EVALUATION OF SEVERE ANEMIA BY QUANTITATIVELY MEASURING MULTI-ORGAN OXYGEN USING ^{19}F MRI IN A RAT MODEL

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Introduction: Banked red blood cells are frequently transfused in anemic patients to improve oxygen delivery and provide adequate oxygenation of tissues. Unfortunately, blood transfusions carry risks of disease transmission, fatal immunogenic reactions, and a decrease in immune function. Prior human studies from our institution have demonstrated that increasing the amount of dissolved oxygen in the blood, although known to only be a small fraction of the total oxygen content, reverses the decline in cognitive function and decreased energy level associated with acute, severe, isovolemic anemia (1). Although previous models have evaluated global effects of severe anemia such as changes in cardiac output, blood pressure, lactate levels, and cellular injury, changes in tissue oxygen levels (the endpoint of interest), in multiple organs have not been examined. A quantitative method using fluorine-based (^{19}F) MRI (2,3) allows direct measure of regional dynamic oxygen pressure (pO_2) changes, is minimally invasive and previously validated. This method uses the linear relationship between longitudinal relaxation rate (R_1) of hexafluorobenzene (HFB), and pO_2. The R_1 of HFB has minimal temperature dependence, and is not significantly influenced by pH or CO_2. We successfully used the method in a rat model to compare tissue oxygen pressures (ptO_2) in multiple organs under normal and hyperoxic conditions (4,5). The goal of this preliminary study is to 1) quantify the decrease in organ oxygen levels induced by severe anemia (hemoglobin < 5 mg/dL) and 2) determine if increasing the arterial oxygen pressure (paO_2) with inspired fraction of oxygen (FiO_2) of 1.0 would reverse the decrease in tissue oxygen levels from severe anemia.

Methods: Sprague-Dawley rats (n=3) were anesthetized with isoflurane and ventilated via tracheostomy. A femoral arterial line was placed for blood pressure monitoring and arterial sampling. Rats were kept euthermic and eucapnic throughout the study. HFB (50 µl) was injected into each organ of interest using a 33 ga. needle. The FiO_2 was randomly selected as 0.3 or 1.0. An FiO_2 of 0.3 was used in place of air in order to produce paO_2 values of hemoglobin saturation near 100% and thereby isolate the effects of increasing dissolved oxygen alone with the increase in FiO_2 to 1.0 (oxygen). After equilibration 0.2 ml of arterial blood was drawn for paO_2, carbon dioxide ($paCO_2$), and hemoglobin (Hb) analysis. A Varian 7T imaging system with a ^{19}F/^{1}H dually tunable birdcage volume coil was used. Data were acquired using the fluorocarbon relaxometry echo planar imaging for dynamic oxygen mapping (FREDOM) sequence combining pulse burst saturation recovery (PBSR) and echo planar imaging (EPI) to acquire longitudinal relaxation time (T_1=1/R_1) weighted ^{19}F images. Alternated relaxation delays with variable acquisitions (ARDVARC) were used to reduce clearance effects. T_1 was calculated voxel by voxel (1x1x5 mm) with a three-parameter fit. PtO_2 was calculated using a linear calibration curve of pO_2 vs. R_1 at 7T. Spin echo proton images were acquired as a reference. After the scan, the inspired gas was changed to the other value (FiO_2=1.0 or 0.3). After equilibration, the imaging procedure was repeated. Each rat then underwent continuous hemodilution by simultaneously withdrawing 45 ml/kg of arterial blood while infusing an equivalent volume of colloid (Hextend, BioTime Inc., Berkeley, CA) via the tail vein over 40 min. After equilibration, the rat was rescanned at FiO_2 of 1.0 and 0.3, with arterial samples taken before and after the set of scans as previously described.

