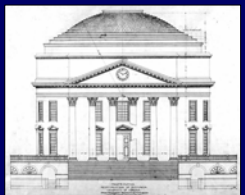


Cardiac Dysfunction Due to Pulmonary Ischemia-Reperfusion is Ameliorated by Antioxidant Therapy

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Background

- Ischemia-Reperfusion (IR) injury in pulmonary transplants, which occurs in 15-20% of patients, increases the risks of poor outcomes including: increased length of ventilation, increased ICU stay, increased hospital stay, increased mortality, and higher cost. (King RC et al., *Ann Thoracic Surg* 69:1681-1685, 2000)
- At our institution, many lung transplant patients with IR injury appear to have cardiac dysfunction out of proportion to their pulmonary injury.
- Reactive oxygen species (ROS) have been shown to be released in models of pulmonary IR injury, and in the cardiac IR literature these same substances have been shown to cause cardiac dysfunction.
- The antioxidant n-(2-mercapto-propionyl)glycine (MPG) has been shown to ameliorate injury in several models of IR injury.

Hypothesis

We hypothesized that pulmonary IR injury causes intrinsic cardiac dysfunction and that use of the antioxidant MPG can ameliorate this dysfunction.

Methods

Using an *in vivo* model of warm lung IR injury, New Zealand white rabbits (3-3.5 kg) were divided into 3 groups (n=6/group):

SHAM: right lung isolation by L hilar occlusion followed by 120 min of ventilation and perfusion.

IR: 90 min of right lung ischemia (R hilar occlusion) followed by 30 min of reperfusion (L hilar occlusion).

MPG: identical to the IR group with the administration of MPG (0.42 mg/kg/min IV).

Single lung isolation permitted avoidance of shunting blood away from the injured lung in the ischemic animals. Sham lungs were isolated for direct comparison among groups.

Procedure:

- Rabbits were anesthetized with ketamine and xylazine followed by tracheotomy and intubation, and ventilated with 100% oxygen.
- Carotid Artery was catheterized for arterial blood gases and mean arterial pressure observation.
- Internal Jugular Vein was catheterized for central venous pressure.

Methods

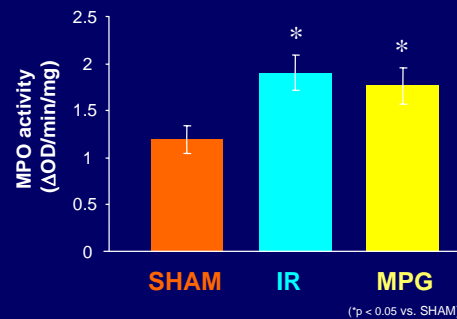
- A median sternotomy was performed before opening the pericardium and both thoraces. The ascending aorta was dissected and an ultrasound flow probe was placed in order to quantify cardiac output.
- All animals were maintained on identical fluid administration, while ventilation and anesthesia was titrated to effect.
- The lung tissue was excised and flash frozen for myeloperoxidase assay (MPO activity) to evaluate neutrophil sequestration.

Measured Parameters

- Cardiac Output (ml/min)
- PO₂ (mm Hg), PCO₂ (mm Hg), and pH
- Heart Rate (beats/min)
- Mean Arterial Pressure (MAP) ~ Afterload (mm Hg)
- Central Venous Pressure (CVP) ~ Preload (mm Hg)
- MPO activity (Δ OD/min/mg protein)

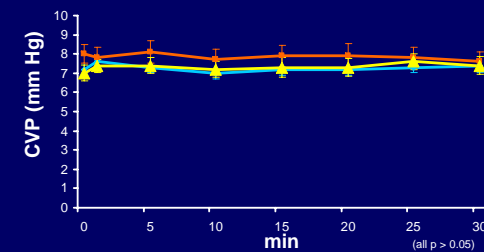
Results

Neutrophil Sequestration (MPO activity) was significantly higher in IR and MPG groups compared to SHAM.



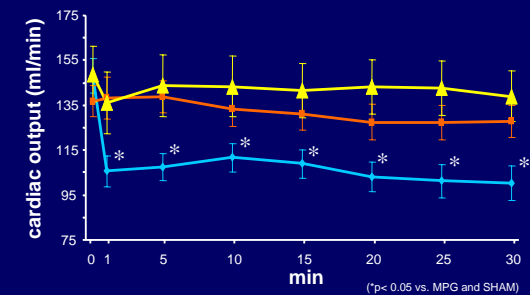
Results

Preload (CVP) did not differ among groups during reperfusion.



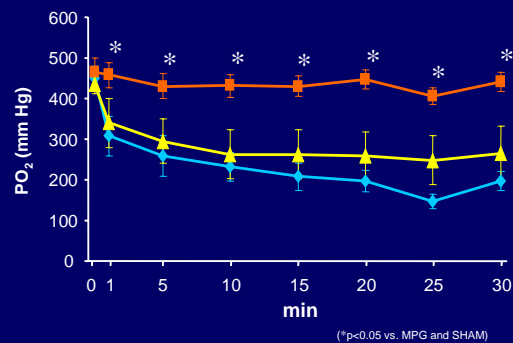
Results

Cardiac output dropped immediately and significantly in the IR group upon reperfusion, and this cardiac dysfunction was sustained throughout reperfusion compared to SHAM. The MPG group, however, experienced a non-significant immediate drop and remained above SHAM levels throughout reperfusion.

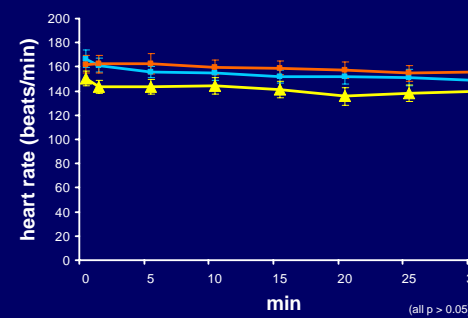


Results

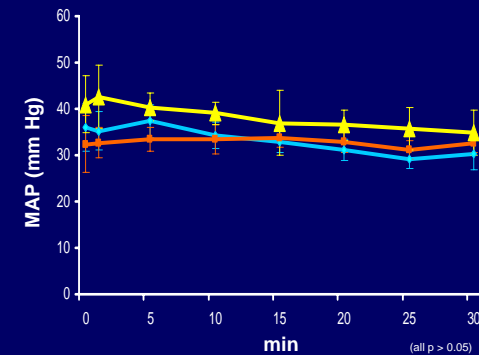
Arterial Oxygenation was significantly lower in both IR and MPG compared to SHAM, demonstrating injury to the lung. Also, the mean PO₂ remained >100 mm Hg and, therefore, unlikely to cause contractility issues.



Heart rates were similar among groups throughout reperfusion.



Afterload (MAP) did not differ among groups during reperfusion.



Summary

- Cardiac Output of IR animals dropped significantly following reperfusion. This dysfunction was sustained throughout reperfusion.
- Cardiac Output of the MPG-treated animals was preserved during reperfusion despite the fact that the IR lung was clearly injured.

Conclusions

- Pulmonary IR injury causes cardiac dysfunction that appears to be a contractility problem independent of preload, afterload and oxygenation.
- The antioxidant MPG improves this dysfunction suggesting that ROS released from the injured lung contributes to cardiac dysfunction following reperfusion of the ischemic lung.