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

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Disclosures of Authors

- **S. A. Elgebaly (Univ. of Connecticut Faculty of Medicine):** Founder, Nour Heart, Inc.
- **C. Van Buren (Univ. of Texas Sch. of Medicine):** Speaker/Speaker's Bureau; Self; Veloxis.
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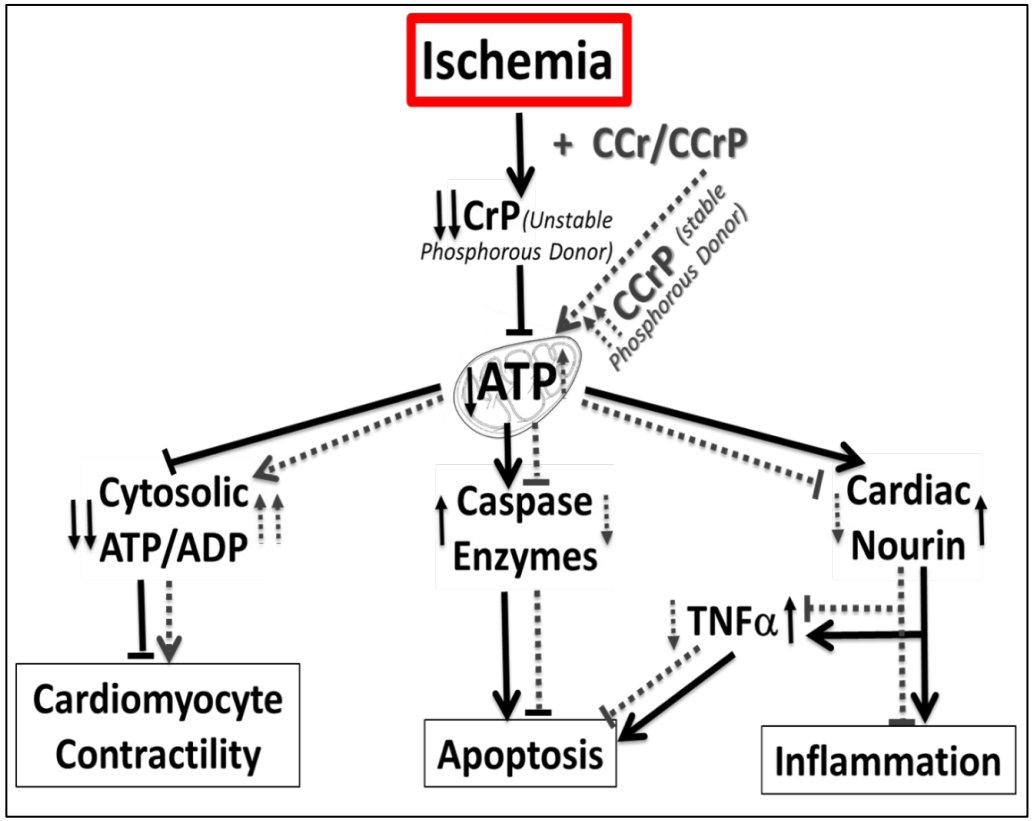
What is Cyclocreatine?

A Novel "Bioenergetic" Compound!

