

13TH EUROPEAN CARDIOLOGY CONFERENCE

December 05-06, 2016 Madrid, Spain



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NOUREXAL™ (Cyclocreatine phosphate): A new cardioprotective therapy against ischemia / reperfusion injury

Myocardial tissue has an extreme sensitivity to ischemia and hypoperfusion. The current available options to address this problem are all directed at restoring tissue perfusion in the myocardium. However, the main mechanism of myocardial ischemia that leads to reduction in cardiac function and irreversible injury is through the exhaustion of the high-energy adenosine triphosphate (ATP). Depletion of ATP during ischemia is one of the major factors that accelerates the apoptotic process of healthy myocardial tissue, leading to tissue progression to necrosis and heart failure.

Our research has demonstrated that reduction of ATP during ischemia also resulted in the rapid release (within 5 minutes) of the potent inflammatory mediator Nourin by ischemic myocardial tissue and coronary arteries. The release of Nourin was associated with early cardiac inflammation characterized by large influx of neutrophils. Our studies also indicated that Nourin purified from human ischemic hearts, is an 'early inflammatory signal' which stimulates leukocyte chemotaxis, adhesion and activation to release high levels of chemokines, cytokines, adhesion molecules and digestive enzymes. Specifically, Nourin stimulates human monocytes to release high levels of tumor necrosis factor- α (TNF- α), which is a major contributor of myocardial apoptosis.

For early reperfusion injury, the first few minutes of reperfusion after ischemic infarct constitute a critical phase that leads to impaired microcirculations and the 'no reflow' phenomenon. Inflammation is central to microcirculation obstruction (MVO) in early reperfusion and also in late reperfusion injury. Since both inflammation and ATP depletion play a key role in MVO and infarct size, we tested the cardioprotective benefits of our patented *Nourexal™* therapy in a number of animal models (dogs, rats and rabbits) of ischemia/reperfusion, including: acute myocardial infarction (AMI), global warm cardiac arrest, cardiopulmonary bypass for coronary revascularization and heart transplantation models (prolonged heart preservation and non-heartbeating donor hearts).

As described in Figure 1, we have demonstrated that administering *Nourexal™* (Cyclocreatine Phosphate - CCRp) minutes before ischemia (a) preserved high levels of ATP in ischemic myocardium; (b) reduced myocardial cell injury, acidosis and edema; (c) reduced Nourin formation in the myocardium and its blood levels; (d) reduced post-ischemic cardiac inflammation and apoptosis; and (e) restored immediate strong cardiac contractility during reperfusion without arrhythmia.

Clinical application is where myocardial ischemia is predictable and pretreatment of patients with *Nourexal™* would improve the patients' outcome and quality of life. These include patients undergoing cardiopulmonary bypass for coronary revascularization, heart transplantation and AMI patients undergoing angioplasty procedures / Percutaneous Coronary Intervention (PCI).

For AMI patients, administering *Nourexal™* during myocardial infarction and reperfusion will likely (a) protect cardiomyocytes from energy depletion and early inflammation; (b) protect the adequacy of microcirculations; (c) increase the amount of salvaged myocardium; and (d) reduce the progression of the ischemic myocardium to necrosis during the critical first 4 to 6 hours of reperfusion. Furthermore, targeting the early inflammatory mediator Nourin will likely produce the right balance between reducing the early harmful effect of inflammation without affecting its beneficial healing and scar formation.