## P629

### Empagliflozin influence on the course of experimental heart failure in normoglycemic rats

A Aleksandr Kulikov[1]; SV Okovityi[2]; DY Ivkin[2]; AA Karpov[3]; DS Lisitskyi[2]; MM Lubishin[2]; PA Alekseeva[2]; NN Pitukhina[2]; AV Smirnov[1]; IG Kaiukov[1]; EV Parusova[1]
*[1]Saint Petersburg Pavlov State Medical University, Saint Petersburg, Russian Federation; [2]Saint-Petersburg State Chemical Pharmaceutical Academy, Saint Petersburg, Russian Federation; [3]Federal Almazov Medical Research Centre, Saint Petersburg, Russian Federation*

**Purpose:** The efficacy of sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin in chronic heart failure in normoglycemic rats was investigated.
**Methods:** Chronic heart failure (CHF) experimental model in rats was created by permanent ligation of the left coronary artery. Rats were randomly divided into 3 groups: empagliflozin treated CHF group (n = 11), untreated CHF group (n = 11), control group with sham operation (n = 9). Empagliflozin was administered in a dose 1 mg / kg/ per day for 3 months. Echocardiography was performed every month up to the end of the study. Sizes and volumes of the left ventricle (LV), LV ejection fraction, LV stroke volume and minute blood volume were measured. All rats were tested on a treadmill at the end of the experiment to evaluate physical endurance.
**Results:** CHF model was effective in both study groups, in a month after the surgery rats of the first and the second groups had significantly lower ejection fraction and larger LV sizes than the rats of the control group. At the end of the study animals on empagliflozin treatment had a better exercise tolerance (maximum working time on a treadmill 900 ± 110 s vs. 645 ± 110 s, p = 0.0004), higher minute blood volume at rest (80 ± 30.1 ml / min vs. 57 ± 19,4 ml / min, p < 0,025), bigger LV end-diastolic volume (0,50 ± 0,14 ml vs. 0.39 ± 0,08 ml, p = 0,028) and bigger LV mass (1 09 ± 0.19 g vs 0,69 ± 0,10 g, p = 0,012), than the animals who did not receive treatment. In the course of the empagliflozin treatment an increase of a LV stroke volume, LV end-diastolic volume, LV ejection fraction and minute blood volume were observed. These changes are not documented in CHF rats without treatment.
**Conclusion:** Antidiabetic drug empagliflozin improves exercise tolerance and the LV functional performance in normoglycemic rats with CHF. Influence of empagliflozin on LV remodeling needs further investigation.

## P630

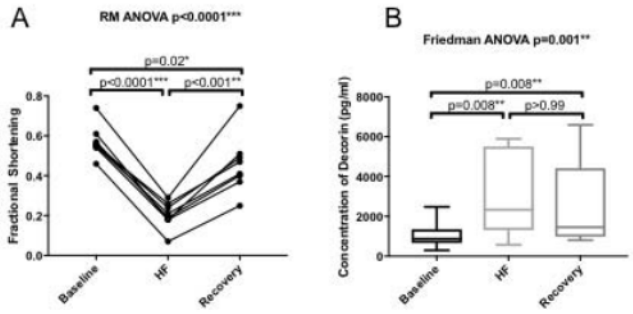
### Serum decorin correlates with the heart failure phenotype

P Parminder Chaggar[1]; A Watkins[2]; W Crtichley[3]; A Patel[3]; P Foden[4]; R Venkateswaran[1]; N Yonan[1]; A Trafford[2]; JE Fildes[3]
*[1]University Hospital of South Manchester NHS Foundation Trust, The Transplant Unit, Manchester, United Kingdom; [2]University of Manchester, Division of Cardiovascular Sciences, Manchester, United Kingdom; [3]University of Manchester, Manchester Collaborative Centre for Inflammation Research, Manchester, United Kingdom; [4]University Hospital of South Manchester NHS Foundation Trust, Department of Medical Statistics, Manchester, United Kingdom*

**Background:** Collagen deposition is the hallmark of cardiac fibrosis which is a feature of adverse remodeling during heart failure. Increased type I and type III collagen deposition impairs ventricular compliance and promotes dilatation. Decorin is a proteoglycan that binds type I and type III collagens, thereby slowing collagen deposition. The temporal dynamics of decorin during myocardial injury and recovery is unknown and warrants further investigation.
**Purpose:** This study was conducted to define the pattern of serum decorin during myocardial injury and recovery in an ovine model of pacing-induced heart failure.
**Methods:** 8 healthy Welsh mountain sheep underwent VVI pacemaker implant and paced at 210bpm until they developed overt clinical signs of heart failure. Pacing was then terminated and the animal was allowed to recover. The severity of LV dysfunction was assessed by serial measurements of fractional shortening (FS) on echocardiography at baseline, heart failure and recovery. FS has previously been validated as an accurate measure of LV function in sheep. Serum decorin was quantified via a protein array at baseline, heart failure and recovery. Temporal changes in FS were analysed using repeated measures ANOVA and temporal changes in serum decorin concentration were analysed using a Friedman test.
**Results:** FS decreased significantly in heart failure compared to baseline and subsequently increased significantly in recovery. The FS in recovery did not reach baseline FS values (Figure 1A). Decorin increased significantly in heart failure compared to baseline and remained elevated during recovery (Table 1 and Figure 1B).
**Conclusion:** Serum decorin increases significantly with the development of heart failure and this may represent a physiological response to attenuate the effects of adverse remodeling. This is the first study to demonstrate temporal changes in serum decorin during myocardial injury and recovery in a large mammal. Decorin may serve as a biomarker of myocardial injury and could be a target for therapeutic manipulation. These findings require validation in a larger series.