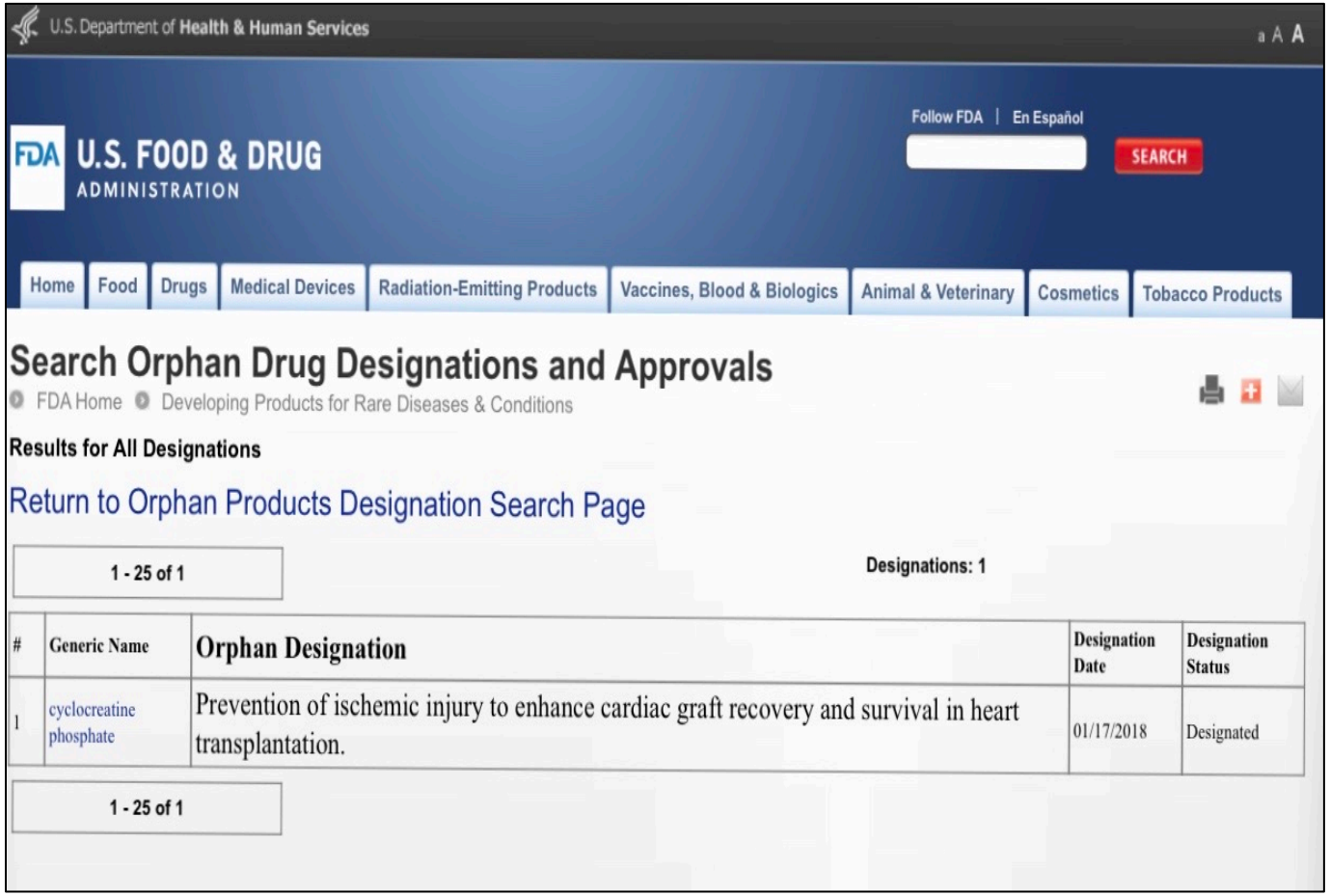
- **Demand ischemia causes irreversible myocardial injury through exhaustion of cellular ATP**
- **Cyclocreatine Phosphate (CCrP) is a "bioenergetic" compound maintains elevated cellular ATP during ischemia**
- **Preservation of cellular ATP by CCrP administration:**
  - **Prevented myocardial ischemic injury**
  - **Reduced post-ischemic cardiac inflammation**
  - **Reduced myocardial apoptosis**
  - **Restored contractile function immediately after reperfusion in animal models of:**
    - **AMI**
    - **Global cardiac arrest**
    - **Cardiopulmonary bypass**
    - **Heart transplantation**



Elgebaly SA, et al. Expert Review of Cardiovascular Therapy – 2019 – REVIEW

What is Unique About Cyclocreatine?

Prevents Myocardial Ischemic Injury!



