Cyclocreatine: A Novel Cardioprotective Therapy

Against Ischemia / Reperfusion Injury

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Outline

1. **Background**
   - Mechanisms of Ischemia / Reperfusion Injury
2. **Problem**
   - Current Pharmacologic Agents
   - Clinical Need
3. **Our Solution**
   - Cyclocreatine and Cyclocreatine Phosphate (CCrP)
     - Heart Attack (AMI) Model
     - Cardiopulmonary Bypass
     - Global Warm Cardiac Arrest
     - Heart Transplant Model
4. **Clinical Applications**
5. **Conclusions**

Therapy of Ischemia

Reperfusion

1. Saved Heart Muscles
2. Increased Patient Survival

Reperfusion Injury

Reperfusion Injury

Accounts for Up to 50% of the Final Infarct Size

Mechanisms of Ischemic and Reperfusion Injury

Ischemic Injury

- Acidosis
- Depletion of the Energy Source Adenosine Triphosphate (**ATP**)

Reperfusion Injury

- ***Transitory injury***:
  - Arrhythmias
  - Myocardial stunning
- ***Permanent injury***:
  - Depletion of the Energy Source Adenosine Triphosphate (**ATP**)
  - Inflammation
  - Apoptosis
  - Necrosis

Current Pharmaceutical Targets

Ischemic Injury

- Acidosis
- Depletion of the Energy Source Adenosine Triphosphate (**ATP**)

Reperfusion Injury

- ***Transitory injury***:
  - Arrhythmias
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- ***Permanent injury***:
  - Depletion of the Energy Source Adenosine Triphosphate (**ATP**)
  - Inflammation
  - Apoptosis
  - Necrosis

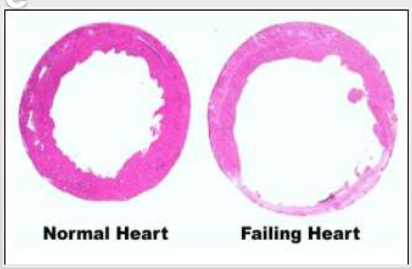
2. Problem – Failed Pharmacologic Agents

Pharmacologic Therapies to Reduce Reperfusion Injury Have Not Been So Successful

Examples of Failed Clinical Trials as Protective Agents Against Reperfusion Injury Are:

- C5a
- ICAM-1
- Corticosteroids
- Allopurinol
- Trimetazidine
- Adenosine
- Inhaled Nitric Oxide
- IV Sodium Nitrite

Clinical Problem - Chronic Heart Failure



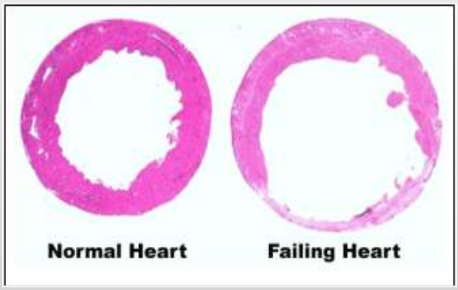
1- The Lack of Successful Pharmacologic Therapies to Reduce Reperfusion

Injury Led to an Increase in the Incidence of Chronic Heart Failure

2- Heart Failure is a Huge Socioeconomic Burden on:

- Heart Failure Individuals

Clinical Need



Designing Novel Strategies for Clinical Cardioprotection During the Early Phase of Reperfusion is a Major Therapeutic Goal of Modern Cardiology

3. Our Solution and Therapeutic Targets

Ischemic Injury

- Acidosis
- Depletion of the Energy Source Adenosine Triphosphate (**ATP**)

Reperfusion Injury

- ***Transitory injury***:
  - Arrhythmias
  - Myocardial stunning
- ***Permanent injury***:
  - Depletion of the Energy Source Adenosine Triphosphate (**ATP**)
  - Inflammation
  - Apoptosis
  - Necrosis

Our Therapeutic Strategy

To Identify Agents that Preserve the Energy Source ATP and Reduce its Depletion During Ischemia & Reperfusion