| Serum decorin in ovine tachy-paced HF | | | |
|---|---|---|---|
| Decorin (pg/mL) | Baseline | Heart Failure | Recovery |
| Median | 873 | 2332* | 1455* |
| Interquartile range | 665-1348 | 1310-5501 | 975-4416 |
| Range | 297-2473 | 572-5887 | 806-6587 |

*p = 0.008 compared to baseline




Changes in FS (A) and decorin (B)

## P631

### Coronary response in the doxorubicin-induced cardiomyopathy

V Cobet[1]; V Lutan[1]; L Tacu[1]; V Rotaru[1]; L Ciobanu[2]; E Cobet[3]; A Rotaru[4]
*[1]State University of Medicine and Pharmacy, Chisinau, Moldova Republic of; [2]Institute of cardiology , Chisinau, Moldova Republic of; [3]State University of Moldova , Biopharmaceutical chemistry , Chisinau, Moldova Republic of; [4]Harvard Medical School, Cambridge, United States of America*

**Background:** Coronary reserve and reactivity traits regarding doxorubicin (Dx) cardiotoxicity are less known comparatively to myocardial contraction and inotropic capacities.
**Aim:** the in vitro evaluation of coronary response to natural vasotropic agent action in Dx-induced cardiomyopathy (Dx-CMP).
Material and methods. Dx-CMP has been reproduced in white rats by Dx administration during 2 weeks (4 i/p Dx injections of 4 mg/kg, cumulative dose 16 mg/kg). The izovolumic isolated heart was perfused by standard Krebs solution according to Langendorff method, and the coronary flow (CF) changes were determined during action of acetylcholine (Ach), adenosine (As), bradykinin (Bk), hydrogen peroxide (H2O2), epoxyeicosatriens 11,12 (EET-11,12) and endothelin 1 (ET-1) in a concentration range of 10-7-10-5 M.
**Results:** The basal CF in DxCMP did not differ from control index (12,7 ± 0,08 vs 13,4 ± 0,09 ml/min). However, the endothelium dependent coronary functional reserve is impaired, manifested by significant lowered CF value during stimulation by Ach (14,8 ± 0,1 vs 17,3 ± 0,12 ml/min), As (13,9 ± 0,09 vs 15,5 ± 0,11 ml/min) and Bk (13,8 ± 0,08 vs 15,3 ± 0,12 ml/min). Remarkably, the coronarodilation mediated by hyperpolarization was not compromised in Dx-CMP. The coronary reserve inherent to H2O2 action was as 15,7% in Dx-CMP (CF, 14,7 ± 0,12 ml/min) and 14,9% in control series (CF, 15,4 ± 0,13 ml/min). In a similar manner CF increased in response to EET-11,12 action: 14,3% in Dx-CMP (CF, 14,52 ± 0,13 ml/min) and 14,1% in control (CF, 15,29 ± 0,14 ml/min). Thus, the mediated by hyperpolarization coronary artery dilatation could be an alternative tool of coronary functional reserve control in Dx-CMP associated by endothelium dysfunction. Importantly, ET-1 in concentration of 10-7 M determined in Dx-CMP o reduction of CF equal to control pattern (11,3%), but in condition of isolated heart pretreatment by apamin (selective blocker of KCa channels) the coronaroconstriction in Dx-CMP has been more pronounced vs control (-17,1 vs -14,2%). In highest concentration (10-5 M) ET-1 led in Dx-CMP to a bigger decline of coronary flow FC (-16,8 vs -14,5%).
**Conclusions:** 1. The coronary functional endothelium dependent reserve is significantly reduced in Dx-CMP during Ach, As and Bk action averagely by 39-43,3% comparing to control, but the mediated by hyperpolarization coronarodilation proper to H2O2 and EET-11,12 action is not compromised.
2. In concentration of 10-5 M endoteline-1 induces a bigger fall of CF in Dx-CMP, but in concentration of 10-7 M the decline is similar to control, however CF decreases more if ET-1 action was preceded by KCa channels blocking.