4D MR Velocity Mapping using PC VIPR to Investigate the Hemodynamics of Acute Pulmonary Hypertension in a Dog Model

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Purpose: To demonstrate the utility of 4D MR Velocity Mapping using PC VIPR to quantify cardiovascular hemodynamics in a dog model.

Background: The pulmonary vasculature is a highly distensible system, which generates little resistance to flow such that pulmonary artery blood pressure is low. In patients with pulmonary arterial hypertension (PAH), blood pressure and resistance in the pulmonary circulation are elevated, inducing changes not only in the structure and function of the pulmonary vasculature but also the right ventricle. PAH is a detrimental, rapidly progressive disease in which the cause of death is typically right ventricular failure. The loss of proximal arterial distensibility is highly correlated with mortality in PAH patients [1, 2]. However, the ways in which pulmonary vascular stiffening accelerates heart failure in patients with PAH are still not well understood. Non-invasive imaging techniques have proven to be useful in PAH diagnosis and as a prognostic tool [1, 3]. Our hypotheses were that i) proximal pulmonary artery stiffening impairs right ventricular (RV) function in PAH by altering blood flow patterns and that ii) magnetic resonance imaging (MRI) could be effectively used to demonstrate this relationship in a dog model of the disease. To establish an experimental basis to test these hypotheses, we introduced an acute model of PAH by micro-bead embolization. 2D phase contrast MR (2D PC) and 4D velocity mapping using PC VIPR [4] were applied to study regional area change (RAC) of the proximal PA and the flow characteristics of the pulmonary circulation both at baseline and after embolization.

Methods: After IACUC approval, four adult female beagles were induced with propofol and maintained under anesthesia with isoflurane. Baseline pulmonary arterial pressures (PAP) were measured by right heart catheterization (RHC).

Induction of pulmonary hypertension was achieved by injecting micro-beads (150-500μm) into the right atrium and ventricle. The embolization effort was confirmed by RV pressure monitoring and digital subtraction angiography (DSA, see fig. 1).

The *MRI studies* were performed before (baseline) and after embolization on 3T clinical systems (Discovery MR 750, GE Healthcare, Waukesha, WI). Due to technical failure, high quality MR images could not be obtained in one dog at baseline. RV function was measured per clinical standard from contiguous axial, ECG-gated bSSFP images. Central pulmonary artery distensibility (relative cross-sectional area change, RAC) was determined from time-resolved 2D PC acquisitions positioned in the main PA (MPA). Quantification of RV function was performed using the CV Mass and Flow Analysis software package on an Advantage Workstation (version 4.2, GE Healthcare, Waukesha, WI).

4D flow-sensitive PC MRI was performed with a previously described, three-dimensional (3D) radially-undersampled PC acquisition, PC VIPR (Phase Contrast Vastly undersampled Isotropic Projection Reconstruction) [4]. Typical imaging settings were: FOV=32x32x22cm, readout=256, TR/TE= 6.7/2.4, spatial resolution=isotropic 1.3mm. Data was reconstructed to 20 time frames for dynamic post-processing using retrospective ECG gating and a temporal filter for view sharing. The heart and thoracic vasculature were segmented using commercial image processing software (Mimics Materialise, Ann Arbor, MI) and stored in a format specific to the visualization software Ensight (CEI, Apex, NC). Particle emitter planes were placed in the superior vena cava (SVC), inferior vena cava (IVC), tricuspid valve (TR), mid RV, MPA, right and left pulmonary artery (RPA, LPA, respectively; see fig. 2) and used to emit time-resolved particle traces and 3D streamlines. Visualization was reviewed in consensus by three expert readers. Flow patterns (vortices, helicity, ante- and retrograde flow) were recorded with respect to their presence in the RA, RV, MPA, RPA and LPA.

Following animal care protocol, three dogs were humanely euthanized with pentobarbital intravenously after the procedures; one dog died of presumed worsening PH before post-embolization tests could be performed.

