The impact of overall injection time on the arterial input function and pharmaco-kinetic analysis using the Tofts model in DCE-MRI for prostate cancer patients

Andrea Holt[1], Edoardo Pasca[1], Stijn W. Heijmink[2], Jelle Teertstra[2], Sara H. Muller[2], and Uulke A. van der Heide[1]

[1]*Department of Radiation Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands,* [2]*Department of Radiology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Purpose: Pharmaco-kinetic analysis (PKA) of dynamic contrast-enhanced (DCE) MRI data using the Tofts Model requires information about the time-dependent concentration of contrast agent (CA) in the arteries feeding the tissue, the so-called arterial input function (AIF) [1]. It can be expected that the injection speed of the CA has a large impact on the form of an AIF which in turn may influence the outcome of PKA. Simulations of AIFs for varying injection protocols showed that injection volume and rate influence the results of PKA [2]. Here, we investigate the impact of the overall CA injection time on the AIF and PKA experimentally.

Material and Methods: In this study, 24 patients with biopsy-proven prostate cancer were included in 6 groups with different overall CA injection times ranging from 5 to 30 s. All MR exams were performed on a 3 Tesla MR scanner. An endorectal coil was used to obtain a high SNR in the prostate. A DCE-MRI exam was carried out, consisting of a T_1-weighted 3D spoiled gradient echo sequence with 80 time points and a time point interval of 2.9 sec (TR/TE 4/1 ms, flip angle 13°, 20 transverse slices, slice thickness 3 mm, FOV 35.2 cm, acquisition matrix 128x128, reconstruction matrix 256x256, resulting in a voxel size in-slice of 1.38x1.38 mm^2). A saturation slab of 60 mm width was placed cranially to the imaging slab using a 40 mm gap. At the 2nd scan of the dynamic series 7.5 mmol gadoteric acid (15 ml, 0.5 M Dotarem, Guerbet, France), corresponding to ~0.1 mmol/kg body weight at a standard patient body weight of 75 kg, was injected with an overall CA injection time of 5, 7.5, 10, 15, 20 or 30 s depending on the group, followed by a 15 ml saline flush with the same injection rate.
For each patient, from the MR phase images AIFs were extracted in both femoral arteries using a straight part of the artery covered by the imaged slab. The phase images were unwrapped, and the baseline was subtracted using the time points before onset of enhancement. Then, 2-4 voxels per slice were manually chosen with exclusion of the outermost slices, with a total of typically 20-40 voxels per femoral artery. Voxel selection criteria were a clear first pass peak presence and a location in the center of the artery to avoid partial volume effects. Possible phase drift was corrected per side using a bony reference region from the femoral heads. The MR phase signal $\Delta\varphi$ averaged over the selected voxels was converted to CA concentration C using eq. 1, with ω_0 being the resonance frequency, χ_M the molar susceptibility of the CA, and F the geometry factor specified in eq. 2 [3]. The angle θ of the artery with respect to the main magnetic field B_0 was determined by manual measurement on the a priori non-angulated imaged slabs. The resulting AIFs were manually shifted to match on onset of enhancement and averaged per group of overall injection time after correction for patient body weight. The averaged AIFs were fitted using eq. 3 from Parker *et al*. [4], where A_n, σ_n, T_n are the scaling constants, centers and widths of the n^{th} Gaussian; α and β are the amplitude and decay constant of the exponential; and s and t are the width and center of the sigmoid, respectively. PKA on prostate tissue was performed on MR magnitude derived concentration curves using the Tofts model and group-averaged phase AIFs corrected for patient body weight.

$$\Delta\varphi = \omega_0 \cdot \chi_M \cdot F \cdot C \cdot \mathrm{TE} \quad (1) \qquad F = \frac{1}{3} - \frac{1}{2}\sin^2\theta \quad (2)$$

$$C_b(t) = \sum_{n=1}^{2} \frac{A_n}{\sigma_n\sqrt{2\pi}} \exp(-(t-T_n)^2/2\sigma_n^2) + \alpha\exp(-\beta t)/(1+\exp(-s(t-\tau))) \quad (3)$$

Results: The AIFs averaged over the groups of different overall injection times were fitted with eq. 3 using only the 1st order Gaussian to cover the first pass peak (Figure A). The 2nd order Gaussian to cover the recirculation peak was excluded during fitting since the recirculation peak was masked in the noise and, in addition, may overlap with the first pass peak at longer overall injection times. The height of the first pass peak decreased with increasing overall injection time (Figure B). The FWHM of the first pass peak was very similar for overall injection times between 5 and 10 s and increased with increasing overall injection time (Figure C). The lower boundary for the FWHM of the first pass peak was found to be 9 s. PKA using a group-averaged AIF resulted in very similar values of K^{trans} for healthy tissue in the peripheral zone (PZ) of the prostate for the different overall injection times, the mean K^{trans} averaged over all groups was 0.069 ± 0.008 min^{-1}. Figure D shows an example of a T_2-weighted transversal slice of the prostate with a lesion in the PZ, and Figure E the corresponding K^{trans}.

