Single-point 19F imaging of fluorinated drugs injected into the eye for the treatment of macular degeneration

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Introduction: Age-related macular degeneration (ARMD) is the most common cause of visual impairment in people over 60 in the western world. Forms of ARMD include the growth of new blood vessels underneath the retina (angiogenesis) and cystoid macular degeneration in which there is a loss of vision due to fluid-filled areas in the macular region. Anti-angiogenic substances like triamcinolone acetonide, pegaptanib and bevacizumab have shown great promise for the treatment of such forms of ARMD. These substances are injected into the vitreous cavity (Fig.1) considering the vitreous as drug reservoir, and allowed to diffuse into the choroid for several months. For a continuous treatment, timely replenishment of the drug is necessary. At present, no accurate noninvasive techniques exist for monitoring the biodistribution of the drug after administration and the necessity of a new injection is usually determined by biopsy or following the treatment effects. Frequent biopsies, however, cause damage to the choroid membrane and constitute a traumatic experience for most patients. At the UMC Utrecht recently a study has been started to explore the potential of ^{19}F MRI and fluorination of drugs for monitoring the status of the distribution of the drug in the eye. As a first step, an *ex vivo* study was performed on the MR visualization of Perfluorooctylbromide (PFOB), after injection into an enucleated bovine eye. Fluor imaging was done with a single-point technique [1] to avoid misregistration artifacts from the multiple peaks of PFOB with their large chemical shifts (Fig.2) and to obtain maximum sensitivity [2,3]

Materials and methods: Fresh enucleated bovine eyes were obtained from the abattoir. Neat PFOB was injected into the choroid membrane on the front side of the eye 3mm from the iris (Fig.1). PFOB is a chemically inert liquid composed primarily of carbon and fluorine atoms. It displays seven resonances over a wide chemical shift range of about 60 ppm (Fig.2). The amount of PFOB injected in the eye was 0.05ml. A 2-cm diameter test tube with pure PFOB was included for SNR measurements and analysis of the detection limits [4]. All imaging experiments were done on a 4.7T animal system with a horizontal bore of 40 cm and a maximum gradient strength of 500mT/m (Varian Inc., Palo Alto). First, conventional ^{1}H images of the specimen were obtained with an axial multislice SE acquisition. Next, the test tube with PFOB and the PFOB distribution in the eye were imaged with a ^{19}F MRI acquisition using a ^{19}F receive coil. These experiments were done with a conventional GE technique (slice orientation axial, slice thickness 5mm, TR=500ms, TE=3.1ms, FOV=40x40mm^2, matrix=128^2,flip angle=20°, read gradient=1.56mT/m) and a single-point projection technique (slice orientation axial, TR=20ms, TE=0.1ms, FOV=40x40mm^2, matrix=64^2, flip angle=5°).

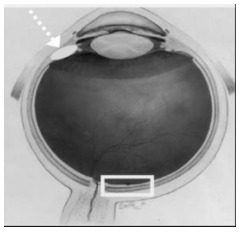

Figure 1: Anatomy of the eye with macula (square) and injection site (arrow)

Results: Figure 3, top row: ^{19}F spectrum of PFOB, ^{19}F image (conventional) and ^{19}F image (SPI) of test tube with PFOB. Figure 3, bottom row: ^{1}H image, ^{19}F image (conventional) and ^{19}F image (SPI) of bovine eye injected with PFOB. In the ^{1}H image the presence of PFOB leads to an absence of signal exactly at the position of the central peak in the ^{19}F image. Other remarkable features are the correspondence between the chemical shift artifacts in the conventional ^{19}F images and the peak positions of the ^{19}Fspectrum, and the immunity of SPI to chemical shift effects.

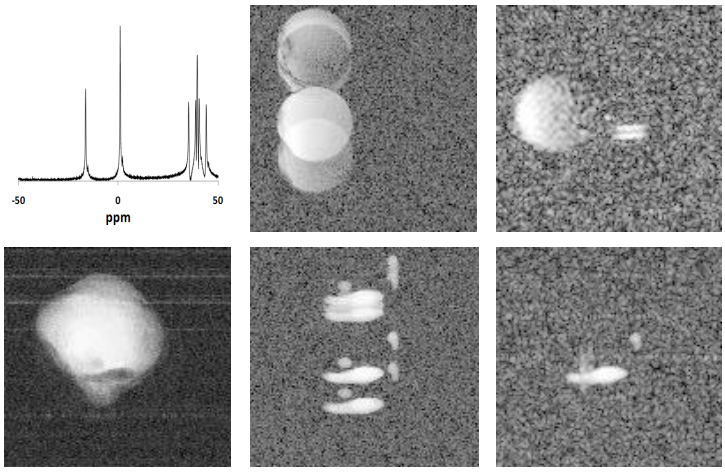

Figure 3. *Top row*: ^{19}F NMR spectrum of PFOB at 4.7T, conventional ^{19}F image, and single-point projection ^{19}F image of a test tube with PFOB. *Bottom row*: ^{1}H spin echo image, conventional ^{19}F image, and single-point ^{19}F image of an enucleated bovine eye with 0.05 ml PFOB injected into the choroid membrane. Note the chemical shift artifacts along the read axis in the conventional images and the absence of such artifacts in the SPI images.

Discussion: ^{19}F SPI as presented above is able to detect PFOB in the eye with high sensitivity. With typically achievable fluorine labeling efficiencies of 10^{20} fluorine spins per mg drug, this sensitivity is expected to be adequate for the intended clinical application. For other applications, the scan protocol, hardware (B_0, coil) and other parameters may have to be optimized to realize the required sensitivity. Experiments were done with ^{19}F SPI so as to be immune to geometric distortions and chemical shift artifacts and to achieve optimal sensitivity. This approach has been shown to be superior to conventional imaging with strong gradients (low SNR) and extensive signal averaging [3]. Since signal is integrated across the entire spectrum, SPI provides large flexibility in the design of fluorinated drugs and averts the need of fluorine compounds resonating at a single resonance frequency [5, 6] or the use of spectrally selective excitation techniques to image only one peak which leads to a loss of sensitivity. With regard to clinical application, the long acquisition time of SPI is a concern. As only one point in k-space is acquired after each excitation, acquisition times in SPI tend to be very long. It should be realized, however, that the distribution volume of the drug in our case is restricted to a small area and that surrounding tissues have a negligible background ^{19}F signal. Excessive scan times can, therefore, be avoided by a reduction of the scan volume or the use of projection images. As compared to ^{1}H imaging of magnetically labeled drugs, ^{19}F imaging has the potential advantages of positive identification and reduced sensitivity to eye motion. The latter is a source of severe artifacts in ^{1}H imaging due to overprojection of signals from the vitreous humor.

Conclusion: ^{19}F single-point imaging promises to provide a useful way of monitoring the distribution of fluorinated drugs injected into the vitreous cavity for the treatment of age-related macular degeneration. Future studies will need to be undertaken to evaluate the efficacy of this approach in a clinical setting and to extend the area of application .

References: [1] S Emid and JHN Creyghton, Physica B 1985;128:81 [2] M Yildrim et al, ISMRM 2007:1249 [3] M Yildrim et al, ISMRM 2008:3257 [4] PR Seevinck et al, AntiCancer Ag Med Chem 2007;7:317 [5] ET Ahrens et al, Nat Biotech 2005;23:983-987 [6] CH Sotak et al, MRM 1993;29:188