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Designations: 1

#	Generic Name	Orphan Designation	Designation Date	Designation Status
1	cyclocreatine phosphate	Prevention of ischemic injury to enhance cardiac graft recovery and survival in heart transplantation.	01/17/2018	Designated

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FDA Awarded Cyclocreatine Phosphate (CCrP) Orphan Drug Status with the Unique Designation *of:*

"Prevention of Ischemic Injury to Enhance Cardiac Graft Recovery and Survival in Heart Transplantation" (DRU-2015-4951)

Clinical Use: **End-Stage Heart Failure Patients Scheduled for Heart Transplantation Procedure**

***Objectives*: To examined whether the administration of Cyclocreatine Phosphate, as a new pharmacologic agent that has the ability to maintain and restore myocardial energetics in the setting of ischemia, would prevent the development of heart failure?**

Hypothesis & Experimental Design

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

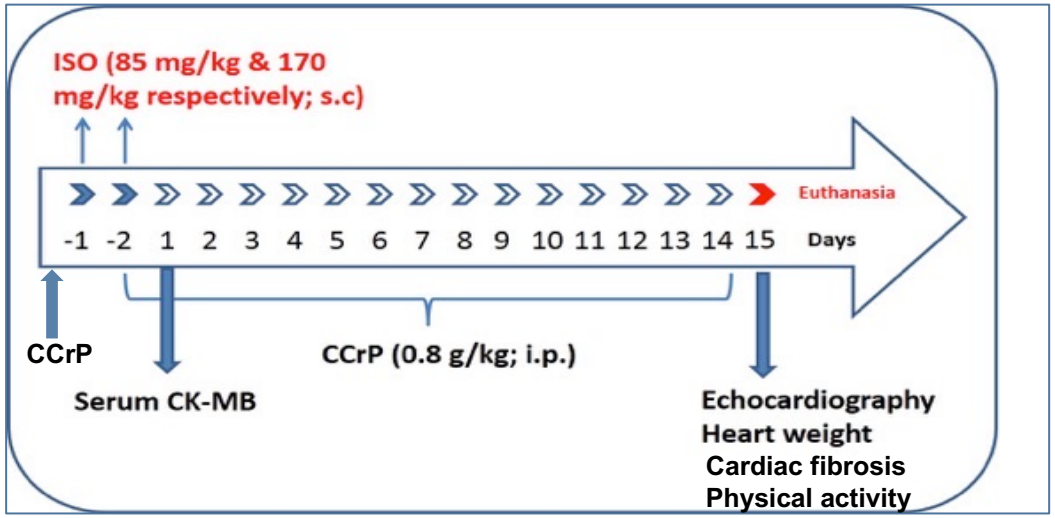
ISO Rat Model: **ISO is a beta-adrenergic agonist which in high doses causes myocardial injury (subendocardial ischemia and cellular ATP depletion)**

GROUPS:

1. **ISO/Saline (n=6)**
2. **ISO/CCrP (0.8 gm/kg/day) (n=5)**
3. **Control/Saline (n=5)**
4. **Control/CCrP (0.8 gm/kg/day) (n=4) (*liver & kidney safety*)**

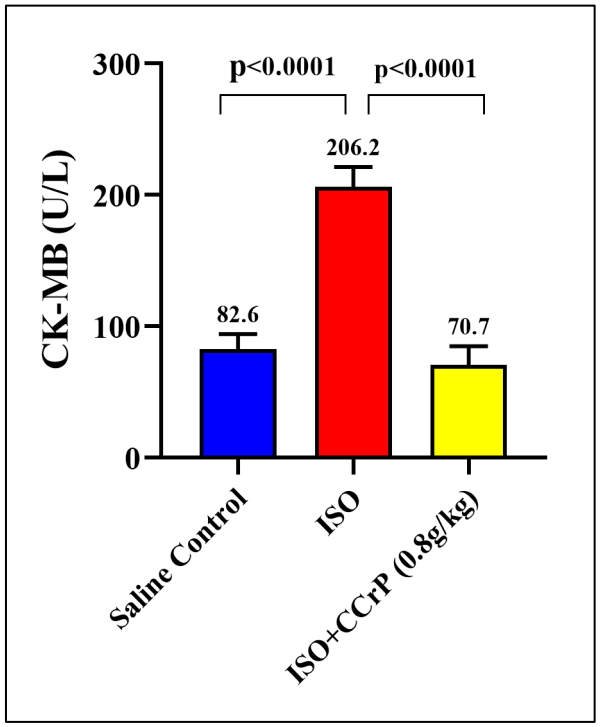
- **CCrP treatment was initiated 24 hrs. before first ISO**
- **Serum CK-MB was measured 1 day after second ISO**
- **After 14 days, ECHO / EF%, collagen %, fibrosis, heart weight, and physical activity were determined**

