Topic 14 – Myocardial hypoxia, reperfusion, stroke – C

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Coronary endothelium plays a key role in exercise induced cardioprotection: a potential paracrine role of NO

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We recently showed that endothelial isoform of NOS (eNOS) plays a key role in exercise-induced cardioprotection during myocardial ischemia reperfusion (IR). Although this enzyme is expressed in both coronary endothelial cells and cardiac myocytes, only 20% of the total cardiac eNOS seems to localize in the cardiomyocytes. The aim of this study was to investigate the role of coronary endothelium in the eNOS exercise-induced cardioprotection. Rats were assigned to sedentary (Sed) or exercised (Ex, 5 days/week for 5 weeks, 70% of maximal aerobic velocity) group. At the end of the exercise training period, hearts were mounted on an isolated hearts Langendorff apparatus and subjected to global ischemia (30 min) and reperfusion (120 minutes) in presence or not of a NOS inhibitor (L-NAME, 50µM). Treatment with L-NAME of isolated hearts during IR abolished exercise-induced cardioprotection, confirming previous results on the role of eNOS during IR. The contribution of the coronary endothelial cells was prevented by perfusing a bolus injection of Triton X-100 in the coronary system before IR. When endothelial cells are inactivated, the beneficial effects of exercise on hearts sensitivity to IR were totally abolished. Moreover cardiomyocytes isolated from sedentary and exercised hearts were subjected to 1 hour anoxia and 1 hour reoxygenation in presence or not of L-NAME (50µM). Interestingly, at the cardiomyocyte level, exercise-induced protection is not clear and L-NAME had no effect, suggesting that eNOS was not involved in such mechanism. In conclusion, the present results show that NO synthesis from coronary endothelial cells plays a major paracrine role in exercise induced cardioprotection.

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Ischemia-reperfusion

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Background: In ST elevation myocardial infarction (STEMI) context, clinical studies have shown the deleterious effect of high aldosterone levels on ventricular arrhythmia (VA) occurrence as well as on cardiac mortality. However, the mechanisms of such harmful effects remain unknown.

Methods and results: We used an in vitro model of "border zone" using rabbit ventricle and standard microelectrode technique, completed by cell-attached experiments of freshly isolated rabbit ventricular cardiomyocytes to assess the acute electrophysiological impact of aldosterone. During simulated ischemia, aldosterone (10 and 100 nmol/L) increased the APD dispersion at 90% between ischemic and normoxic zones (from 95±4 ms to 117±5 ms and 131±6 ms respectively, $P<0.05$) and reperfusion-induced sustained premature ventricular contractions occurrence (from 17% to 67% and 83% respectively, $P<0.05$). Furthermore, aldosterone induced a resting membrane potential hyperpolarization, evoking an implication of a K+ current. Adding potassium canrenoate to aldosterone superfusion prevented these deleterious effects contrary to RU 28318, a specific mineralocorticoid receptor (MR) antagonist. Cell-attached experiments, designed to identify the K+ current involved, showed that aldosterone 10 nmol/L activated (within 6.2±0.4 min) a 30 pS K+-selective channel, inward rectifier, with pharmacological and biophysical properties consistent with the IK1 current (NPo=1.96±0.36 in control vs NPo=3.01±0.43, n=10, $P<0.05$).

Conclusions: In this in vitro model of "border zone", aldosterone had a deleterious impact via a rapid and MR-independent IK1 current activation. These conclusions may help to better understanding recent clinical studies results underlying the involvement of aldosterone in VA occurrence in STEMI context.