Thursday, August 28th
Cardiac dysfunction
Poster Session - PCD

PCD1

LOW-DOSE METFORMIN THERAPY ATTENUATES LEFT VENTRICULAR DYSFUNCTION AND REDUCES MORTALITY IN A MURINE MODEL OF HEART FAILURE

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Clinical studies indicate that metformin protects against cardiovascular disease in patients with diabetes and metabolic syndrome by actions that cannot be solely attributed to its glucose-lowering effects. We sought to investigate the potential cardioprotective effects of an acute, low-dose metformin treatment (i.e. 286-fold less than the maximum anti-hyperglycemic dose) in a murine model of heart failure (HF). Mice were subjected to myocardial ischemia for 60 min followed by reperfusion. Metformin (125 μg/kg) or vehicle (saline) was administered as a single bolus (i.v.) at the time of reperfusion and then daily (intraperitoneal) for 4 wks. Administration of metformin reduced infarct size by 30% ($p<0.001$) at 24 hrs of reperfusion and significantly ($p<0.01$) improved LV function at 4 wks of reperfusion without altering blood glucose levels. At 4 wks of reperfusion, metformin therapy significantly ($p<0.05$) increased the phosphorylation status of AMPK and eNOS, increased the expression of PGC-1 , and improved mitochondrial ATP synthesis and oxygen consumption in the hearts of treated mice. In an additional group of mice subjected to a complete occlusion of the left coronary artery, metformin reduced mortality by 50% ($p<0.05$). These findings suggest that low-dose metformin therapy may have a practical clinical use for the treatment of HF. This work was supported by the National Institutes of Health (HL-060849-08 to D.J.L. and F32 DK 077380-01 to J.W.C.) and the American Diabetes Association (7-04-RA-59 to D.J.L.).

PCD2

PREVALENT ROLE OF AKT AND ERK ACTIVATION IN CARDIOPROTECTIVE EFFECT OF CA^{2+} CHANNEL- AND ß-BLOCKERS

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We studied cardioprotective as well as Akt and ERK activating effect of a Ca antagonist and a β-blocker during ischemia-reperfusion cycle in Langendorff-perfused isolated rat hearts, and compared these properties of the substances to that of a poly(ADP-ribose) polymerase (PARP) inhibitor used as a positive control throughout the experiments. Although in different extent, all substances improved recovery of creatine phosphate, ATP, intracellular pH, and reutilization of inorganic phosphate. These favorable changes were accompanied by improved recovery of heart function parameters and reduced infarct size. In addition, all studied substances decreased oxidative damage (lipid peroxidation and protein oxidation), and activated Akt, and ERK1/2. Correlation between cardioprotective and kinase activating effectivity of the compounds proved to be statistically significant. Inhibition of Akt by LY294002 and ERK1/2 by PD98059 compromised the cardioprotective effect of all the substances studied corroborating the significance found. In conclusion, we demonstrated at the first time that activation of PI-3K/Akt and ERK2 pathways significantly contributed to cardioprotective effect of a Ca^{2+} antagonist and a β-blocker. Furthermore, we found a strong correlation between cardioprotective and kinase activating potencies of the substances studied that suggests potentiality of these kinases as drug-targets in the therapy of ischemic heart disease.

PCD3

PARTICULATE MATTER INHALATION IMPAIRS CORONARY MICROVASCULAR REACTIVITY

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We have recently shown that systemic microvascular function is impaired after inhalation exposure to fine and ultrafine particulate matter (PM). Studies have shown that exposure to airborne particle pollution increases the risk of ischemic cardiovascular events. However, it remains unclear how the coronary microcirculation contributes to such insults. We tested the hypothesis that microvascular reactivity is impaired after PM exposure in rat coronary arterioles. Rats were exposed to filtered air (control), fine PM, or ultrafine PM via inhalation at concentrations relevant to ambient air pollution (4-90 □g measured pulmonary deposition). Coronary arterioles were subsequently isolated and responses to flow (FID), acetylcholine (ACh), endothelin and dea-NONO-ate were assessed. Exposure to either fine or ultrafine PM significantly impaired FID, but neither group displayed an altered response to ACh. Interestingly, vascular smooth muscle nitric oxide (NO) sensitivity (dea-NONO-ate) was decreased by exposure to ultrafine PM, but not fine PM. Furthermore, ultrafine PM exposure diminished vasoconstrictor responses to endothelin, whereas fine PM exposure had no effect on endothelin reactivity. These results suggest that ultrafine PM exposure causes significantly more microvascular dysfunction than fine PM. It is probable that such disturbances in coronary microvascular function contribute to the cardiac events associated with particle pollution exposure. Support: R01-ES015022 and HEI#4730 (TRN) and R01-HL077224 (JMD).

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