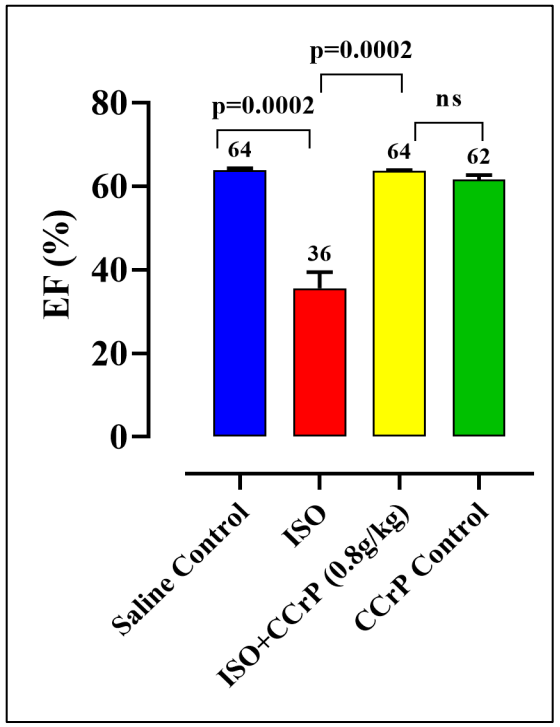
20 male Wistar rats (180-220 g)

