Cadiac MRI Evaluation of a Rat Model of Pulmonary Hypertension

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Background:

Primary pulmonary hypertension (PPH) is a life threatening disease characterized by increased pulmonary vascular resistance. This results in right ventricle (RV) hypertrophy, dilation, and potential RV failure due to increased right ventricular afterload[1]. The pathological process involves progressive endothelial dysfunction, smooth muscle hypertrophy and hyperplasia leading to intimal fibrosis and thrombosis of small pulmonary arterioles. Current treatment strategies involve the use of pulmonary vasodilators, primarily intravenous administration of prostacyclin (PGI2) which improves symptoms, morbidity and mortality of patients. Potential therapies include gene therapy to up regulate endogenous pulmonary vasodilators.

Introduction:

Animal models of pulmonary hypertension have included knockout mice, hypoxia in rats and mice, and monocrotaline (MCT) induced pulmonary hypertension in rats. MCT is a toxic plant alkaloid that causes endothelial cell damage, pulmonary vascular injury, and pulmonary hypertension after a single injection in rats and thus has become a well-established model to study this disease[2]. Most animal studies use pressure catheters and echocardiograms to analyze the pulmonary arterial pressure, cardiac output, and right ventricle thickness. 2D-Echocardiography can be used to evaluate RV ejection times and wall thickness, but not RV mass, volumes or ejection fraction. MRI is being used clinically on patients with PH receiving treatment as a way to monitor the RV size and function[3]. Therefore we sought to use MRI to characterize the RV size and ejection fraction and to determine the potential use of MRI in evaluation of the RV during experimental therapies in the rat model of MCT induced PH.

Methods:

Rats weighing 200-225g were divided into five groups (4 escalating doses of MCT and a PBS control) and evaluated by MRI and pressure catheters for hemodynamics at 4 weeks post-injection. MRI of the rat cardiac cycle was performed at the University of Florida, McKnight Brain Institute's Advanced Magnetic Resonance Imaging and Spectroscopy Facility. Animals were imaged on a 4.7T Oxford Magnet using a Bruker Avance console and Paravision software. The animals were anesthetized with 1.5-2% isoflurane and 1L/min oxygen and monitored using the Small Animal Instrument (SAI) monitoring and gating system for respiration rate and cardiac triggering. The heart was centered in a custom built receive-only quadrature saddle surface coil tuned to 200 Mhz. The animal and receive coil were inserted into an 8.8cm diameter transmit-only quadrature volume coil. Dorsal and sagittal images were acquired using a cardiac gated cinetographic gradient echo sequence with the following parameters: FOV=70x30mm, matrix=256x128, TR=12msec, TE=2.2msec, NEX=4AVG, slice thickness=1.5mm, 14 frames with one frame per 12ms. Based on the sagittal and dorsal views, short axis images were prescribed from base to apex and collected with the Cine-GE sequence described above except with FOV=40x30mm, TR=12msec, TE=2.3msec, and 14 frames to capture the entire cardiac cycle. After MRI images were obtained, a pressure transducer catheter was placed into the RV of the rats and advanced into the pulmonary artery (PA) to acquire hemodynamic measurements. Tissues were harvested for histological evaluation. LV, RV, and cardiac cross sectional areas (CSA) were measured using a semi-automated segmentation program (IDL) on the short axis midventricle images (Fig 1).

Results:

Measurements were made of the RV free wall thickness as a measure of RV hypertrophy (Figure 1). There is a 2-fold increase in RV wall thickness between the PBS and 100 mg/kg MCT groups which is significant (Table 1). The measurements of the RV free wall by MRI have excellent correlation with the measured PA pressure (Pearson r = .98, p=.0002). End systolic RV CSA was significantly elevated in the MCT treated group compared to the PBS controls (0.17±0.02 cm^2 vs. 0.08±0.01 cm^2; mean±SEM;p=0.002). The RV:LV area ratio in diastole was also significantly elevated (0.87±0.03 vs. 0.51±0.04; mean±SEM; p=0.001).

Discussion:

MRI with cardiac gating for rats resulted in excellent images of rats with PH. RV wall measurements can be made with precision. We are confident that accurate RV mass, volumes and ejection fraction can be measured and correlated with invasive hemodynamics. MRI is a useful modality for characterization of the RV in animal models of PH and will be useful for evaluation of treatment strategies for this condition.

References:

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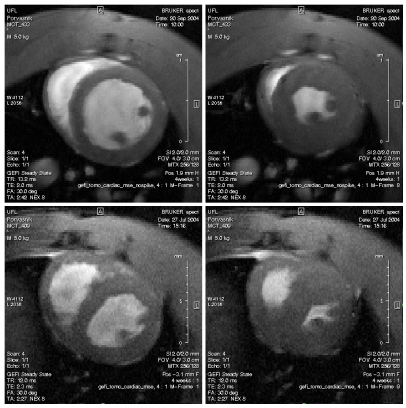

Fig. 1: Four weeks post-injection, PBS injected animal (top frames) with normal, thin RV wall while the lower frames exhibit RV hypertrophy and enlargement after 100mg/kg dose of MCT.

Table 1:

Group	RV wall (mm)	PA pressure (mmHg)
PBS (n=3)	0.68 +/- .08	19 +/- 2
100mg/kg MCT (n=3)	1.39 +/- .07	47 +/- 4
p value	.01	.0007