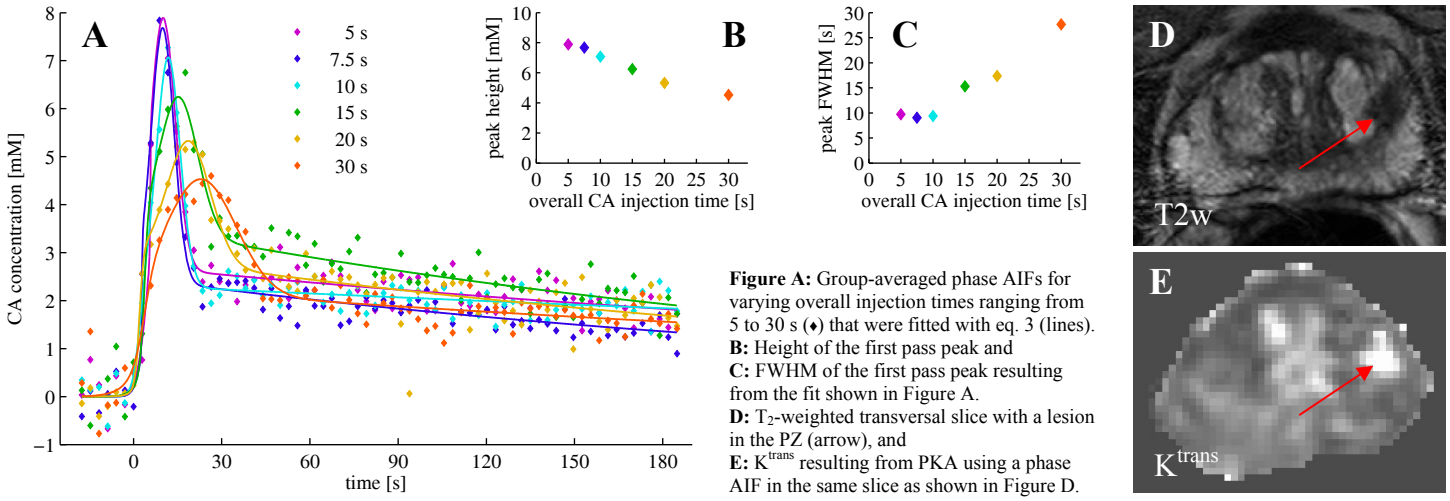

Figure A: Group-averaged phase AIFs for varying overall injection times ranging from 5 to 30 s (♦) that were fitted with eq. 3 (lines).
B: Height of the first pass peak and
C: FWHM of the first pass peak resulting from the fit shown in Figure A.
D: T_2-weighted transversal slice with a lesion in the PZ (arrow), and
E: K^{trans} resulting from PKA using a phase AIF in the same slice as shown in Figure D.

Discussion: The averaged AIFs presented in Figure A were determined from MR phase images since the phase signal does not suffer from saturation effects compared to the magnitude signal [3]. The SNR of the AIFs extracted from the phase images was low, which impaired fitting of the recirculation peak. This may be improved by optimizing the MR scan protocol. The lower boundary of the FWHM of the first pass peak is determined by the intrinsic dispersion of the CA bolus during lung passage and by the time point interval. According to the Nyquist sampling theorem the minimal detectable FWHM of peaks is twice the time point interval.
Based on regions of healthy tissue in the PZ of the prostate we found no effect of overall injection time on K^{trans} (with n = 4 patients per group of overall injection time), in agreement with the results presented in Aerts *et al* [2]. However, any effects on K^{trans} may be less pronounced in healthy tissue since it shows only slow enhancement, and hence, the shape of the AIF may be less critical for estimation of K^{trans}. Since tumor tissue is known to exhibit large heterogeneity between patients, it is preferable to study the effects on K^{trans} in faster enhancing tumor tissue in a repeat study with different overall injection times.

Conclusion: Below an overall CA injection time of 10 s no further sharpening of the first pass peak of the AIF is observed, which suggests that an overall injection time of ~10 s at a time point interval of ~3 s allows reliable determination of the first pass peak of the AIF.

[1] Tofts et al, JMRI 1999(10:223-32) [2] Aerts et al, MRM 2008(59:1111-9) [3] Korporaal et al, MRM 2011(doi:10.1002/mrm.22905) [4] Parker et al, MRM 2006(56:993-1000)