

Abstract No. **22**

Category: **Heart Failure and Cardiomyopathies**

Title: **Sirtuins activation improves calcium handling by preserving mitochondrial function in cardiomyocytes from a pulmonary arterial hypertension murine model**

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Abstract:

Introduction: Pulmonary arterial hypertension (PAH) is characterized by a chronic increase in pulmonary vasculature pressure promoting remodeling of the right ventricle (RV) and causing RV dysfunction. Mitochondrial dysfunction promoting proliferation and apoptosis suppression has been observed in PAH. In particular, sirtuin 3 deficiency, have been shown a increased acetylation profile and inhibition of several mitochondrial complexes, causing energetic failure. Resveratrol (RES) is a potent Sirtuins-activating compound that has been attributed a variety of beneficial effects, including mitochondrial protection.

This study seeks to describe the beneficial effects on cardiomyocyte function after daily oral administration of RES in a murine model of HAP. RV myocyte calcium transients were assessed using Fluo-4 by confocal microscopy under different pace stimulation (0.5, 1, and 2 Hz) before and after β -adrenergic stimulation by isoproterenol perfusion. Spontaneous calcium sparks were determined at basal conditions by confocal microscopy Mitochondrial function was evaluated by measuring the mitochondrial membrane potential and calcium retention capacity, mitochondrial density was evaluated with calcein incubated with cobalt and respiratory activity using high performance oxymetry. Expression of calcium handling proteins, acetylation profile and Sirtuins expression was determined by Western blot. PAH treated group showed higher calcium transients amplitudes than control (CT) group, while PAH+RES treated group showed the highest amplitudes. Time to 50% decay (T50%) from PAH+RES treated group was similar to CT; however, PAH group showed a significant increase at 0.5 and 1 Hz. All three groups were able to respond to β -adrenergic stimulation by increasing their transient amplitudes. MC showed 38% transient amplitude increase while PAH+RES showed 17%, both compared to CT. Calcium re-uptake kinetics did not show difference between groups.

Importantly, treatment with PAH decreased the mitochondrial membrane potential, calcium retention capacity, and oxidative phosphorylation whereas treatment with RES preserved CT levels. PAH slightly decrease mitochondrial density, while PAH+RES treated group showed 17.5% decrease. Acetylation profile and Sirtuins expression was reduced in PAH animals and RES improves the acetylation profile and protein expression. RES administration in PAH murine model prevents changes in calcium signaling by preserving mitochondrial function preserving a higher energy state in the cell. Our results supports the theory suggesting that the PAH has a mitochondrial dysfunction basis, and identifies Sirtuins as a potential therapeutic target.