induced in heart failure (HF) of diverse etiologies. However, the physiologic and pathophysiologic roles of myocardial CTGF remain unresolved.

**Methods and Results:** To elucidate the actions of myocardial CTGF and its putative role in HF, transgenic mice with cardiac-restricted (α-MHC promoter) overexpression of CTGF were generated. Transgenic CTGF (Tg-CTGF) mice had slightly lower cardiac mass than that of non-transgenic littermate controls (NLC) (heart weight/tibia length of 4 months old male Tg-CTGF vs. NLC; 58.9±2.7 vs. 68.1±1.2 mg/cm, p<0.05). Consistently, echocardiography revealed slightly smaller left ventricular (LV) dimensions in Tg-CTGF vs. NLC mice. Simultaneous in vivo LV pressure-volume analysis did not disclose significant alterations of contractility and cardiac output, nor evidence of restrictive left ventricular dysfunction in Tg-CTGF vs. NLC mice. Analysis of myocardial gene expression by real-time qPCR revealed increased expression of antihypertrophic TGF-β2 and GDF-15 mRNA, and decreased expression of EGF mRNA in Tg-CTGF vs. NLC mice. Also, increased myocardial expression of ER stress response genes and scavengers of free oxygen radical were detected. Tg-CTGF and NLC mice were subsequently subjected to chronic pressure overload by abdominal aortic banding (AB) or sham-operation (SH). Four weeks after AB, significant elevations of cardiac mass were observed both in Tg-CTGF-AB and NLC-AB mice. However, cardiac hypertrophy was significantly diminished in Tg-CTGF-AB versus NLC-AB. Simultaneous PV-analysis provided evidence of cardiac dysfunction in NLC-AB mice, i.e. significantly increased LVEDD, LVEDP, and decreased stroke volume and cardiac output compared to NLC-SH mice. Strikingly, Tg-CTGF-AB revealed essentially preserved LV pressure-volume relations. Elevations of myocardial BNP mRNA levels were significantly attenuated in Tg-CTGF-AB compared to NLC-AB mice.

**Conclusion:** Myocardial CTGF exerts antihypertrophic effects and preserves left ventricular function due to pressure overload and delays onset of HF.