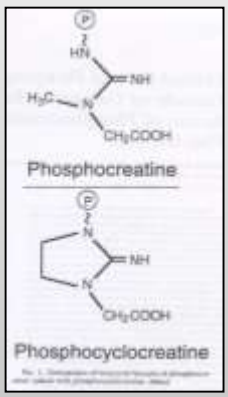
Depletion of the Energy Source ATP is Associated With:

- **Loss of Contractility (only 20% ATP depletion)**
- **Acute and Chronic Cardiac Inflammation**
- **Apoptosis (slow programmed death)**
- **Necrosis (immediate death)**

Cyclocreatine and Cyclocreatine Phosphate

Creatine (Cr)

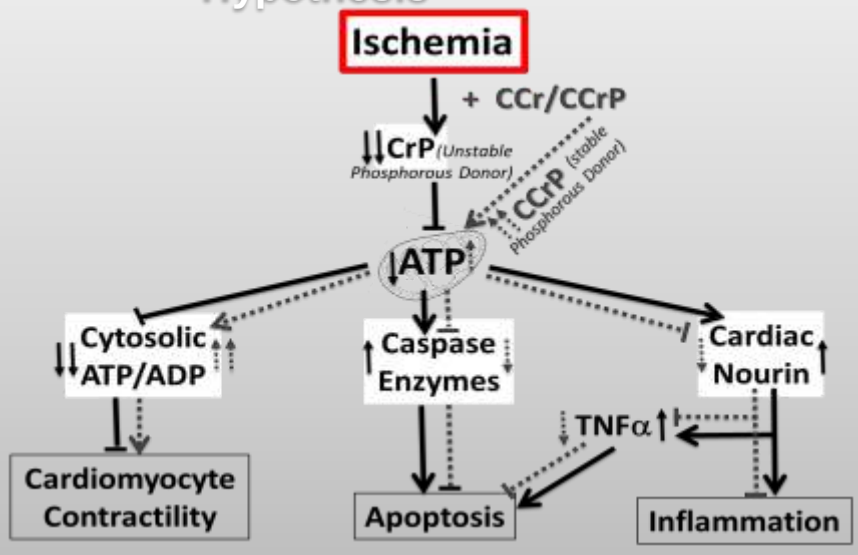
- **Creatine is necessary for contractility**
- **Creatine Phosphate (CrP) is the source of P for ADP**
- **CrP stops working at low acidity in ischemic hearts**



Cyclocreatine (CCr)
Cyclocreatine Phosphate (CCrP)

- **CCr is a synthetic analogue of Creatine**
- **CCrP is more stable and superior than CrP in phosphorylating ADP to ATP during ischemia at low acidity**
- **CCrP continues to synthesize ATP during ischemia**

Cyclocreatine Hypothesis



Mechanism of Action of Cyclocreatine and Cyclocreatine Phosphate

Cyclocreatine and Cyclocreatine Phosphate Treatment:

- Restores immediate cardiac contractility during early reperfusion
- Preserves high ATP in ischemic and perfused hearts
- Reduces circulating Nourin (cardiac-derived inflammatory mediator)
- Reduces myocardial cell inflammation
- Reduces myocardial cell injury
- Reduces myocardial edema
- Reduces myocardial acidity
- Reduces tissue apoptosis
- Restoration of cardiac contractility without arrhythmia

FDA ODD Approval, U.S. Patents, Publications & Presentat

1. **FDA Orphan Drug Designation (ODD) – January 17, 2018**
   - FDA Designation for the "*Prevention of ischemic Injury in Heart Transplant*

2. **U.S. Patents**
   - Nine (9) Issued Patents by the U.S. Patent Office in Washington DC

3. **Publications *in Peer-reviewed Journals***
   - American Journal of Thoracic & Cardiovascular Surgery
   - American Journal of Molecular and Cellular Cardiology
   - American Journal of Transplantation
   - American Journal Pharmacology Experimental Therapy
   - American Journal of Pathology

4. **Presentations**
   - American Heart Association
   - American College of Surgeons
   - American Association of Immunologists
   - American Society for Cardiovascular Angiography and Interventions
   - International Society for Heart Research (ISHR)
   - World Congress of the International College of Surgeons

