A Novel High Energy Phosphate Source Resuscitates Poorly Functioning Donor Hearts

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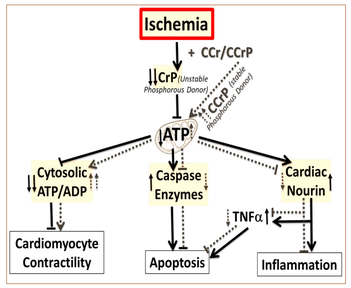
INTRODUCTION

- **CCrP is an *FDA Orphan Designated Drug* for "*Prevention of Ischemic Injury to Enhance Cardiac Graft Recovery and Survival in Heart Transplantation*" (DRU-2015-4951).**
- Over 60% of the time donor hearts cannot be *utilized* for transplant because of: 1) limited transport time to 4 hours; and 2) poor left ventricular ejection fraction (EF) of ≤40% due to stress cardiomyopathy (i.e., demand ischemia) with depletion of myocardial adenosine triphosphate (ATP).
- Cyclocreatine Phosphate (CCrP) is a bioenergetic compound which maintains elevated cellular ATP during ischemia. It is a *s*ynthetic analogue of the naturally occurring Creatine Phosphate (CrP). Since CCrP is more stable and superior to CrP in phosphorylating ADP to ATP (CrP stops working due to acidity), it continues to synthesize ATP during ischemia, prevents myocardial ischemic injury, and blocks the harmful downstream events of ischemia that lead to cardiac dysfunction (**Fig.1**) [1,2]. *Loss of 20% ATP affects contractility*. CCrP preserved contractility with a loss of 15% ATP, while saline group lost 34% ($p<0.05$), with no contractility [1].

Fig. 1: *CCrP* and Myocardial ischemia

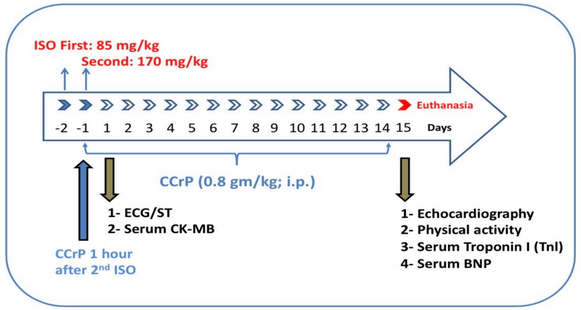


➢ *When CCrP is given **prophylactically** in an isoprenaline (ISO) rat model of demand ischemia-induced stress cardiomyopathy, it prevented ischemic injury, remodeling, and restored cardiac function with normal physical activity [3].*

HYPOTHESIS

We hypothesized that administering **CCrP <u>therapeutically</u>** after ISO-induced myocardial dysfunction in rats (simulating rejected donor hearts due to poor heart function), will prevent ischemic injury and sustain long-term restoration of EF.

METHODS



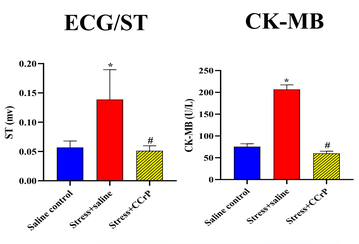
Wistar male rats (180-220 g) were injected SC with ISO (85 and 170 mg/kg/day) for two consecutive days. CCrP (n=6, 0.8 gm/kg/day ip) and saline control (n=4) were administered *1 hour* after completing the course of ISO injections and then daily for 2 weeks. A negative control group was injected with saline (n=4). Serum CK-MB and ECG/ST were measured 24 hours after last ISO injection. Evidence of stress cardiomyopathy was assessed after 14 days by ECHO analysis for EF and levels of hs-Troponin I (TnI) and BNP.

Statistical analysis was performed using One way ANOVA followed by Tukey's post-hoc test. Data are expressed as mean ± S.E.M of 4 to 6 rats per group.
**p < 0.05 vs. control,*
#p < 0.05 vs. stress+saline.

RESULTS

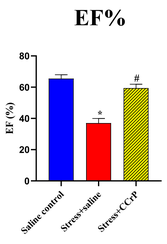
Two main benefits of therapeutically administered CCrP in this stress cardiomyopathy model.

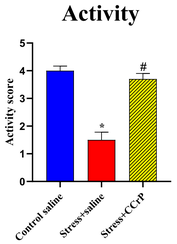
24 hours

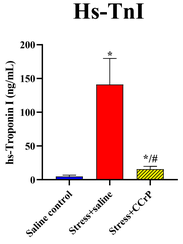


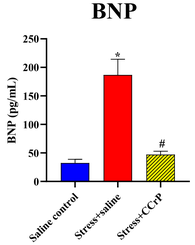
Poor heart function was quickly restored in the acute phase (24 hours), as indicated by normal ECG/ST and CK-MB levels.

14 days







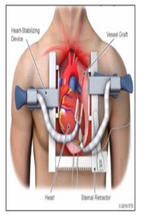


The restoration of heart function was sustained over the long term (14 days), as indicated by normal EF% and physical activity, as well as normal serum levels of hs-TnI and BNP. These results suggests that CCrP can salvage poorly functioning donor hearts from stress cardiomyopathy.

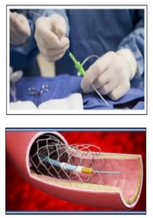
CONCLUSIONS

The bioenergetic CCrP is a novel cardioprotective drug that appears to salvage cardiac dysfunction and preserves normal EF% and physical activity in a rat model of stress cardiomyopathy. If this benefit translates into clinical organ donors with poor heart function, CCrP could be used to ***increase heart utilization for transplantation.***

Additional clinical applications of CCrP cardioprotection include high-risk cardiac surgery and interventional cardiology, as well as protection against development of heart failure after cardiac injury.



1. High-risk Cardiac Surgery



2. High-risk Interventional Cardiology

3. Reduce Heart Failure

REFERENCES

1. Elgebaly SA, Poston R, Todd R, et al.: Cyclocreatine Protects Against Ischemic Injury and Enhances Cardiac Recovery During Early Reperfusion .*Expert Review of Cardiovascular Therapy*, 2019, 17:9, 683-697 (REVIEW).
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3. Elgebaly, S.A.; Van Buren, C.; Todd, R.; et.al. Cyclocreatine Phosphate: A Novel Mechanism for Preventing Development of Heart Failure. *Circulation J.* 17 Nov 2020.142:A13311.

http://nourheart.com/ for additional publications and presentations.