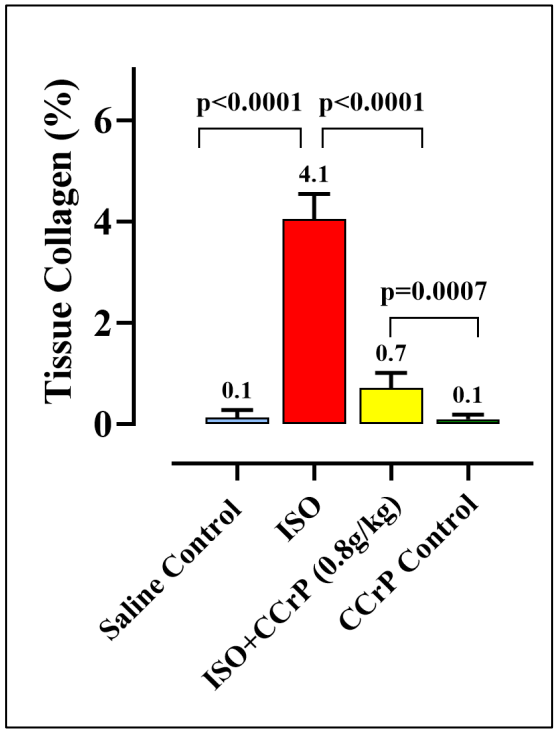


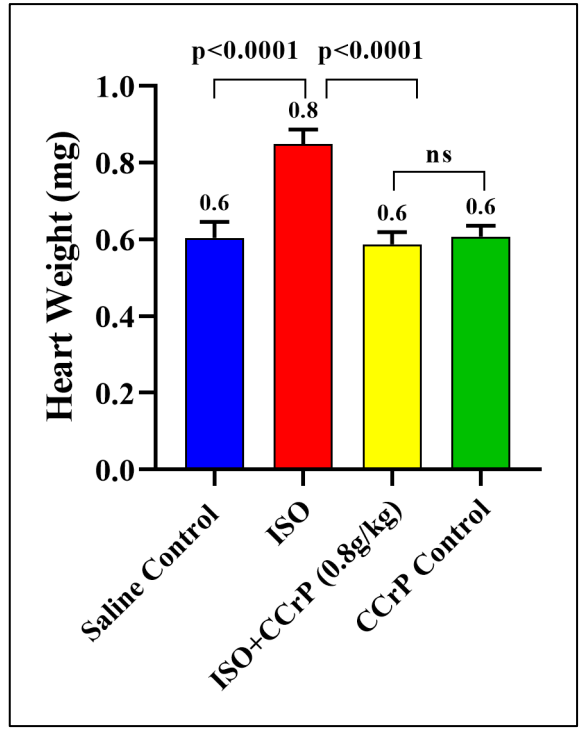
Results

Serum CK-MB Level (*after 1 day*)
EF%, Collagen % and Heart Height (after 14 days)









CK-MB
ISO/CCrP maintained normal CK-MB level, thus, prevented ischemic injury

EF%
ISO/CCrP maintained normal EF%

Collagen%
ISO/CCrP showed 83% reduction in collagen% compared to ISO

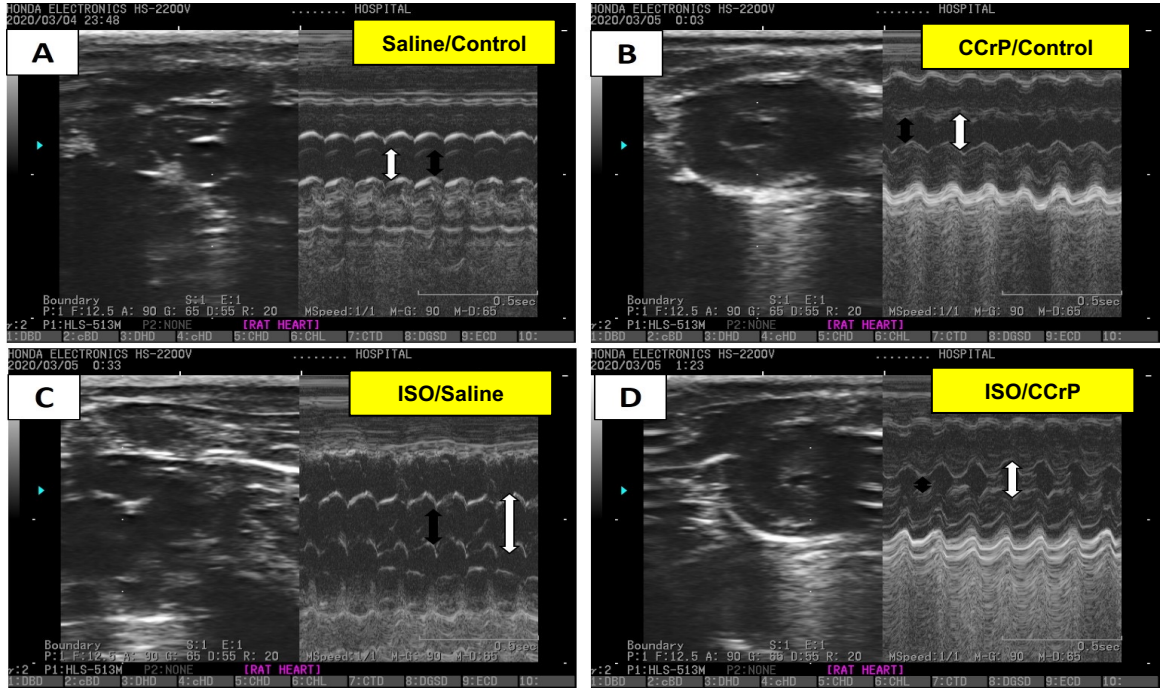
Heart Weight
ISO/CCrP maintained normal heart weight