Restoration of Cardiac Contractility During Early Reperfusion

Animal Models

1- Heart Attack (AMI)
2- Cardiopulmonary Bypass Surgery
3- Global Warm Cardiac Arrest
4- Heart Transplant

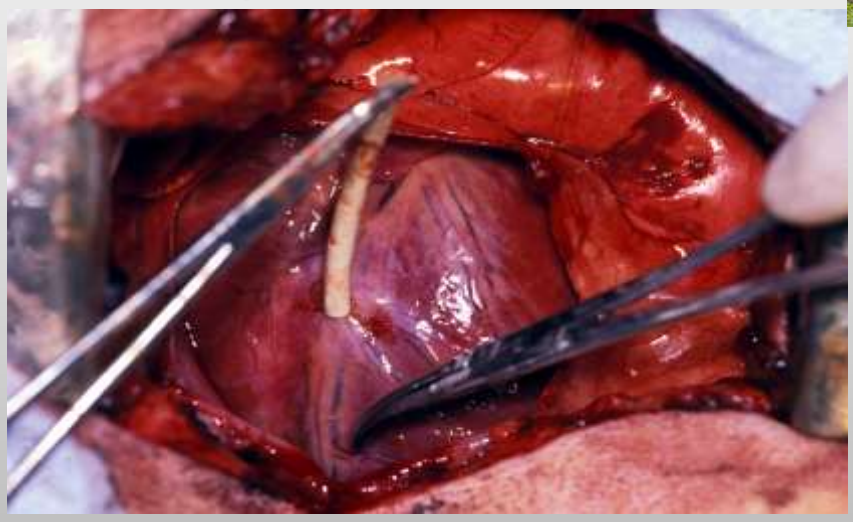
Species:

Dogs
Rats

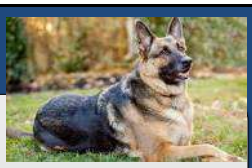
Funded by Grants from the National Institute of Health (NIH)

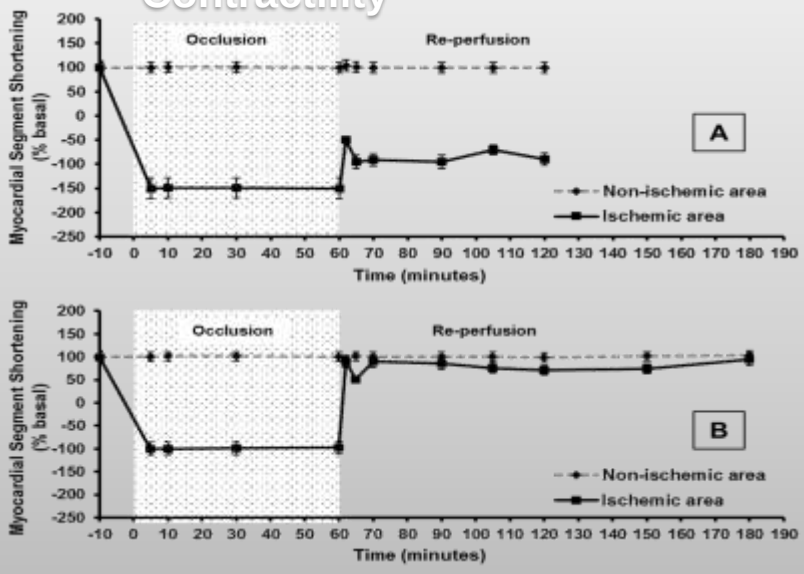
and Grants from the State of Connecticut and Maryland

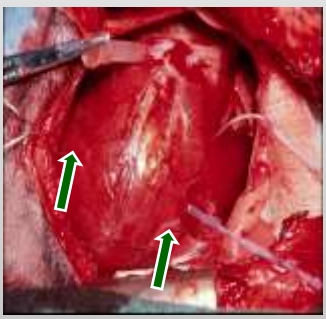
Heart Attack Model (LAD Occlusion)



Cyclocreatine Restores Strong Contractility







Cyclocreatine Preserves High Levels of ATP

Cyclocreatine Hearts:

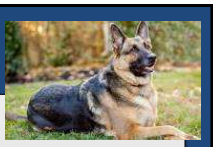
- ATP synthesis continued during ischemia & reperfusion
- ATP - 85% preservation with a loss of only 15%** after 2 hours of reperfusion