Results: Mean paO_2 was 117.7±27.8 mmHg (FiO_2=0.3) and 498.0±27.5 mmHg (FiO_2=1.0) before hemodilution, 108.7±31.5 mmHg (FiO_2=0.3) and 492.0±34.7 mmHg (FiO_2=1.0) after hemodilution. Mean Hb was 12.0±0.8 g/dL before hemodilution, and 4.2±0.6 g/dL after hemodilution. All organ ptO_2 values were increased by increasing the FiO_2 from 0.3 to 1.0 under both normal and anemic conditions. All organ ptO_2 values at FiO_2 of 0.3 were decreased by hemodilution, although only by a small amount.

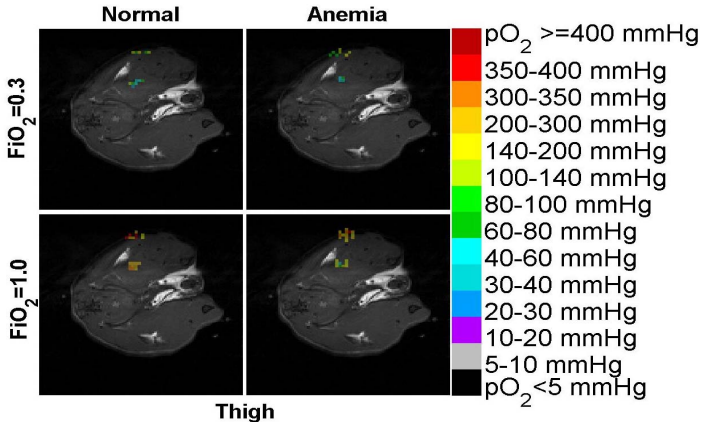

Figure 1. PtO_2 mapping of muscle and skin from one study superimposed on the corresponding proton images at FiO_2=0.3 and 1.0 under normal and anemic

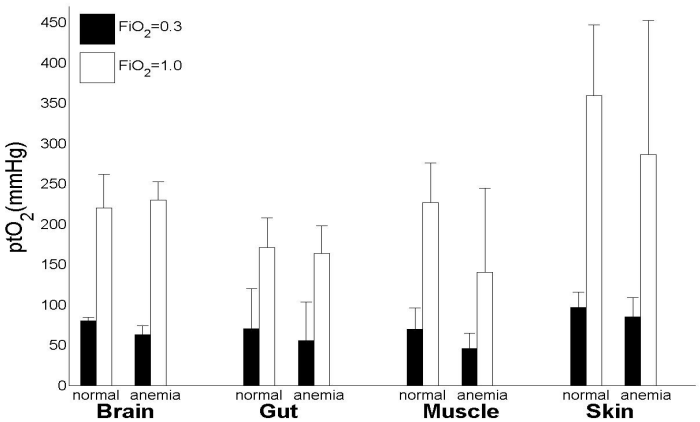

Figure 2. Mean values of ptO_2 over the selected ROI ± standard deviation among 3 rats at FiO_2=0.3 and 1.0 under normal and anemic conditions.

Discussion: The ^{19}F MRI method allows quantitative measurement of decreases in oxygen levels in multiple organs during severe anemia. Although the small number of rats (n=3) did not allow adequate power for statistical analysis, all organs had a decrease in ptO_2 at FiO_2=0.3 with severe isovolemic anemia. This decrease was more than reversed by increasing the FiO_2 (dissolved oxygen). These preliminary findings suggest the value of supplemental oxygen in increasing organ oxygen levels may be greater than the small amount of increase in arterial oxygen content. In addition, this ^{19}F MRI method may have value in assessing the effectiveness of artificial blood substitutes and other resuscitation fluids and protocols.

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References: **1** Weiskopf RB, et.al., (2002) *Anesthesiology,* 96(4):871-7. **2** Mason RP, et al., (1996) *NMR Biomed*, 9(3): 125-34. **3** Zhao D, et al., (2004) *Methods Enzymol,* 386:378-418. **4** Liu S, et al., (2008) *16th ISMRM, Toronto,* p197. **5** Liu S, et al., (2008) *5th UCSF Radiology Imaging Research Symposium,* p12.