408-3 Induction of Atrial Fibrillation and Nerve Sprouting by Prolonged Left Atrial Pacing in Dogs

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Background: In a canine model of sustained atrial fibrillation (AF) induced by chronic rapid RA pacing, nerve sprouting (NS) is greater in the RA than in the LA. The mechanism is unclear. We hypothesize that NS is induced by electrical current. Therefore, if LA is paced, then NS will be greater in the LA than in the RA.

Methods: Restenosis is a major limitation of percutaneous coronary interventions. Barotrauma caused by balloon angioplasty has been shown to trigger early onset of apoptosis in vascular smooth muscle cells (SMC), which may promote migration and proliferation. z-VAD.FMK is a broad spectrum synthetic caspase inhibitor that inhibits apoptosis.

Purpose: To evaluate if a locally delivered caspase inhibitor, z-VAD.FMK, can protect arterial medial SMCs from balloon injury mediated apoptosis, reducing the subsequent SMC proliferation, thereby limiting restenosis.

Methods: Bilateral iliac artery angioplasty was performed in 12 male NZW rabbits (n=6; Chronic 4:4). Simultaneous with balloon injury, the artery was treated locally with normal saline (control) or z-VAD.FMK (contralateral artery). Acute animals were treated with high dose (45,000 ng, n=5) or low dose (4,500 ng, n=5) z-VAD and sacrificed at 4 hours. Apoptosis was detected using TUNEL assay. Apoptotic index was calculated (smooth muscle cell nuclei positive for apoptosis/200 smooth muscle cells nuclei counted). In chronic studies, high dose (45,000 ng) z-VAD was delivered locally and animals were sacrificed at 4 weeks. Intimal area (Internal elastic lamina area - Luminal area) and medial area (External elastic lamina thickness - Internal elastic lamina area) were measured. Results: The reduction in apoptotic index was 45%, (p<0.001) with high dose and 33%, (p<0.02) with low dose z-VAD. In the chronic animals, the difference in necrotic area was 39% (4.0 ± 0.6 mm2 vs. 2.4 ± 0.5 mm2) (p=0.0004) and in medial area was 20% (7.7 ± 0.7 mm2 vs. 6.3 ± 0.4 mm2) (p=0.001). A significant increase in z-VAD treated arteries.

Conclusion: Significant inhibition of balloon injury mediated apoptosis of arterial SMCs can be achieved using locally delivered z-VAD, resulting in a significant decrease in both necrotic formation and medial proliferation. This novel antirestenotic strategy is in contrast to the conventional approach of causing smooth muscle cell death after onset of cell proliferation.

11:45 a.m.

408-4 Acute Neuroprotective Effects of Corticosteroids Mediated by Nontranscriptional Activation of Endothelial Nitric Oxide Synthase

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Background: Cellular responses to corticosteroids involve the transcriptional modulation of target genes by the glucocorticoid receptor (GR). A rapid, non-transcriptional effect of GR was found to mediate neuroprotection via the activation of endothelial nitric oxide synthase (eNOS).

Methods & Results: In a concentration-dependent manner, dexamethasone stimulated eNOS activity by about 2.5-fold, which was completely inhibited by the GR antagonist, RU486, but not by the transcriptional inhibitor, actinomycin D. Pretreatment with the phosphatidylinositol 3-kinase (PI3K) inhibitor, wortmannin, also inhibited Dex-stimulated eNOS activity, indicating a PI3K-dependent mechanism. Dex activated PI3K in a ligand-dependent manner, leading to the phosphorylation and activation of protein kinase Akt and eNOS. In a mouse filament model of transient cerebral ischemia, a bolus injection of Dex (20 mg/kg, Lp.), administered 1 hr before middle cerebral artery occlusion, increased vascular eNOS activity by 2.5-fold, enhanced post-ischemic cerebral blood flow, and decreased cerebral infarct size by 32% (108 ± 9 to 74 ± 8 mm³, n=10, p<0.05). These neuroprotective effects of Dex occurred in the absence of significant changes in physiological parameters and were still evident when Dex was administered 2 hrs after ischemia (112 ± 8 to 64 ± 7 mm³, n=10, p<0.05). The beneficial effects of Dex on infarct size were completely absent in eNOS−/− mice, suggesting a novel eNOS-dependent mechanism for stroke protection by corticosteroids.

Conclusion: The non-genomic activation of PI3K/Akt and eNOS by GR represents a physiologically important neuroprotective effect of corticosteroids.

Noon

408-5 The Selective Estrogen Receptor Modulator,Raloxifene, Improves the Severity of Myocardial Ischemia in Canine Hearts

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Background: We have reported that 17β-estradiol increases coronary blood flow and improves myocardial ischemia. However, little is known as to whether the selective estrogen receptor modulator, raloxifene, mediates coronary vasodilation and improves myocardial ischemia, and what cellular mechanisms are involved in these effects.

Methods: In open-chest anesthetized dogs, the left anterior descending coronary artery (LAD) was perfused through an extracorporeal bypass tube from the left carotid artery. Ral-