Control Hearts:

- ATP - maintained only 66% with a loss of 34%** after 2 hours of reperfusion

***ATP depletion of more than 20% ceases contractility*

Cyclocreatine Reduces Mycocardial Cell Injury

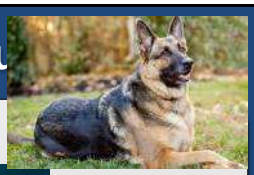


Normal Heart ➡

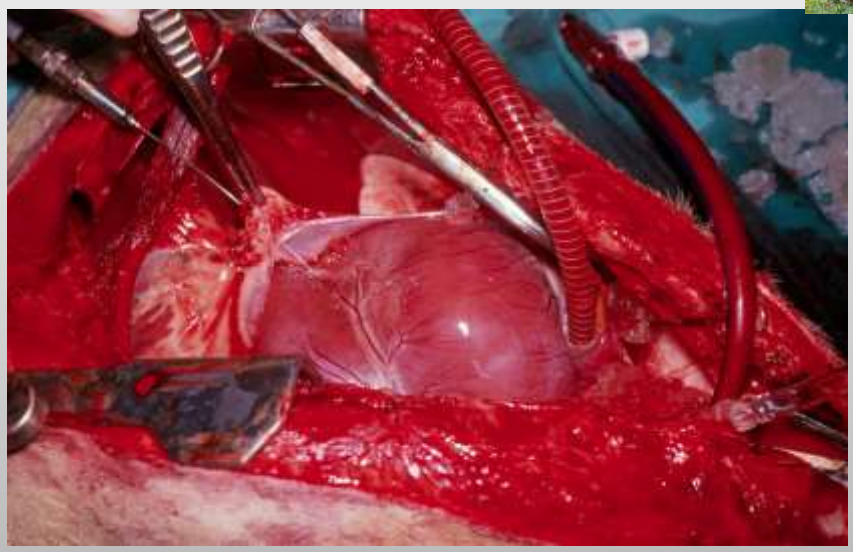
Cyclocreatine ➡

Control Saline ➡

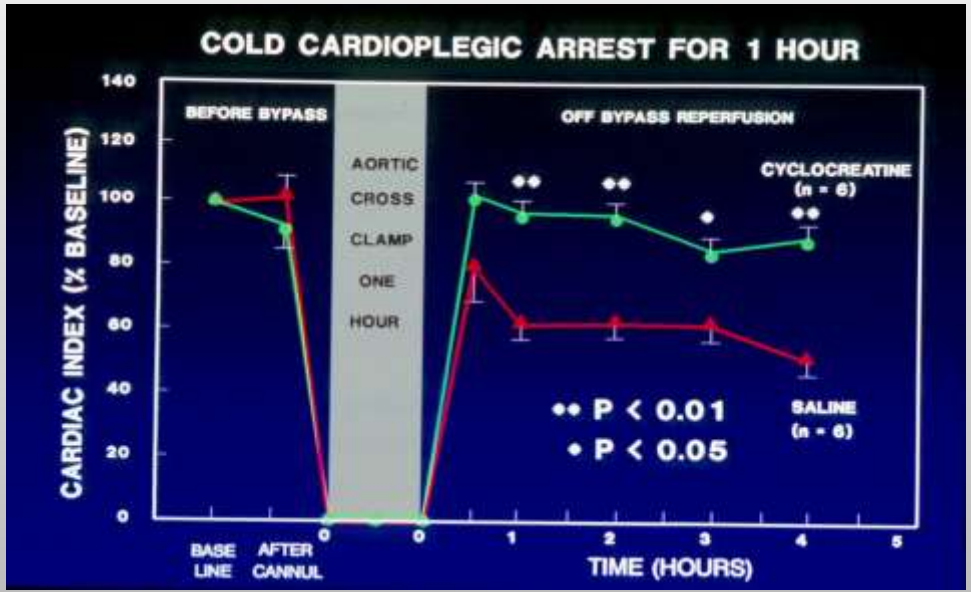
Cardiac Arrest / Bypass Surgery - Dog Stu



