Temperature-sensitive imaging by means of exchangeable functionalized 129Xe

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Purpose: Molecular imaging using functionalized xenon and cage-based Xe biosensors was improved by using chemical exchange saturation transfer of hyperpolarized nuclei (HYPER-CEST) [1]. Here we studied the temperature dependence of the HYPER-CEST effect in ^{129}Xe CSI datasets and found that the accelerated exchange of Xe into the biosensor at higher temperatures improves the HYPER-CEST contrast. Optimization of exchange at temperatures near body temperature (37°C) will be important for highly sensitive *in vivo* applications.

Methods: A previously proposed Xe biosensor [2] that selectively binds the protein avidin via its biotin targeting moiety was used in a dual compartment phantom to monitor signal differentiation achieved with the HYPER-CEST effect at 26°C, 29°C, and 32°C. The dual compartment phantom consisted of a control compartment containing agarose beads, where no signal decrease was expected, and the active compartment containing agarose beads cross-linked to avidin covalently bound to the biosensor [1]. Temperature was controlled by adjusting the power settings of a heating cable attached to the input of the water supply line of a perfusion setup previously described [1]. Due to the limited heat conductivity in this initial setup, the maximum temperature of water achieved was 32°C. The water was saturated with hyperpolarized xenon gas from a commercial xenon hyperpolarizer (XenoSpin, Amersham Health) by bubbling, and then flowed directly to the phantom for imaging. All data was collected on a 7.05 T Varian Unity Inova system with a 10 mm double-resonant ^{1}H/^{129}Xe probe and a three-axis gradient coil assembly (Resonance Research Inc.). A 1.5 sec continuous wave (cw) pulse of amplitude 1.6 μT was used to saturate the weak Xe biosensor signal at ca. 65 ppm (on-resonance). Exchange of the saturated xenon back into the reservoir of hyperpolarized xenon in water during the cw pulse resulted in a decrease in signal at the resonance of free Xe (~193 ppm) detected by a CSI sequence (10mm slice, 8x8 phase encoding steps, FOV = 12mm x 12mm). For each temperature, a reference dataset was collected with the same parameters except that the cw pulse was applied at 321 ppm (same offset from the free xenon but away from the caged xenon peak to control for off resonance effects) [1]. Data processing was done in MATLAB® (MathWorks, Inc., Natick, MA).

Results: The relatively slow exchange of xenon in and out of the biosensor at 26°C resulted in poor HYPER-CEST contrast between the on-resonance and reference spectra (Fig. 1A). At this temperature, the difference in SNR of a representative voxel in the active compartment of the phantom between the on-resonance and reference spectra was +8% (which is within the noise level of the method). Increasing the temperature to 29°C induced a signal decrease of 25% in the same voxel when the cw pulse was on-resonance with the biosensor resonance frequency (Fig. 1B). Saturation of the functionalized Xe in this voxel at 32°C resulted in high contrast, a -46% difference in SNR (Fig. 1C). This data supports our hypothesis that the exchange rate is a critical parameter in the sensitivity of the HYPER-CEST contrast mechanism. Imaging at body temperature (37°C) will have better contrast than phantom studies done previously at lower temperature.

Conclusion: HYPER-CEST with Xe biosensors is very sensitive to the environmental temperature and contrast increases dramatically with small temperature increases. Temperature dependent data suggests that further increases in exchange rate, e.g. from modification of the cage, may further improve HYPER-CEST contrast for future *in vivo* applications of the biosensor. Determination of exchange rates from images could also have an application in detection of localized disease-related temperature changes (e.g. 'hot' atherosclerotic plaques) and non-invasive temperature monitoring during hyperthermic therapy.

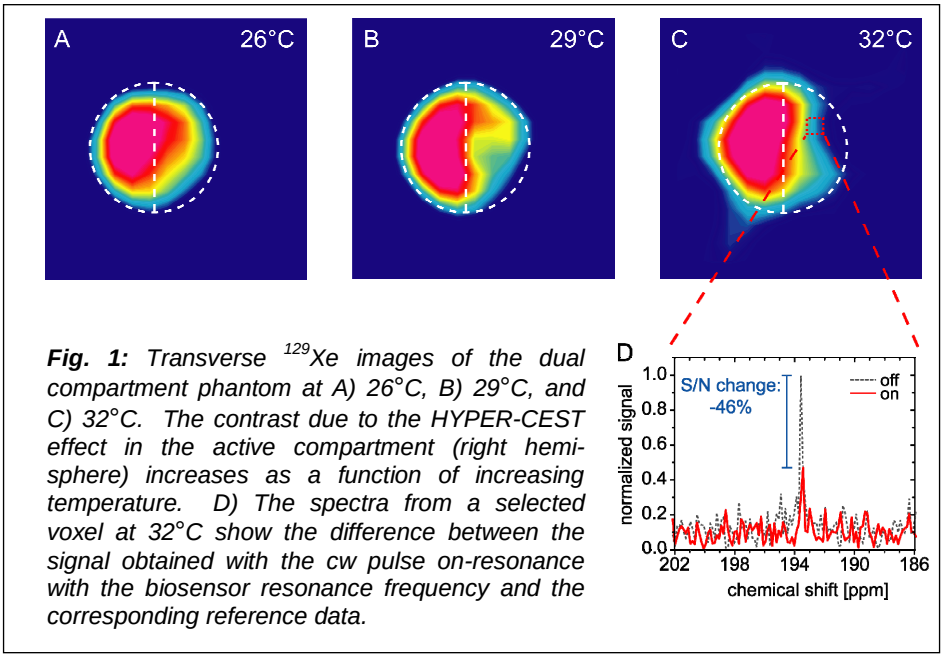

Fig. 1: *Transverse ^{129}Xe images of the dual compartment phantom at A) 26°C, B) 29°C, and C) 32°C. The contrast due to the HYPER-CEST effect in the active compartment (right hemi-sphere) increases as a function of increasing temperature. D) The spectra from a selected voxel at 32°C show the difference between the signal obtained with the cw pulse on-resonance with the biosensor resonance frequency and the corresponding reference data.*

REFERENCES:

[1] Schröder L, *et al.*, *Science* **314**, 446-449 (2006)

[2] Lowery T.J., *et al.*, *ChemBioChem* **7**, 65-73 (2006)