Abstract: **P606**

**Istaroxime improves diabetic diastolic dysfunction through SERCA stimulation**

**Authors:**
E Torre, AM Lodrini, P Barassi, M Ferrandi, E Boz, C Bussadori, P Ferrari, G Bianchi, M Rocchetti,
University of Milan-Bicocca - Milan - Italy, CVie Therapeutics Limited - Taipei - Taiwan ROC, Clinica Veterinaria Gran Sasso - Milan - Italy,

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Calcium handling is generally impaired in heart failure (HF). Mechanisms that can restore cardiac relaxation (lusitropic effect) improving cellular Ca2+ cycling, represent a promising therapeutic approach for HF. Istaroxime is a Na-K ATPase (NKA) inhibitor with the property of accelerating Ca2+ re-uptake into sarcoplasmic reticulum (SR) through the SR Ca2+ pump (SERCA) stimulation by displacing the interaction between SERCA and its inhibitor, phospholamban (PLB).

The project aims to characterize Istaroxime effects in a model of mild diabetes (type 1) with diastolic dysfunction and preserved global systolic function. Istaroxime was tested at a concentration mostly unafffecting NKA to isolate its effects dependent on SERCA only. Streptozotocin (STZ)-treated rats were evaluated at 9 weeks after STZ injection in comparison to control (CTR) ones. STZ-induced changes were evaluated in vivo (echocardiography), in isolated left ventricular (LV) myocytes and in SERCA2a-enriched microsomes. SERCA and PLB protein levels were measured by western blot and SERCA activity as 32P hydrolysis. Action potential rate-dependency and intracellular Ca2+ handling were evaluated in patch clamped or field-stimulated (2Hz) cells.

STZ-induced cardiomyopathy was characterized by cardiac hypotrophy, heart rate and cardiac output reduction. Echo parameters showed impaired diastolic relaxation which was associated to reduced SERCA protein level and activity at the cellular level. Moreover, the monomeric PLB/SERCA ratio was increased, implying that SERCA was not only reduced but also much more inhibited in STZ-treated animals. In STZ group, action potentials (AP) were significantly prolonged at each cycle length and the beat-to-beat variability increased; Ca2+ transients were characterized by slower decay, delayed onset and increased diastolic Ca2+. Istaroxime at a concentration of 100 nM significantly stimulated SERCA activity and SR Ca re-uptake after caffeine depletion in STZ group only. Moreover, Istaroxime reduced STZ-induced diastolic Ca2+ enhancement, without altering Ca2+ transient amplitude and SR Ca2+ content. STZ-induced AP prolongation was not affected by Istaroxime.

Overall, SERCA stimulation can be considered a promising therapeutic approach for diastolic dysfunction treatment.