**SILENCING OF THE CARDIAC 18-kDa TRANSLOCATOR PROTEIN PREVENTS HEART FAILURE DUE TO PRESSURE OVERLOAD**

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**Rationale:**Heart failure (HF) is characterized by abnormal mitochondrial calcium (Ca2+) handling and energy production which ultimately results in contractile dysfunction and myocyte death. We have previously shown that the 18-kDa mitochondrial translocator protein of the outer mitochondrial membrane (TSPO, previously called the peripheral benzodiazepine receptor) plays a role in mitochondrial Ca2+ uptake regulation by changing the open probability of the voltage dependent anion channel (VDAC).

**Objective:** Experiments were designed to elucidate the role of the TSPO in a murine pressure-overload model of HF induced by transverse aortic constriction (TAC).

**Methods and Results:**Conditional, cardiac-specific TSPO KO (KO) mice were generated using the Cre-*lox*P system. TSPO KO and wild-type (WT) mice underwent TAC for 8 weeks. TAC-induced HF significantly increased TSPO expression in WT mice, which was associated with a marked reduction in systolic function and energetic failure. Mitochondrial Ca2+ uptake was significantly decreased in WT TAC myocytes in parallel with an increase in reactive oxygen species (ROS) generation, FAD oxidation, a decline in the mitochondrial membrane potential (αΨm) and enhanced permeability transition pore (mPTP) opening. In contrast, TSPO KO mice undergoing TAC had relatively preserved ejection fraction, and exhibited fewer clinical signs of HF, along with less cardiac dilation and less fibrosis. TSPO KO restored mitochondrial Ca2+ uptake and ATP levels following TAC, prevented the increase in ROS and FAD oxidation, and restored αΨm without any effect on mPTP activity.

**Conclusions:** HF due to pressure overload increases TSPO expression, while abrogating this increase limits the progression of HF, preserves mitochondrial Ca2+ transport and ATP production and decreases oxidative stress, thereby preventing metabolic failure in HF. These findings suggest that pharmacological interventions directed at TSPO may provide novel therapeutics to prevent or treat HF.