Results

Echocardiographic LVEDD, LVESD and EF%

GROUPS	LVEDD (mm)	LVESD (mm)	EF (%)
Saline Control	7.77 ± 0.15	5.43 ± 0.03	63.87 ± 0.29
CCrP Control	7.93 ± 0.03	5.53 ± 0.09	61.57 ± 0.64
ISO + Saline	10.07* ± 0.12	9.00* ± 0.15	35.57* ± 2.25
ISO + CCrP	8.03# ± 0.09	6.27# ± 0.07	63.67# ± 0.13

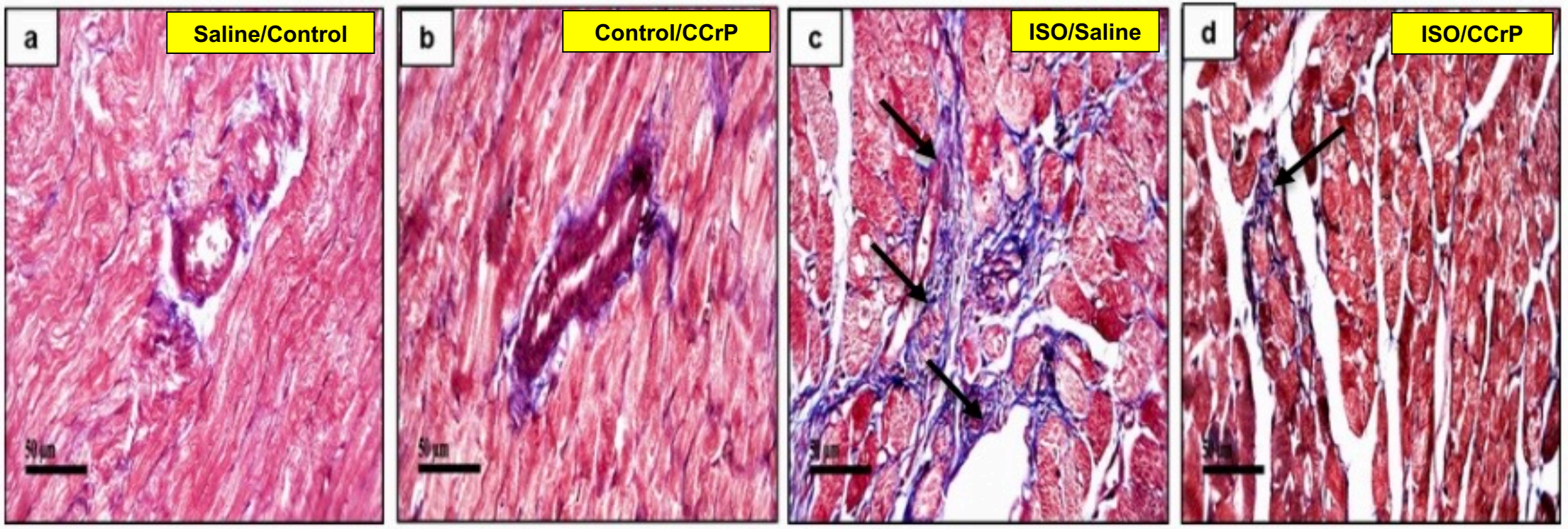
After 14 days, ISO/CCrP rats showed normal EF% (63.67%), while ISO/saline rats showed significant drop in EF% (35.57%). **p < 0.0001 for* ISO/Saline vs. Saline, and *#p < 0.0001 for ISO/CCrP* vs. ISO/Saline. Data are expressed as mean ± S.E.M. Statistical analysis was performed using One-way ANOVA followed by Tukey's post-hoc test.



Echocardiography images demonstrate the effect of CCrP on ISO-induced changes in M-mode in left ventricular end-diastolic diameter; LVEDD (⇕) and left ventricular end-systolic diameter; LVESD (⇕). Groups include: Saline/Control (A), CCrP/Control (B), ISO/Saline (C), and ISO+ CCrP (D). CCrP dose is 0.8 g/kg/day.

