ESC Congress 2022 in Barcelona

Topic: Heart Failure with Preserved Ejection Fraction (HFpEF)
Title: The therapeutic potential of relaxin for heart failure with preserved ejection fraction
Session: HFpEF and HFmrEF: what's new in treatment?

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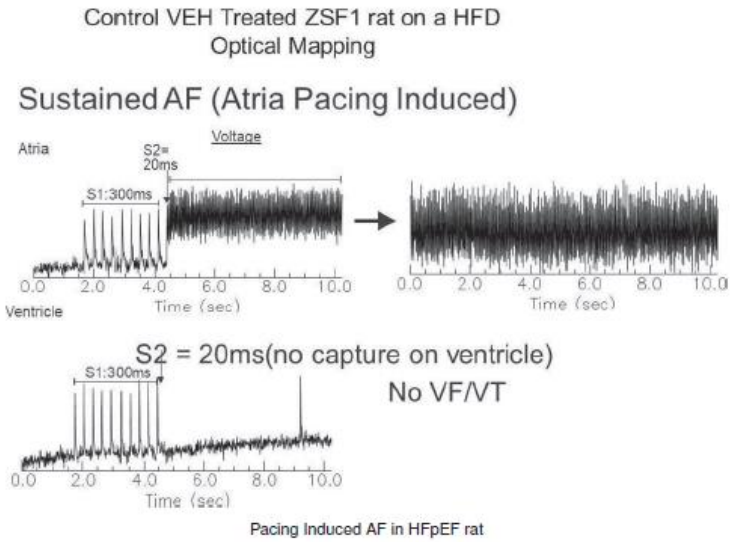
Background and Significance: Heart Failure (HF) is the leading cause of cardiovascular deaths and ~50% of HF patients have HF with preserved ejection fraction (HFpEF). Patients with chronic HFpEF have a near normal ejection fraction, reduced left ventricular (LV) diastolic compliance, increase of LV pressure, fibrosis, and ion channel remodeling leading to supraventricular arrythmia which increases morbidity and mortality. HFpEF patients typically have co-morbidities such as atrial fibrillation (AF), diabetes, lung edema and hypertension. The later is a predictor of mortality and is targeted to prolong survival given the lack of a direct treatment of HFpEF. To address this unmet public health problem, we investigate the therapeutic potential of the insulin-like hormone Relaxin (RLX) in a rat model of HFpEF that recapitulates most aspects of clinical HFpEF.

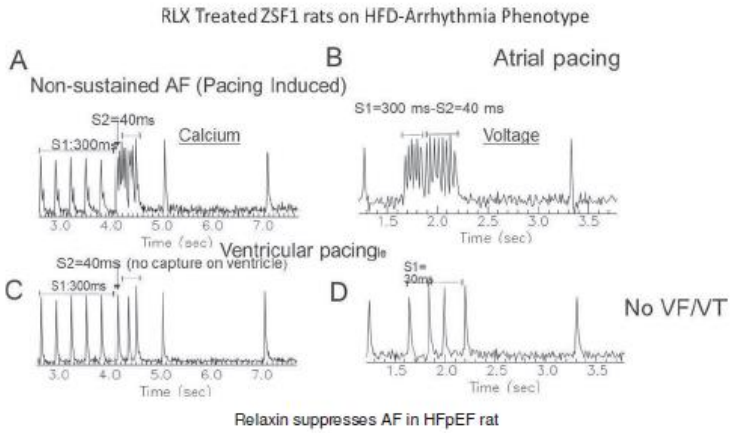
Methods: ZSF1 diabetic rats (9-weeks old) were placed on a high fat diet (HFD) for 11-weeks and serial echocardiograms were used to track the development of diastolic dysfunction. At week 20, osmotic mini-pumps were implanted to continuously release vehicle (Control, Na-acetate) or RLX (400 µg/kg/day for 2-weeks). After 2-weeks, hearts were perfused with a voltage-sensitive dye (RH237) and a Ca^{2+} indicator (Rhod-2/AM) in a Langendorff apparatus to optically map action potentials (Aps) and Ca^{2+} transients (CaTs) to analyze the arrhythmia phenotype. Alternatively, left ventricular (LV) tissue sections were used for immune-flourescence (IF) imaging to examine changes in fibrosis (collagen 1), connexin 43, Wnt1 and β-catenin in LV myocytes. Blood samples were before the HFD, before and after RLX-treatment to measure changes in serum NT-pro-ANP, ET-1 and RLX.

Results: ZSF1 rats on a HFD developed HFpEF with E/e' (an echo marker of diastolic dysfunction) decreasing to -24.4 from -17.9 MV (n=12) and was reversed to 18.6 MV by RLX (n=6; p<0.0001). In HFpEF rats, that receive the vehicle (n=6), a premature stimulus (S1-S2= 30 ms) elicited: a) no arrhythmia b) non-sustained AF c) sustained arrhythmia (with 1/3 of rats in each group). RLX treatment blocked sustained supraventricular (n=0/12) and 4/12 had non-sustained AF. RLX improved th conduction velocity (CV), particularly at short cycle lengths (150 ms) from 0.74 to 0.9 m/s (n=4/group). IF indicated that RLX increased Cx43 expression (26.8 ± 0.03%, p<0.0001, n=6), and β-catenin (52.8 ± 0.05%, p=0.0001) at intercalated disks. As expected, RLX reduced collagen deposition in HFpEF rats (25 ± 0.04%, p<0.04) or back to normal levels. RLX caused a marked increase of cytosolic Wnt1 (47.3 ± 0.06%; p<0.0001) compared to HFpEF rats treated with the vehicle. In IF data, values are given as mean ± SEM.

Conclusions: The ZSF1 diabetic rat on a high-fat diet recapitulates most of the phenotypes associated with human HFpEF, including supraventricular arrythmias, fibrosis, and lung edema. RLX treatment post-development of HFpEF reversed the pro-arrhythmic phenotype, increased conduction velocity particularly in fast heart rates, reversed fibrosis, reduced NT-pro-ANP and ET-1 in male rats. Most intriguing, RLX treatment activated Wnt1 and β-catenin indicating that the beneficial actions of RLX occur via genomic remodeling of the heart.



Pacing Induced AF in HFpEF rat



Relaxin suppresses AF in HFpEF rat