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

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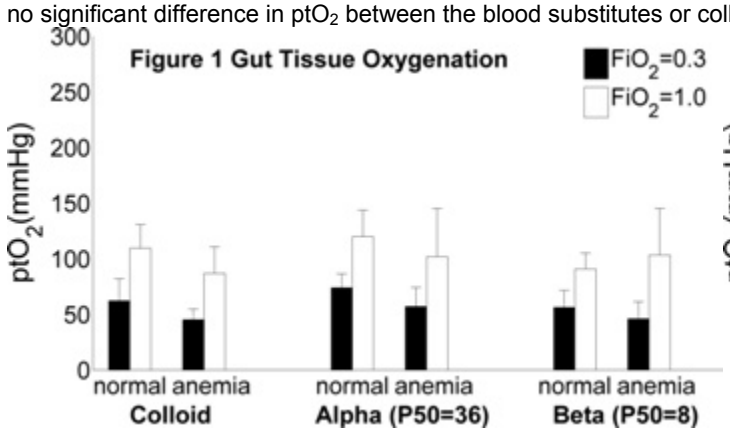
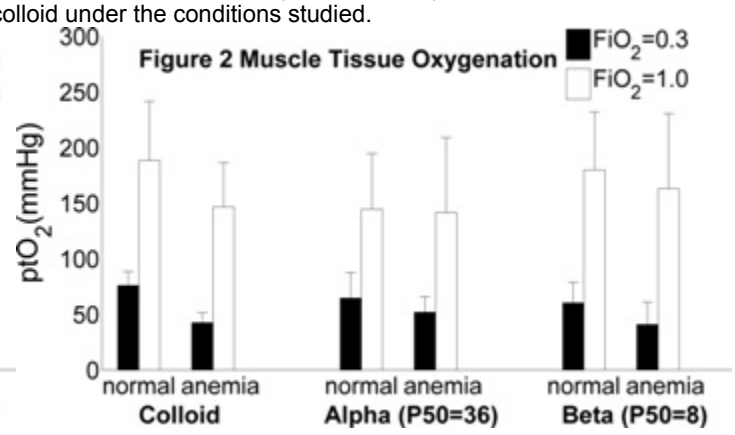
Introduction: A variety of oxygen-carrying artificial blood substitutes are under development to reduce the need for blood transfusion, in an effort to reduce risks of disease transmission, fatal immunogenic reactions, and a decrease in immune function associated with donated blood. A recent meta-analysis examining safety of hemoglobin based oxygen carriers (HBOCs) noted an increased risk of death and myocardial infarction with their use in clinical trials (1). Delivery of oxygen to tissue is complex and relies on a variety of factors including hemoglobin oxygen affinity, yet current HBOCs under development vary greatly on oxygen binding characteristics and little if any research has examined the effects of these binding characteristics on tissue oxygen delivery. A minimally invasive ^{19}F MRI method (2-3) has been validated to quantitatively image tissue oxygen pressure (ptO_2). It is based on the linear relationship between longitudinal relaxation rate (R_1) of hexafluorobenzene (HFB), and oxygen pressure (pO_2). Using this ^{19}F MRI technique, we compared ptO_2 changes in multiple organs during isovolemic anemic hemodilution using high affinity or low affinity HBOCs compared to a colloid control under both normoxic and hyperoxic conditions in a rat model.

Methods: Two polymerized HBOCs matched for Hb concentration, molecular size, and oncotic pressure, but with differing P50 values (the partial pressure of oxygen at which 50% of the Hb is saturated; normally 27mmHg in human adults) were created and donated by Sangart Inc. for the study. The two HBOCs used had a P50 of 36 (alpha) and 8 (beta). Rats (n=8 per group) were anesthetized and ventilated via tracheotomy. An arterial line was placed for blood pressure monitoring and arterial blood gases (ABG). Rats were kept euthermic and eucapnic throughout. HFB (50 µl) was injected into each organ of interest (muscle, skin, and gut). The fraction of inspired oxygen, FiO_2 (0.3 or 1.0) was administered in random order and ABG and hematocrit measured. A 7T magnet with ^{19}F/^{1}H dually tunable birdcage coil was used for imaging. 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 (2-3). The alternated relaxation delays with variable acquisitions (ARDVARC) scheme was used to reduce clearance effects. The corresponding number of averages was set to 1 for all delays. T_1 was calculated voxel by voxel (1x 1x 5 mm) with a three-parameter fit. PtO_2 was calculated using a linear calibration of ptO_2 vs. R_1 of HFB at 7T. Spin echo multiple slice proton images of the corresponding organs were acquired as a reference. The FiO_2 was then changed to the alternate value (FiO_2=1.0 or 0.3) and imaging repeated. Rats were randomly assigned to a substitute group (alpha, beta, or colloid). Each rat underwent hemodilution by simultaneously withdrawing 45 ml/kg of arterial blood while infusing an equivalent substitute volume via the tail vein over 40 min. After equilibration, the rat was rescanned at a FiO_2 of 1.0 and 0.3, with arterial and hematocrit samples taken before and after. Wilcoxon and Kruskal-Wallis tests were used for statistical analysis.

Results: Mean arterial oxygen pressure (paO_2) was 114±14 mmHg (FiO_2=0.3) and 538±55 mmHg (FiO_2=1.0). Mean hematocrit was 39 ± 3% before hemodilution, and 12 ± 1% after. Figures show mean ptO_2 changes in gut and muscle. The ptO_2 was significantly increased with FiO_2 = 1.0 compared to 0.3 under all conditions ($p<.05$). The ptO_2 was variably decreased by hemodilution. There was no significant difference in ptO_2 between the blood substitutes or colloid under the conditions studied.





Discussion: The ^{19}F MRI method allows quantitative measurement of decreases in tissue oxygen in multiple organs during severe anemia. Although these experiments do not support a significant effect of HBOC binding characteristics on ptO_2 for the conditions studied, they emphasize the need for further research in determining modifiable characteristics to optimize oxygen delivery. These findings also highlight the impact of high inspired oxygen on organ oxygen levels. In our study, the FiO_2 appears to be a greater factor than oxygen carrier, despite the known small contribution of dissolved oxygen to total content.

Acknowledgement: Research support by The Foundation for Anesthesia Education and Research, and a UCSF CTSI Award.

References: 1) Natanson C, et al., (2008) JAMA, 299(19):2304-12. **2)** Mason RP, et al., (1996) *NMR Biomed*, 9(3): 125-34. **3)** Zhao D, et al., (2004) *Methods Enzymol,* 386:378-418.