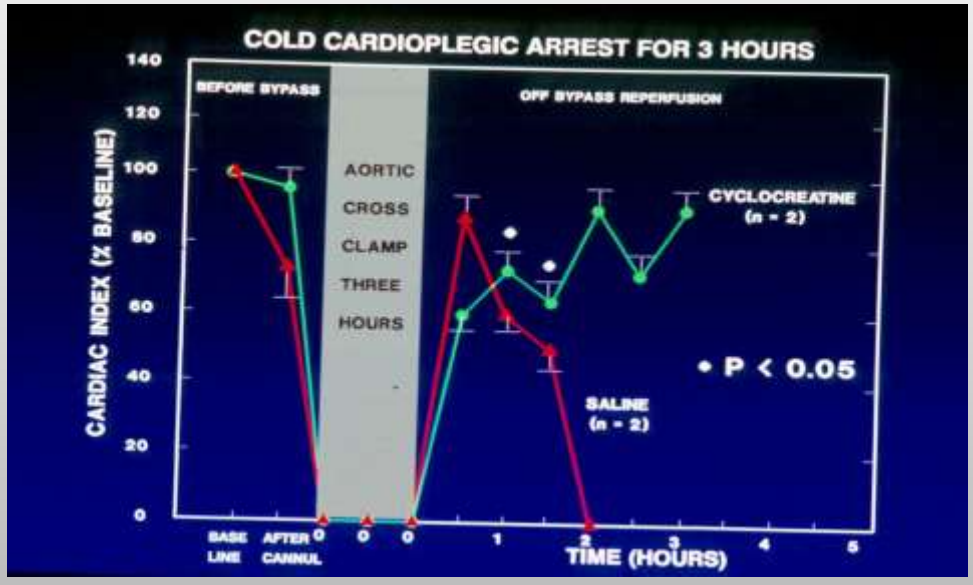
Cardiac Arrest for 1 hour Followed by Reperfusion for 2 hours



