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METABOLISM AND PHYSIOLOGY
SESSION TITLE: HEART FAILURE I

Abstract 13311: Cyclocreatine Phosphate: A Novel Mechanism for Preventing Development of Heart Failure

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Abstract

Introduction: Demand ischemia causes irreversible myocardial injury (MI) through exhaustion of cellular adenosine triphosphate (ATP). We demonstrated that enhancing myocardial ATP stores during ischemia using Cyclocreatine Phosphate (CCrP), prevents myocardial injury and maintains cardiac contractility in a variety of models. The FDA has granted CCrP Orphan Drug Status with the designation of "*Prevention of Ischemic Injury to Enhance Cardiac Graft Recovery and Survival in Heart Transplantation*".

Hypothesis: CCrP administration will prevent ischemic injury and the subsequent development of heart failure in standard isoproterenol (ISO) rat model.

Methods: 20 male Wistar rats (180-220 g) were used: ISO/saline (n=6), ISO/CCrP 0.8 gm/kg/day (n=5), control/saline (n=5), control/CCrP 0.8 gm/kg/day (n=4). Rats were injected S.C. with ISO for two consecutive days at doses of 85 and 170 mg/kg/day, respectively, then left for 2 weeks. CCrP and saline were injected IP (1 ml) 24 hours and 1 hour before ISO administration, then daily for 2 weeks. Serum CK-MB (U/L) measured 24 hours after last ISO injection. After 14 days, ECHO analysis for Ejection Fraction (EF%) was conducted, as well as heart weight (mg), fibrosis and deposition of collagen. Mean ± S.E.M and one-way ANOVA analysis were used.

Results: Table I shows evidence of MI after 24 hours by high elevation of CK-MB in ISO rats, while significant protection was seen in ISO/CCrP rats. After 14 days, ISO/CCrP rats showed normal EF% and heart weight, while ISO/saline rats showed significant drop in EF% and an increase in heart weight. Blinded pathology indicated marked increase of fibrin and collagen deposition in ISO/saline rats, which were not seen in ISO/CCrP rats. Healthy rats treated with CCrP for 14 days, showed no toxicity in liver and renal function.

Conclusions: The bioenergetic Cyclocreatine Phosphate is a promising first-in-class cardio-protective drug that prevents the development of heart failure due to ischemia.

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Footnotes

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