Results

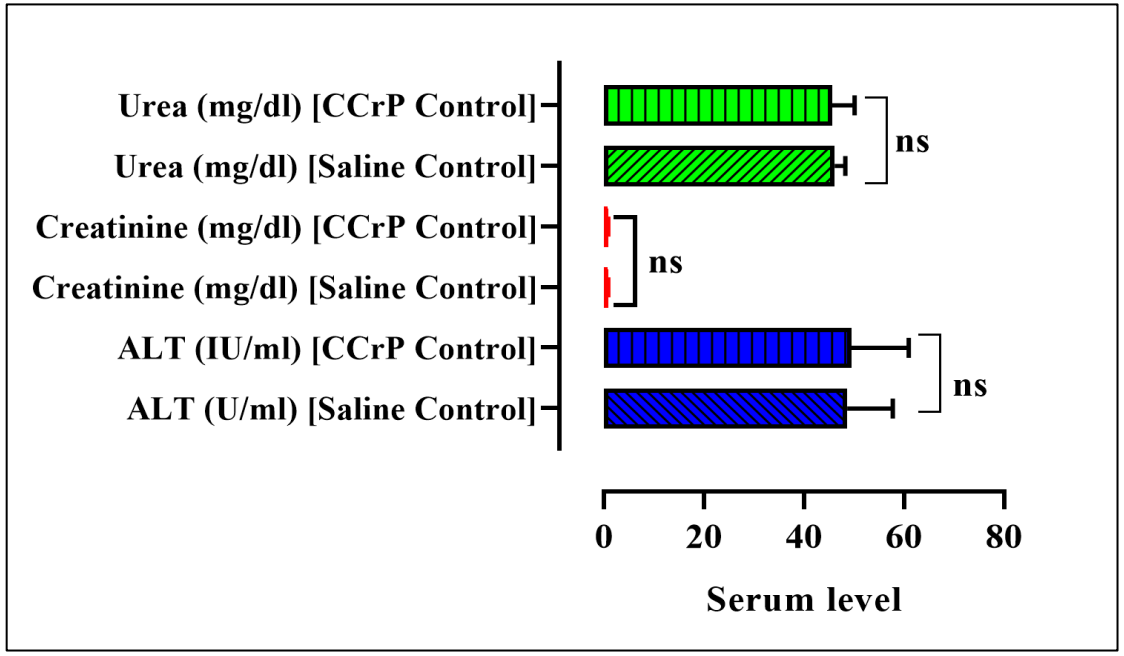
Cardiac Fibrosis



Blinded histopathological analysis showed extensive fibrous deposition in ISO/saline rats, while ISO/CCrP rats showed delicate fibrous tissue between the myocardial bundles, almost close to normal. Specimens (a-d) were stained with Masson's trichrome for estimation of myocardial fibrosis (blue color). Analysis was conducted using 10 randomly selected fields from 2 sections for each heart. Groups are: (a) Saline/Control, (b) CCrP/Control (0.8 g/kg/day), (c) ISO/Saline and (d) ISO/CCrP (0.8 g/kg/day). CCrP protected rats against cardiac fibrosis.

Results

Physical Activity
CCrP Safety - Liver & Kidney



Low to no activity in ISO/Saline rats (Video is Attached)

High activity in ISO/CCrP rats (Video is Attached)

Healthy rats treated daily with CCrP (0.8 g/kg/day) for 14 days showed no toxicity in liver and renal function

Conclusions

- **Myriad efforts to mitigate heart failure by targeting specific "downstream pathways" have been largely disappointing. The enhancement of myocardial bioenergetics is a novel treatment approach that makes downstream pathways less likely to be activated in response to various forms of myocardial injury including demand ischemia. Cyclocreatine phosphate is a first-in-class agent that specifically targets myocardial bioenergetics**

- **Cyclocreatine phosphate is a unique bioenergetic compound that prevented ischemia-induced heart failure, presumably by its documented capacity to maintain elevated levels of cellular ATP during ischemic insults. Preservation of ATP ties all results together by: preventing ischemic injury and cardiac remodeling (fibrosis and collagen deposition), and maintaining normal heart weight, leading to normal ejection fraction and physical activity**

- **Initial studies indicated that Cyclocreatine Phosphate is a safe compound with no toxic effect on cardiac, liver and kidney function**

Thank You.

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