# Hyperpolarized $^{129}$Xe MR of the sickle cell disease: preliminary findings

**Y. Chang[1], T. Altes[1], I. M. Dregely[2], S. Ketel[3], I. C. Ruset[2,3], J. F. Mata[1], F. Hersman[2,3], J. P. Mugler III[1], and K. Ruppert[1]**

[1]Radiology, University of Virginia, Charlottesville, VA, United States, [2]Physics, University of New Hampshire, Durham, NH, United States, [3]Xemed LLC, Durham, NH, United States

**Introduction:** Sickle cell disease (SCD), or sickle cell anemia (SCA), is caused by genetic mutations in hemoglobin (HGB) with the most common mutation termed HGB-S. Patients with two copies of the HGB-S gene (homozygous) have chronic anemia, increased susceptibility to certain infections and recurrent episodes of pain. The pain crises are caused by the abnormal sickle-shaped conformation of the red blood cells that obstruct capillaries of some organs causing ischemia and pain. In the lung, these veno-occlusive events are termed acute chest syndrome. A common cause of morbidity in later life is lung disease characterized by pulmonary hypertension. However, the relationship between the development of pulmonary hypertension and chronic anemia, episodes of acute chest syndrome, and perhaps other factors is not well understood. In recent years hyperpolarized $^{3}$He and $^{129}$Xe were used widely as contrast agents in studies of the lung non-invasively [1, 2]. Xenon, a heavy inert gas, not only dissolves in tissue and blood plasma (TP Xe), but also binds to hemoglobin (BL Xe). These two types of dissolved-phase xenon exhibit distinct chemical shifts in human lungs: TP Xe at 197 ppm and BL Xe at 217 ppm. Thus, they can be easily distinguished and compared. In addition to observing the dissolved-phase Xe directly, Xe exchange spectroscopy and Xenon polarization Transfer Contrast (XTC) MRI [4, 5] are also powerful in studying the gas exchange processes in the lung. All of these make NMR of hyperpolarized $^{129}$Xe an ideal tool to study SCD in a non-invasive manner.

**Methods:** Data were acquired in two subjects with SCD and one healthy subject at 1.5T (Avanto, Siemens Medical Solutions) using a flexible chest RF coil (Clinical MR Solutions, Brookfield, WI). Enriched xenon gas (87% Xe129) was polarized by collisional spin exchange with an optically-pumped rubidium vapor using a prototype commercial system (Xemed LLC, Durham NH) ; the Xe129 polarization was 15-20%. All experiments were performed under a Physician's IND for imaging with HXe-129 using a protocol approved by our institutional review board. Informed consent was obtained in all cases. The two SCD subjects are homogygous for the HGB-S mutation (Subject 1: 23 yr old male, HBG 5.4 g/dL, hematocrit 15.5%, FEV1 66% predicted; Subject 2: 18 yr old male, HGB 9.1 g/dL, hematocrit 25.4%, FEV1 83% predicted). Note the lower limit of normal for HGB is 14 g/dL and for hematocrit is 40% so both subjects were anemic. The normal subject subject inhaled approximately one liter of gas containing a mixture of HXe-129 (~ 0.5 L), room air and oxygen. This dose had to be reduced for the SCD subjects due to their low xenon. Instead, subject 1 (subject 2) inhaled a mix of 150 (250) cc xenon gas and 300 (500) cc of RA and $O_2$. Data were collected during the breath holds after the inhalation of Xe. The MR sequence acquires a single FID (bandwidth 32.6 Hz, 1024 data points) following a 90 degree RF excitation pulse (1.8 ms Gaussian) at 208 ppm. To ensure a fair comparison, the excitation RF pulses were placed 900 ms after the dissolved-phase Xe was completely saturated with three successive 90 degree pulses for both normal and SCD subjects. For data analysis, the real channel of the dissolved-phase signals were fitted with a double-Lorenzian function [3], one for TP Xe at 197 ppm and one for BL Xe at 217.5 ppm. To phase both Lorenzians correctly without the influence of one another, two phase factors were introduced in the function, one for each Lorenzian. Then the fitted function was plotted with both phase factors set to zero for a better visual comparison between the amplitudes of the TP Xe and BL Xe peaks. This procedure is illustrated in Fig. 1. For exchange spectroscopy the BL peak at 217.5 ppm was selectively saturated [6]. For subject 2 a blood-selective XTC depolarization map was obtained [7].