Results Bypass – 1 hour Arrest



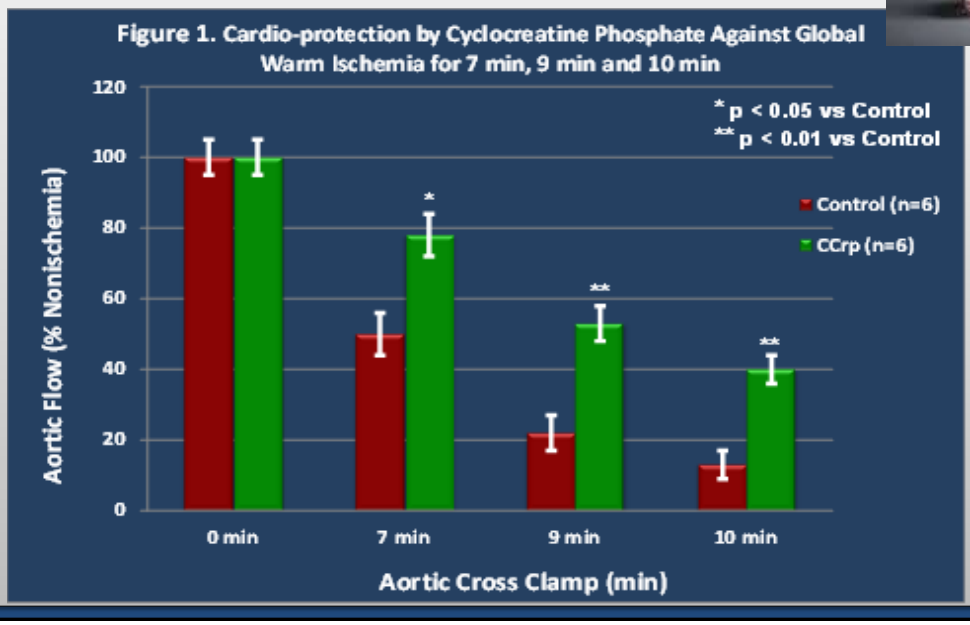
Results Bypass – 3 hour Arrest



Protection Against Arrhythmias

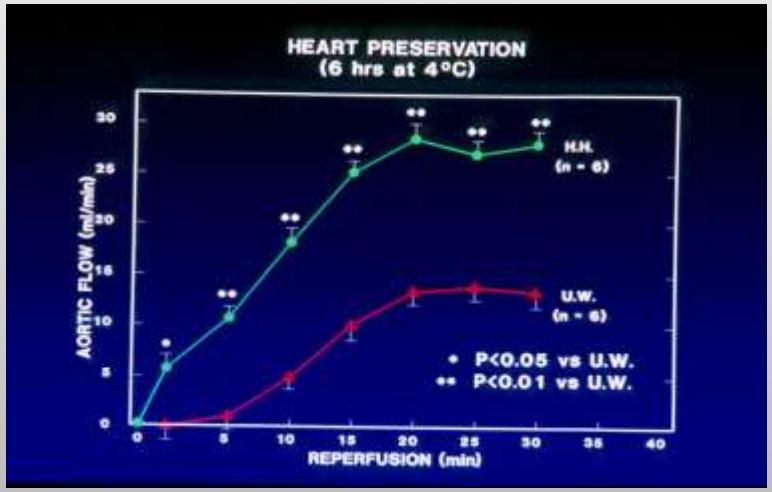
- Cyclocreatine-treated dogs resumed contractility without arrhythmias
- Saline-treated dogs required defibrillation before resuming contractility

Global Warm Cardiac Arrest – Rat Studi



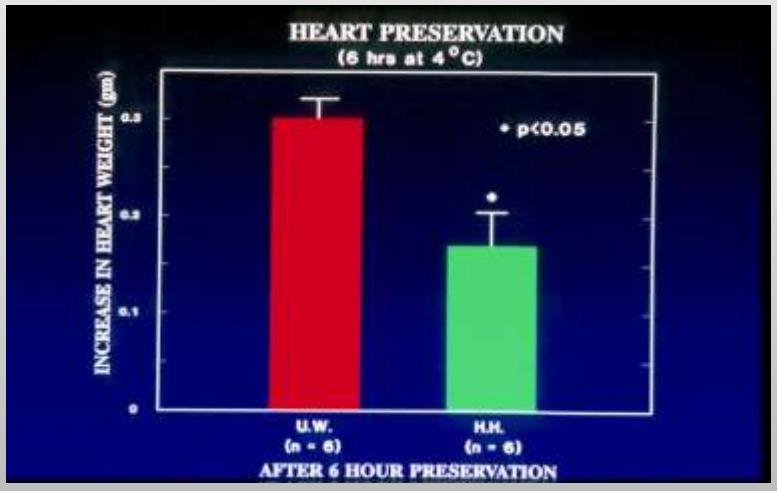
Heart Transplant - Rat Studies

Cardioprotection and better Aortic Flow function in *CCrP* Hearts (HH) compared to control (UW) after 6 hrs. of Cold Storage



Results - Heart Transplant

Reduction of weight gain in *CCrP* hearts (HH) Compared to Control (UW) after 6 hrs. of Cold Storage



Heart Transplant (Non-heartbeating donor) - Dog Studies

Protocol:

- ***Cyclocreatine*** **injected IV 60 min. before ischemia**
- **Prolonged preservation from non-heartbeating donor:**
  - **Aortic cross clamp for 1 hour (warm ischemia)**
  - **Perfuse hearts with buffer alone and *Cyclocreatine Phosphate* for 4 hours**

Measurements:

- **Myocardial ATP, acidity, cell injury marker and edema**
- **Contractility on Langendorff apparatus**
- **Measure apoptosis**

Results – Heart Beating & Acicity

Stop Heart Beating after Aortic Cross Clamping:

- Cyclocreatine: 9 minutes
- Controls: 2 minutes

Myocardial pH – Measured after 1 hr. arrest

- Baseline level: pH of 7.11
- Cyclocreatine: pH of 7.04 ± 0.1
- Controls: pH of 6.00 ± 0.25 and never returned back

Lactic Acidosis

- Reduced lactic acidosis in Cyclocreatine heart
- Measured by spectroscopic imaging on MRI

Results – ATP, Contractility & Cell Injury

Myocardial ATP

Three-fold increase in Cyclocreatine heart

Contractility

- Cyclocreatine: strong contractility for 1 hr. period
- Controls: declined after 15-20 min.

