Water Relaxation Parameters and the State of Coagulation of a Protein for Vascular Repair

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Target audience: Interventionalists, Biophysicists

Purpose: To measure the MR relaxation properties of a protein solution undergoing coagulation to determine the most definitive MR methodology enabling the detection of coagulation. Coagulation of a protein biomaterial by MR-induced RF heating is a novel means to effect repair of vascular defects such as aneurysms or arteriovenous malformations. These defects are conventionally repaired by surgical clipping or by filling/occluding with endovascularly delivered wire coils, and in some cases with particles or a polymeric material [1]. Our novel method, MR Coagulation, is intended to achieve a comparable result by coagulating a thermosetting material (such as a protein solution) delivered endovascularly by catheter and coagulated by RF-induced heating of an intracatheter resonant wire antenna in the MRI scanner.

Human serum albumin (HSA) is the most abundant protein in the blood. Because of its natural biocompatibility and coagulability when heated with lasers or other energy sources, it has been used surgically to seal blood vessels [2] and to stem diffuse bleeding [3]. In an image guided MR coagulation procedure it is necessary to establish the rheological state of the biomaterial and to determine when coagulation is complete using its MR characteristics. Egg white, essentially a 20 wt% protein solution with about half the protein being ovalbumin, can be used as an inexpensive substitute for HSA for investigating heat coagulation behavior and MR relaxation properties. In this study, the MR relaxation properties of egg white were studied as a function of temperature and degree of coagulation to determine which relaxation time constants would be most appropriate for future imaging studies to ascertain the coagulation state in vivo.

Methods: Experiments were performed on a Bruker 14 T (600 MHz) Avance widebore NMR spectrometer with variable temperature control. Egg white in 5 mm NMR tubes was brought to equilibrium at six temperatures (20 °C, 30 °C, 40 °C, 50 °C, 60 °C and 70 °C) in increasing sequence. At each temperature, a 20 minute interval was provided to allow the coagulation to proceed and stabilize, the relaxation time was measured, and then the temperature was increased to the next value. Separate runs with fresh sample were performed for each relaxation time, using inversion recovery, CPMG or spinlock pulse sequences to measure the water spin-lattice relaxation time T_1, spin-spin relaxation time T_2, or rotating frame spin-lattice relaxation time $T_{1\rho}$ respectively. At temperatures inducing significant coagulation, the spectral line of the resonance exhibited a complex lineshape changing significantly with increasing temperature and coagulation. The lineshapes were therefore fit to a sum of Lorentzian lineshape functions to extract the water resonance. To establish the degree of coagulation by an independent method, the exact same temperature sequence was run, but instead of MR measurement, the NMR tube was removed from the magnet and a light scattering measurement at a wavelength of 617 nm was performed at room temperature with a Beckman spectrophotometer.

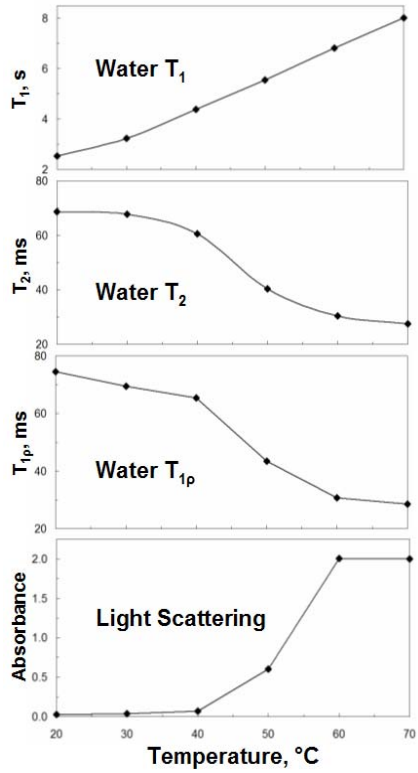

Figure 1. Egg white water MR relaxation properties and light scattering properties as a function of temperature.

Results: It was found that water T_2 and $T_{1\rho}$ gave the most definitive indication of the change from uncoagulated at low temperature to fully coagulated at 60 °C, while water T_1 showed only the expected increase with temperature, and no response to coagulation. The optical absorbance vs. temperature curve showed a definitive transition from uncoagulated to coagulated state over the same temperature interval as did T_2 and $T_{1\rho}$.

Discussion: In pure liquid water, T_1 exhibits a minimum value when the correlation time for molecular reorientation matches the inverse of the Larmor frequency; as the correlation time either increases or decreases, T_1 will increase [3]. Unlike T_1, T_2 decreases as the correlation time increases [3]. In the presence of a soluble or coagulated protein, chemical and spin exchange between bulk water protons, bound water protons and protein protons complicates the relaxation behavior. Because T_2 and $T_{1\rho}$ are affected strongly by "static" and low frequency molecular motions, respectively, they are expected to be influenced strongly by the transition of solution proteins from the ordered to the agglomerated state, as borne out by our results. T_2-weighted images are quick to and easy measure with low SAR, while $T_{1\rho}$ (or magnetization transfer) weighted imaging may impose elevated SAR exposure, which would complicate the MR coagulation procedure.

Conclusion: The NMR and light scattering experiments show that egg white protein fully coagulates at 60ºC, which is relatively easy to achieve by MR-induced heating of an intracatheter antenna. T_2 weighted imaging is expected to be the optimum method to establish the coagulation condition of the biomaterial.

References: [1] Brisman JL, Song JK, Newell DW. N Engl J Med 2006;355:928-939. [2] Takao H, et al. Neurosurgery 2009;65:601-609. [3] Mueller GR, Wolf RF, Hansen PD, Gregory KW, Prahl SA. J Gastrointest Surg 2010;14:1764-1769.