P141
Prevention of microtubule disruption with paclitaxel does not protect against infarction in isolated rat hearts
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Background: Microtubules are highly dynamic polymers present in eukaryote cells that are essential components of cell cytoskeleton. They play an important role in intracellular transport, in maintaining organelle organization and function, and in transmitting mechanical forces within the myocardium. However, this intracellular network becomes disrupted during myocardial ischemia/reperfusion, and it has been proposed that microtubule disruption is an early sign of irreversible ischemic injury, and that prevention of microtubule disruption during ischemia-reperfusion could be beneficial. In this study we aimed to assess the effects of prevention of microtubule disruption with paclitaxel on ischemia-reperfusion injury in both isolated rat cardiomyocytes and isolated, Langendorff-perfused, rat hearts.

Methods and results: Isolated rat cardiomyocytes were submitted to normoxia (1h), or to 50 min of anoxia (pH 6.4, 0% O2, 37°C) and 15 min reoxygenation, without or with treatment during anoxia with the microtubule stabilizer paclitaxel (10 μM) or the inhibitor of microtubule polymerization colchicine (5 μM). The condition of microtubule network was assessed by immunofluorescence detection of α-tubulin. Anoxia/reoxygenation leads to disruption of the microtubule network before the onset of ischemic contracture (650 ± 21 vs. 328 ± 11 arbitrary units of fluorescence (auf), p ≤ 0.05). Paclitaxel attenuated both microtubule disruption (377 ± 15 auf, p ≤ 0.05 vs. anoxia/reoxygenation) and the incidence of hypercontracture (31 ± 7 % vs. 56 ± 8 % in anoxia/reoxygenation, p ≤ 0.05) induced by anoxia/reoxygenation, whereas treatment with colchicine mimicked the effects of anoxia/reoxygenation (fluorescence: 198 ± 16 auf, p ≤ 0.01 vs. anoxia/reoxygenation; hypercontracture: 65 ± 7 %). In isolated rat hearts under normoxic conditions, paclitaxel induced a concentration-dependent increase in perfusion pressure and a decrease in heart rate and left ventricular developed pressure. Despite protection against cell hypercontracture, paclitaxel pretreatment did not modify infarct size (60.37 ± 2.27 % in control hearts vs. 58.75 ± 10.25, 55.44 ± 10.32 and 50.06 ± 10.14 % in hearts pretreated with 10-6, 3 × 10-6 and 10-5 M of paclitaxel respectively), LDH release or functional recovery after 60 min of global ischemia and reperfusion in isolated rat hearts.

Conclusions: Microtubule stabilization with paclitaxel reduces hypercontracture in isolated rat cardiomyocytes but does not protect against infarction in isolated rat hearts.