Results: Mean PA pressure significantly increased in embolized dogs (38.6 ± 2.5 mmHg vs. 21 ± 6.5 mmHg, p=0.01) (Fig. 3A) confirming the development of pulmonary hypertension initially verified by DSA (Fig. 1). PA RAC (43.3 ± 4.7% vs. 34.9 ± 3.8%, p = 0.07) and RV ejection fraction (RVEF) (54.7 ± 8.2% vs. 48.4.9 ± 8.5%, p = 0.4) tended to decrease in the hypertensive dogs and a good correlation (R^2 = 0.64) was found between RVEF and PA RAC (Fig 3B.), which supports our hypothesis. Furthermore, abnormal blood flow features in the hypertensive dogs were evident (Fig. 2). These include higher flow velocities, increased vorticity in the right ventricle and pulmonary artery during systole and very low flow in the RV outflow track during diastole. Early pulse wave return was also seen in the hypertensive dogs as evidenced by the shorter travel distance of the streamlines compared to the dogs at baseline.

Summary: Acute PAH was successfully induced in dogs by micro-bead embolization. While the observed decreases in RAC and RVEF were not statistically significant, the correlation analysis between RVEF and PA RAC supports previous findings in humans the likely mechanism by which loss of PA distensibility impairs RV function is the abnormal hemodynamics after embolization. As PA distensibility decreases, pulse waves return more quickly to the RV and the afterload during ejection is increased. We interpret this as the most likely cause of the reduced RV function. Future work will focus on larger number of animals and expanding this initial work to a chronic model. This approach may provide valuable insights into the mechanisms of RV failure in acute and chronic PAH in patients.

**References:** [1]Gan Chest. 2007; [2]Hunter AHJ. 2008; [3]Kreitner ER. 2007; [4] Gu, AJNR 2005
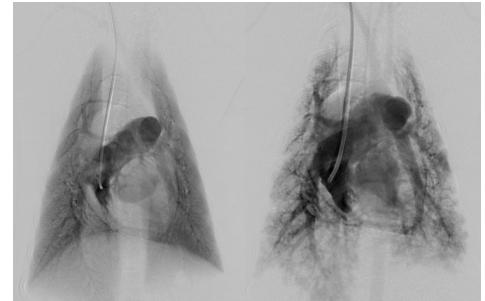
Fig. 1. Confirmation of embolization success. DSA images from before (left) and after (right) embolization show the creation of multiple wedge-shaped areas with decreased contrast indicative of the embolization with micro-beads.
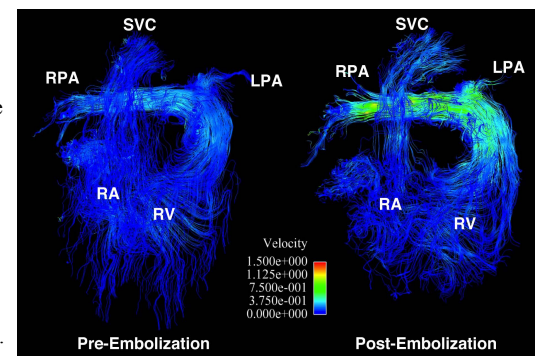
Fig. 2. Streamline visualizations in the right heart pre- and post-embolization. In addition to alterations in flow patterns in the RV, flow acceleration is observed in the main and branch pulmonary arteries.
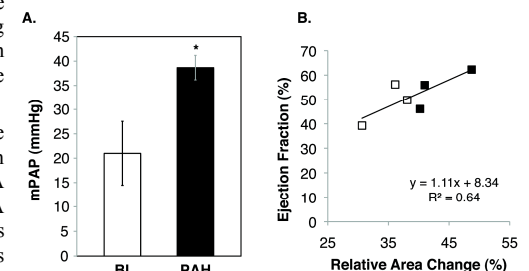
Fig. 3. A. Pulmonary arterial pressure. Significant differences is represented by * (p<0.05). B. Correlation between relative area change and right ventricular ejection fraction. RAC = (A$_{sys}$ – A$_{dias}$)/A$_{sys}$, where A$_{sys}$ and A$_{dias}$ are PA cross sectional areas at peak systole and diastole, respectively.