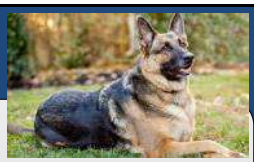
Intracellular Edema

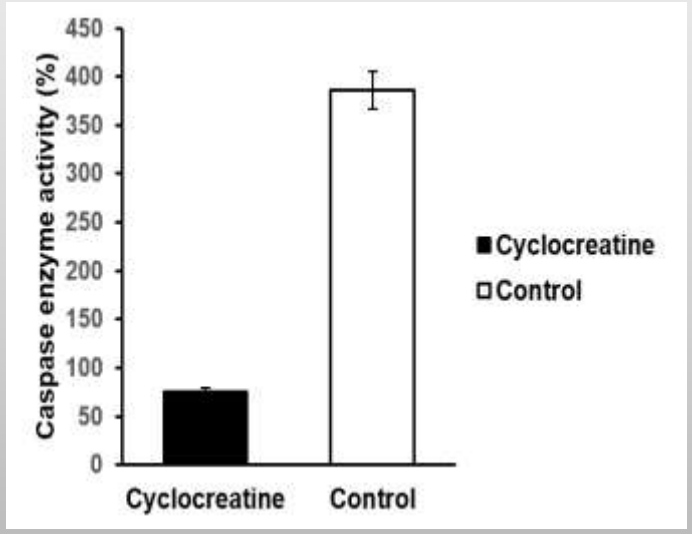
Reduced in Cyclocreatine heart as measured by diffusion weighted imaging on MRI

Cell Injury Marker Malondialdehyde

Reduced level in Cyclocreatine heart

Results – Apoptosis





4. Clinical Applications – *Predictable Ischemia*

1- AMI Patients Undergoing Percutaneous Coronary Intervention (PCI)

2- Cardiopulmonary Bypass Patients Undergoing Coronary Revascularization

3- Heart Transplantation Patients

4- High Risk Patients

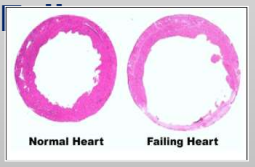
Administration of *Cyclocreatine Phosphate* Post AMI

***Cyclocreatine Phosphate (CCrP)* Administration '*Schedule*':**

1. **IV injection during ongoing myocardial infarction** (after initial assessment)
2. **Intracoronary injection immediately at reperfusion**
3. **Infuse *CCrP* for the first 6 hours of reperfusion**
4. **IV injection of *CCrP* daily for an additional 7 days** (to preserve ATP)

Administration of Cyclocreatine *Phosphate* Post AMI

1. **Provide Early Protection Critical for AMI patients:**
   - **Who have long transport time to the hospital**
   - **Who cannot get timely PCI revascularization and other treatments**
2. **Protect Hearts Against Reperfusion Injury**
3. **Increase the Salvaged Myocardium** (critical first 3 to 4 hrs.)
4. **Reduce Infarct Size and the Incidence of Heart**
5. **Improve Patients' Outcome and Quality of Life**
6. **Ease the Burden on Health Care Systems**



Other Clinical Applications - Independent Studies

Cyclocreatine & Cyclocreatine Phosphate as a Potent Bioenergetic Agents:

Clinically:

- Cyclocreatine:
  Subset of children with Autism as an important energy provider in the brain

Experimentally:

- Cyclocreatine:
  Significantly enhanced skin flap survival in the rat skin transplantation model
- Cyclocreatine:
  Neuroprotective against ischemic injury - Stroke

5. Conclusion

Cyclocreatine Phosphate Treatment:

1- Protected Heart Tissue Against Ischemic and Reperfusion Injury

2- Restored Strong Contractility During Early Reperfusion

***Cyclocreatine Phosphate Can*:**

1- Provide Early Heart Protection for AMI and Surgical Patients

2- Reduce the Incidence of Chronic Heart Failure

3- Improve Patients' Outcome and Quality of Life

Thank You.

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