The early mineralocorticoid receptor antagonism mitigates the metabolic syndrome symptoms and transition to heart failure in the SHHF cp/cp rat model

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Mineralocorticoid Receptor Antagonists (MRA) have proven their cardioprotective effects in individuals with chronic heart failure (CHF) by minimizing the cardiovascular damages caused by the excessive aldosterone production observed in those patients. Metabolic syndrome (MetS) that represents one of the major risk factors for CHF has been also reported to be associated with increased aldosterone levels and MR activation and may contribute in that way to the pathogenesis of HF. Thus, we hypothesized that targeting the MetS by the early antagonism of the MR may prevent or delay the subsequent transition to CHF in a rat model of HF associated or not with a MetS. MRA (Eplerenone (100 mg/kg/day) or placebo was administrated to 1.5 month-old obese and lean Spontaneously Hypertensive Heart Failure male rats (SHHFp2p and SHHFp2p respectively) for a period of 11 months. Animal metabolic and cardiac parameters were regularly monitored during the protocol. When compared to the SHHFp2p, MetS rats induces of mortality of 30% respectively, LV diameter (9.9±0.14 vs 11.4±0.13 mm), systolic blood pressure decrease, cardiac parameters of Eple-SHHF cp/cp rats were preserved compared to SHHFp2p: LV diameter (9.9±0.14 vs 11.4±0.13 mm, respectively), LV mass (1760±72 vs 2195±73 mg), ejection fraction (70±1 vs 74±2%), isovolumic relaxation time (30±1 vs 22±1 ms) and E/A ratio (1.7±0.1 vs 3±0.3). Altogether, our data demonstrated that administration of Eplerenone at the very early stages of MetS delayed their progression to CHF (1.7±0.1 vs 3±0.3).
Background: Despite the prevalence of right ventricular (RV) failure in congenital heart diseases, cell therapy applied to RV is poorly studied. Our aim is to evaluate in a large animal model of overloaded RV dysfunction such therapy using cardiac progenitors (CP) issued from human embryonic stem cells.

Methods: A combined overloaded RV dysfunction was created in pigs using a surgical procedure mimicking repaired tetralogy of Fallot. At 4 months, cell therapy was surgically administrated using either multiple transsepicardial injections of HUES-24 derived CP into RV myocardium or CP seeded collagen patches sewn on RV free wall. SHAM animals received either multiple transepicardial injections of medium or acellular patches. Myocardial function was determined 3 months later by conductance catheter technique with maximal elastance (Emax) slope. Ventricular arrhythmia risks were tested by programmed ventricular stimulation. A histological study analyzed the structural remodelling. CP fate was studied using anti-Ki67, CD31, CD34, GFP, Islet1 and Connexin 43 antibodies. All pigs were immunosuppressed by Tacrolimus.

Results: All pigs survived. Neither complication nor ventricular arrhythmia occurred. In injected animals (SHAM: n=6, HUES-24: n=6) the Emax slope value evaluated similarly in both groups. Whereas total fibrosis increased significantly with time in the SHAM group, it returned to baseline in HUES-24 group. However, CP could not be found. In contrast, in patched animals, CP were found in the patch zone and close to the myocardium. These CP were able to proliferate, migrate, express cardiac markers and establish connexions.

Conclusion: Cell therapy using transepicardial injections of human CP seems to have a beneficial effect on overloaded RV tissue remodelling, but this administration mode did not improve myocardial contractility. Seeded patches seem to be more conservative for engrafted cells; their impact on overloaded RV function requires further experiments.