Investigation of Atherosclerotic Plaques by Hyperpolarized ^{129}Xe

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According to the statistics of the American Heart Association[1] cardiovascular disease (CVD) is the leading cause of death among American men and women, with estimates that approximately 59 million Americans have one or more forms of CVD. CVD killed 945,836 Americans in 2000. Statistics shows that life expectancy would rise by 7 years, from today's 77 years, if all forms of CVD were eliminated (compare to 3 years for elimination of cancer). The main cause of CVD is atherosclerosis. CT, ultrasound and MRI have been used, with certain success, in imaging atherosclerotic plaques *in vivo*. However, atherosclerotic plaque *composition* rather than the degree of arterial stenosis seems to be the critical factor for the risk of rupture. Gd-enhanced MRI has been shown[2] to be able to characterize the fibrous tissue, necrotic core, and neovasculature of the plaques, due to the difference in Gd-diffusivity in the different tissue compartments. Here, we investigate a new avenue for plaque characterization, whereas the extreme sensitivity of ^{129}Xe's chemical shift to its chemical environment is utilized to delineate tissues based on their morphological and physiological differences. Xenon has fairly high tissue-specific solubility[3] *in vivo* and can cross cell membranes in ~ 12 *ms*.[4] Moreover, the ability to *hyperpolarize* ^{129}Xe suggests the design of xenon-biomarkers that would intrinsically have very high SNR.

MATERIALS AND METHODS: Sections from human aorta were excised and thin strips from the tissue were cut and placed into a 5-*mm* NMR tube. We tested tissue from four different humans, all of whom were 70 years or older (2 men, 2 women). Pure hyperpolarized (10 % polarization, natural abundance) Xe gas was constantly delivered to the sample in the magnet (500 *MHz*) through a Pasteur pipette inserted into the NMR tube in such a way that Xe flowed over the tissue. The source of the xenon gas was a plastic bag (courtesy of Dr. B. Driehuys, Amersham Health, Duram NC) set outside the magnet that was connected to the Pasteur pipette via 3-*m* long tubing. All experiments were performed at 25^oC. No deuterium lock was used; the drift of the magnetic field over the experimental time was monitored using the frequency shift of thermally polarized pressurized Xe dissolved in acetone. Xe magnetization was sampled with relatively small angle (~ 35°); and a number of scans were acquired to achieve the desired SNR.

RESULTS: Figure 1 shows photographs of the normal (left) and atherosclerotic (right) tissue. Even in the normal tissue some small fat streaks can be seen. In two of the samples (not shown) there were visible ulcerations and the aorta was extensively calcified. Figure 2 shows the ^{129}Xe spectra. In Figure 2a, the large peak at approx. 0.5 *ppm* stands for gaseous Xe inside the test tube, while the feature extending over 190-200 *ppm* corresponds to Xe dissolved in the tissue. The number of scans was 132 and 256 for the diseased (red) and normal (black) tissue respectively. Figure 2b shows the detailed spectra of Xe dissolved in the tissue. As seen, the dissolved peak in the diseased tissue is significantly broader than that of normal tissue and has an additional non-resolved feature positioned at about 200 *ppm*. The position of this feature, which is missing in the spectrum of normal tissue, indicates that it is most likely associated with Xe dissolved in the fat core of the plaque. The spectra of Xe in both normal and diseased tissues are quite broad and anisotropic; this anisotropy might partially be due to non-uniform filling of the test tube with the sample or to susceptibility variations between tissue/gas. Another plausible source of anisotropy is the non-uniform distribution of the magnetic field on the surface of the tissue, so that Xe frequency in the tissue becomes a function of its position. We tried to measure T_1 of the dissolved peak but the obtained result (~ 6 *min*) suggested that this T_1 is dominated by exchange with the gas phase rather than by the tissue itself. Figures 2c-d show the inter-human reproducibility of our results: Although some variations are observed in the spectra, the general appearance of a broad unresolved peak at around 200 *ppm* observed in plaques is not observed in normal tissue.

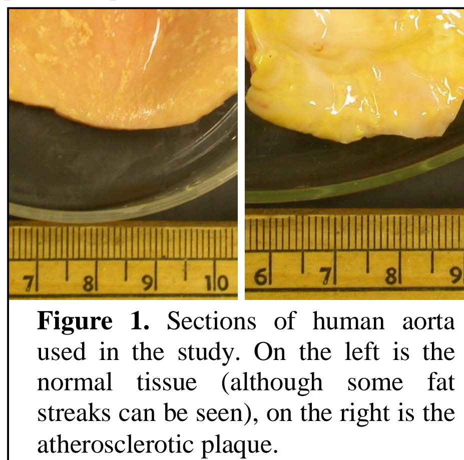

Figure 1. Sections of human aorta used in the study. On the left is the normal tissue (although some fat streaks can be seen), on the right is the atherosclerotic plaque.

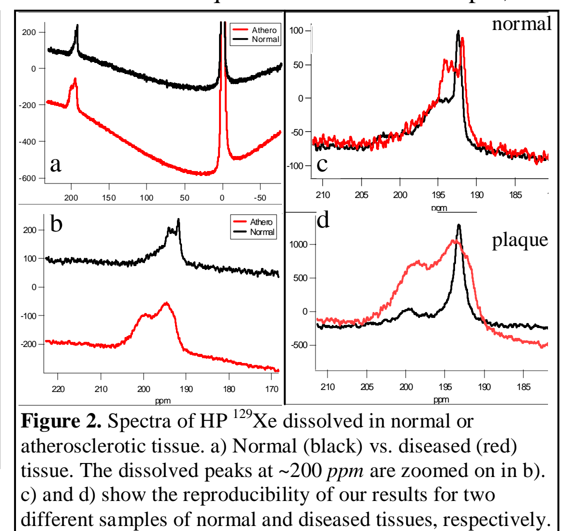

Figure 2. Spectra of HP ^{129}Xe dissolved in normal or atherosclerotic tissue. a) Normal (black) vs. diseased (red) tissue. The dissolved peaks at ~200 *ppm* are zoomed on in b). c) and d) show the reproducibility of our results for two different samples of normal and diseased tissues, respectively.

References: 1."Heart disease and stroke statistics," American Heart Association, (2003). 2. C. Yuan, W. Kerwin, M. Ferguson, et al., Contrast-enhanced high resolution MRI for atherosclerotic carotid artery tissue characterization, *J Magn Reson Imag* **15,** 62-67 (2002). 3.R. Chen, F.-C. Fan, S. Kim, et al., Tissue-blood partition coefficient for xenon: temperature and hematocrit dependence, *J Appl Physiol* **49,** 178-183 (1980). 4.A. Bifone, Y.-Q. Song, R. Seydoux, R. E. Taylor, B. M. Goodson, T. Pietrass, T. F. Budinger, G. Navon, and A. Pines, NMR of laser-polarized xenon in human blood, *Proc. Natl. Acad. Sci. USA* **93,** 12932-12936 (1996).
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