

Abstract No. **26**

Category: **Heart Failure and Cardiomyopathies**

Title: **Changes in the stoichiometry of Uniplex decreases mitochondrial calcium overload and contributes to tolerance of cardiac ischemia-reperfusion injury in hypothyroidism**

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**Abstract:**

Background: Thyroid hormone status in hypothyroidism down regulates key elements in calcium handling within the heart, reducing contractility and increasing the risk of cardiovascular disease. Specially, mitochondrial calcium transport is reduced in hypothyroidism which hampers the basal energetic balance. While tolerance to reperfusion damage has been documented, the precise mechanism behind this is not well understood.

Objective: To determine the composition and activity of the mitochondrial calcium uniporter or Uniplex in a hypothyroid model and the relevance to the opening of the mPTP during ischemia-reperfusion injury.

Methods: A hypothyroidism model was established in Wistar rats by treatment of 6-propylthiouracil for 28 days. Hearts were perfused ex vivo to evaluate contractility and ischemia-reperfusion injury. Isolated cardiac mitochondrial were used to determine calcium transport and uniplex composition.

Results: The stoichiometric ratio between the two subunits of Uniplex (MICU1/MCU) was also found to be increased by 25% in hypothyroid animals. Mitochondrial from hypothyroid animals reduce calcium content 40% and were less prone to the opening of the permeability transition pore. During ischemia-reperfusion injury, ischemic contracture and the onset of ventricular fibrillation was delayed in hypothyroid animals, concomitant a reduction of oxidative damage and mitochondrial dysfunction.

Conclusions: Our results suggest that thyroid hormones in hypothyroidism increase the cardiac MICU1 to MCU ratio thereby changing the stoichiometry between these subunits to increase the threshold to cytosolic calcium, and reducing the mitochondrial calcium overload. Therefore, the hypothyroidism-induced tolerance to cardiac damage might be useful in investigating the physiological relevance of mitochondrial calcium transport in cardiac diseases.