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BOOK OF ABSTRACTS

6TH MEETING
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Neuregulin-1 decreases the passive force of cardiomyocytes from the right ventricle in pulmonary arterial hypertension

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Neuregulin (NRG)-1 is implicated in the maintenance and structural integrity of the cardiovascular system. Recent studies showed the involvement of NRG-1 in the preservation of left ventricular performance in pathophysiological conditions [1]. Nevertheless, the role of NRG-1 in pulmonary arterial hypertension (PAH) and right ventricular (RV) failure is still unknown. Therefore, the goal of this study was to evaluate the effects of a NRG-1 chronic treatment on intrinsic myocardial properties, namely on the modulation of active and passive force of cardiomyocytes isolated from the right ventricle of animals with PAH.

Male Wistar rats (180-200g) randomly received monocrotaline (MCT,60mg/Kg,sc) or vehicle. After 14 days, animals from these groups were randomly assigned to receive treatment with either NRG-1 (4ug/Kg/day,ip) or vehicle. The study resulted in 4 experimental groups: control (CTRL,n=9); CTRL+NRG (n=12); MCT (n=12); MCT+NRG (n=18). Between 21 and 24 days after MCT administration, samples were collected for functional studies. Right ventricular samples were mechanically disrupted and incubated in relaxing solution supplemented with Triton (0.2%). Single cardiomyocytes were subsequently attached with silicone adhesive between a force transducer and a piezoelectric motor and active and passive forces were measured. Only significant results ($p<0.05$) are given.

MCT-group isolated cardiomyocytes developed higher passive force when compared to CTRL-group cells at the sarcomere lengths of 2.0 (MCT vs. CTRL: 1.76±0.26 vs. 1.43±0.29N/m^2), 2.2 (MCT vs. CTRL: 3.74±0.71 vs. 2.68±0.24N/m^2), and 2.3µm (MCT vs. CTRL: 5.73±1.22 vs. 3.86±0.87N/m^2). Treatment with NRG-1 was able to restore passive force development to levels similar to the CTRL-group cardiomyocytes, at 2.0, 2.2, and 2.3µm (MCT+NRG: 1.28±0.25, 3.04±0.55, and 3.63±0.89N/m^2, respectively). CTRL+NRG-group cardiomyocytes developed significantly less passive force when compared to CTRL-group cells (CTRL+NRG: 1.19±0.25, 2.32±0.55, and 3.16±0.54N/m^2, at 2.0, 2.2, and 2.3µm respectively). The analysis of the active force showed that in the MCT+NRG-group cardiomyocytes active force development was decreased when compared to MCT-group cells (MCT+NRG: 9.67±2.83N/m^2).

NRG-1 chronic treatment is able to reverse the changes in both active and passive myocardial forces that occur in the presence of PAH. Interestingly, NRG-1 chronic treatment also decreases the passive force of cardiomyocytes isolated from the right ventricle of healthy animals. These findings suggest that the NRG-1 pathway has a relevant role in the regulation of diastolic function and in pathophysiology of PAH by decreasing passive force and thus myocardial stiffness, pointing to its potential role as a therapeutic target.

[1] De Keulenaer, G.W., Doggen, K. and Lemmens, K. (2010).*The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anticancer therapy*. Circ Res, 106, 35-46.