**Results:** Figure 2 is a direct comparison of the dissolved-phase Xe signal between a normal subject and a SCD patient, normalized for the TP peak. From the plot we see that the relative BL Xe-signal strength for the SCD patient is significantly lower than that of the normal subject, about half in amplitude, which is the case for both SCD patients. It shows that for the same amount of Xe, the amount of Xe bound to hemoglobin in a subject with SCD is only about half of that of a normal lung. This has two possible explanations. One is a reduced hemoglobin volume due to anemia; the other is that HGB-S does not bind xenon as well as normal hemoglobin. Further studies, e.g., Xe uptake spectroscopy [3], are needed to distinguish the contributions of these two factors to a lower-than-normal xenon blood peak in the SCD patients. In the exchange experiments, the average depolarization for the normal and SCD subjects at 100 ms delay are 2.56% ± 0.11% and 2.15% ± 0.07%, respectively. The lower level of depolarization for the SCD patients agrees with the smaller BL Xe peak in the dissolved-phase. The XTC study (Fig. 3) confirms these global findings but also indicates possible regional differences.

**Conclusion:** This work demonstrates that hyperpolarized $^{129}$Xe MRS and XTC MRI are sensitive to some of the pathological changes in lung function as they occur in SCD.

**References** [1] Fain et. al. J Magn Reson Imaging 2007; 25:910-923. [2] Patz et. al. Euro J Radiol 2007; 64:335-344. [3] Chang et. al. ISMRM 2008, 201. [4] Ruppert et. al. MRM 2000; 44:349-357. [5] Ruppert et. al. MRM 2004; 51:676-687. [6] Chang et al. ISMRM 2009; submitted. [7] Ruppert et. al. ISMRM 2009; submitted.

**Acknowledgements:** Supported by NIH grants R41 CA128895, R41 HL091578, R01 EB003202 and R01 HL079077, and Siemens Medical Solutions.

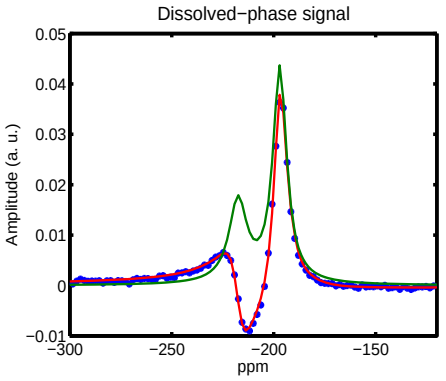


**Figure 1** Analysis of the dissolved-phase Xe signal. Blue points are the real channel data points; red curve is the double-Lorenzian fit with centers at 197 ppm and 217.5 ppm and their own phase factors. The green curve is a re-plot of the double-Lorenzian with both phase factors set to zero.

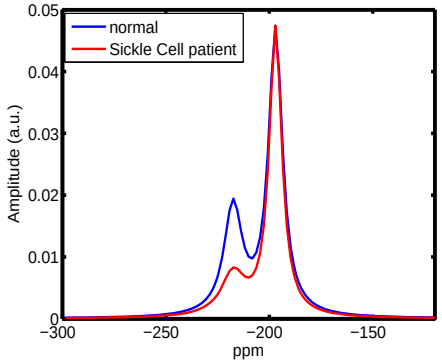


**Figure 2** Comparison of the dissolved-phase signal between a normal and a SCD patent. The TP Xe peak is normalized. The relative peak of the BL Xe is much smaller for the SCD patient than that of the normal subiect.

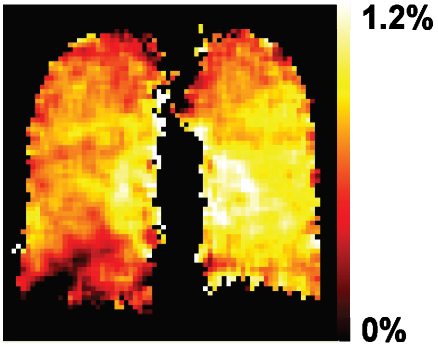


**Figure 3** A depolarization map of SCD subject 2 indicates possible regional differences in the observed lower pulmonary blood volume.