Cardiac Function in Post-Cardiac Arrest Mice by MRI and Effect of Nitrite Treatment

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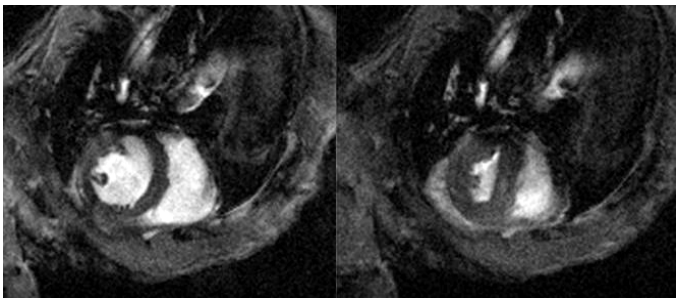
Introduction: We have examined a mouse model of cardiac arrest by cardiovascular MRI and describe the features of post-arrest cardiac function and the effect of nitrite treatment. In pre-clinical studies, nitrite (NO2) therapy has been shown to be cytoprotective following focal heart, brain and liver ischemia-reperfusion(1). We hypothesized that systemic NO2 is depleted during global ischemia (cardiac arrest) and its early repletion could protect the heart from reperfusion injury. NO2-treated mice had improved survival 22 hours post-CPR compared to saline-treated controls (HR 2.72 [95% CI:1.1-6.7]). Deaths occurred 1-6 h post-CPR and were associated with worsened cardiac ejection fraction by echo 1.5h post-CPR. Neurologic function and thermoregulation were significantly improved in NO2-treated 22h survivors vs. paired controls. Cardiac arrest depleted whole blood and plasma NO2. NO2 therapy restored levels near pre-arrest baseline with associated improvements in post-CPR oxygenation, ventilation and pH, without altering metabolic acidosis. Intravenous NO2 as adjunctive therapy to epinephrine early in CPR shows promise in improving cardiac and neurologic outcomes in a mouse model of cardiac arrest. Both left ventricle (LV) and right ventricle (RV) functional information and indicators of pressure overload in the RV obtained by MRI were of particular utility in determining the effects of nitrite treatment on the heart.
Methods: Animal experiments were performed in accordance with our institution's animal care and use guidelines. Male C57BL/6 mice (Charles River Labs, Wilmington, MA) were anesthetized with ketamine/xylazine. Mice were orally intubated and catheters placed in the right carotid artery and jugular vein. Mice were mechanically ventilated for at least 10 minutes before cardiac arrest during which time they were warmed to 36.5°C and baseline measures of temperature, mean arterial pressure (MAP), expired end-tidal CO2 (EtCO2) and heart rate by limb EKG were recorded. Cardiac arrest was initiated by potassium chloride bolus with interruption of ventilation. After 11:45 minutes of normothermic (36.5C) asystole, the animal was given 50nmol of nitrite or equivalent volume of saline placebo IV flushed in with 500ul of epinephrine (20ug/ml). At 12min post-arrest, ventilation was resumed and rapid finger compressions delivered until the return of spontaneous circulation (ROSC). Animals were ventilated an additional 60 minutes with close invasive monitoring and received protocolized post-ROSC care. Animals were examined by MRI 24 hours post-arrest. MRI Experiments were carried out in a 7.0T, 16 cm horizontal Bruker MR imaging system (Bruker, Billerica, MA) with Bruker ParaVision 3.0.2 software. Mice were anesthetized with 1.0-2.0% isoflurane and imaged with ECG, temperature and respiratory detection using a 38 mm Bruker birdcage volume coil. Magnevist (Berlex, Montville, NJ) diluted 1:10 with sterile 0.9% saline, was administered subcutaneously at a dose of 0.3 mmol Gd /kg. T1 weighted gradient echo cine images (TR/TE= 12 to 15/3.2 ms, 30 degree flip angle, 2-4 averages, 1.0 mm slice thickness, 2.5 to 2.8 cm field of view, 256x256 matrix, respiratory and ECG-gated, were acquired in short axis from base to apex (6 slices). Cardiac MRI data was processed using CAAS-MRV-FARM software (Pie Medical Imaging, Netherlands.)
Results and discussion: RV and LV volumes and ejection fractions (EF) were determined by MRI for nitrite treated and saline treated mice. At 24 hours post arrest RV dilation is a prominent feature post-cardiac arrest in both treated and untreated groups. Cardiac MRI demonstrates marked RV dilation and reduction in RVEF. The RV EFs were decreased and RV volume increased in both groups compared to normal mice, and nitrite treated mice had higher RVEF than saline treated. The LVEF was near normal and not statistically different between groups. RV pressure overload evidenced by septal bowing (**Fig. 1**), was observed in 4/6 nitrite treated *vs.* 3/7 saline treated mice. The nitrite treated mice had higher mean RV EF. This finding suggests that nitrite does not reduce RV pressure overload but improves RV contractility.
Conclusions: Cardiovascular MRI demonstrated the existence and extent of RV dysfunction in a mouse model of cardiac arrest. MRI outcomes indicate RV ejection fraction and contractility are improved by nitrite treatment. In other measures of therapeutic efficacy, systemic nitrite after global ischemia is associated with improved pulmonary blood flow, cardiac function, survival and neurological function in survivors (1). Nitrite therapy offers promise in future trials of therapy after cardiac arrest.



A **B**

Figure 1. Short axis gradient echo cine frames of a mouse 24 hrs. post-cardiac arrest with features of right ventricular dysfunction; A. End-diastole, RV dilation; B. End- systole, septal bowing.

References: 1. Dezfulian C. *et al.*, Cardiovasc.Res. 75(2), 2007
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