A population-based AIF for quantitative DCE-MRI of the rat abdomen acquired using dynamic high temporally and spatially resolved CT

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Introduction

Quantitative dynamic contrast-enhanced (DCE) MRI is a widely used technique for studies of tumor progress and viability. The method requires knowledge of the arterial plasma concentration of the contrast agent (CA) in the vessels feeding the tissue of interest. This arterial input function (AIF) must be sampled with a high temporal and spatial resolution to enable stable pharmacokinetic modelling of the DCE-MRI data [1]. In small animals the CA dynamic is very fast, and with current MR techniques it is difficult to acquire concurrent AIF data that reliably describe bolus arrival and first pass of the CA. In this study we therefore aim to acquire a population based AIF (popAIF) for rats based on computed tomography (CT) applying CA and injection dose identical to that used in MR. We hypothesise that the high temporal and spatial resolution, and the low sensitivity to flow artefacts provided by this technique will make it possible to reliably catch the bolus shape even in a small rat aorta. The popAIF is then applied to a one-compartment pharmacokinetic model for quantitative DCE-MRI of liver-tumor bearing rats.

Methods

Acquisition and modelling of AIF: DCE CT was performed on 11 healthy female buffalo rats using a clinical CT scanner (Siemens Somatom, Erlangen, Germany). All animal experiments were approved by the local ethics committee. Dynamic acquisition was performed with three axial slices (thickness = 4.8 mm, in plane resolution = 0.3 mm^2, 40 mAs) centred over the upper abdomen. A double dose of Gd-DTPA (0,2 mmol/kg, Magnevist, Schering) was injected as a bolus after 4.5 s. Bolus arrival and first pass was sampled every $\Delta t = 0.75$s until 75s. After this period, blocks of 9 images (with $\Delta t = 0.75$ s) where acquired with time delays of either 32 s (until 3 min) or 53 s (until 600 s). Each of these blocks was averaged to a single time point to increase SNR of the low temporal resolution data.

The mean Hounsfield unit (HU) of the inner area of the aorta was manually detected (No. of pixels in ROI > 9) over time. The dynamic data for the different animals were shifted in time so that peak HU value occurred at the same time, and subsequently averaged into a single mean HU time curve. Then the HU values were converted to Gd-DTPA concentration C_{Gd} by applying a calibrated conversion factor previously determined from phantom CT measurements of gel samples with different C_{Gd}. Finally the C_{Gd} was converted to plasma concentration C_p assuming a hematocrit of 0.45.

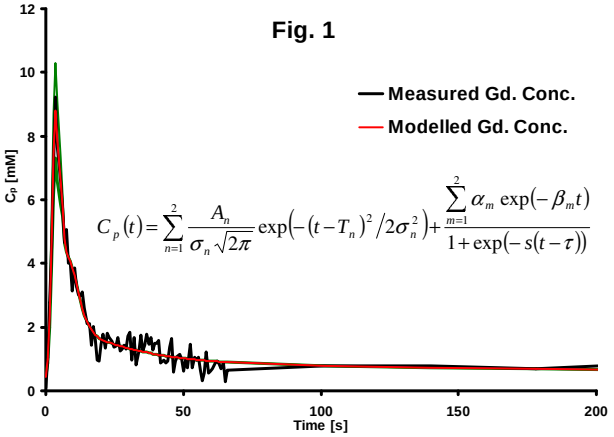
To obtain a smooth concentration curve while preserving the peak information, the data was fitted to a model similar to the one described in [2], but with an additional exponential to account for both recirculation and renal clearance (Eq. in fig 1). Initial start parameters for the fit where carefully selected manually to obtain a converging fit. Since the acquired data was limited to 600 s, it was not possible to reliably model the renal clearance. Instead this parameter was held fixed during fitting and seven popAIF curves with different clearance half-lives between 6-24 min ($0.000481<\beta_2<0.00128$) were modelled and subsequently applied to the DCE modelling. To study the effect of variations in peak amplitude of C_p (e.g due to measurement error or individual animal variations) two additional popAIF sets were constructed with the amplitude of the first gaussian (A1) increased or decreased by 20% (popAIF$_{-20}$, and popAIF$_{+20}$). The change in total area under the curve for these modified popAIF's were ≤ 1%.

DCE-MRI and pharmacokinetic modelling: DCE-MRI data was acquired in 11 liver-tumor bearing female Buffalo rats using a 2D single-shot Look-Locker T_1 mapping technique [3]. T1 maps were dynamically acquired during 1100 s at a temporal resolution of 6 s (0-300 s), or 24 s (300-1100 s). A double dose bolus of Gd-DTPA was injected after 60 s scanning. Spatial resolution was 0.8 mm^2 x 2 mm. ROI's covering the tumor tissue were drawn in the T1 maps, and the T1 values were converted to C_p assuming the fast exchange limit regime, $r1_{Gd} = 4.1$ (mMs)$^{-1}$, and hematocrit = 0.45. Quantitative pharmacokinetic modelling [4] was performed using all the seven popAIF's for each rat and for different time delays in the range $-6<t<6$ s. The modelled curve with the smallest sum of relative squared residuals for each evaluated ROI was assumed to be the best fit, and the Ktrans and ve from these fits were saved. This procedure was repeated for popAIF$_{-20}$ and popAIF$_{+20}$.

Results

The mean fitted model parameter values for the popAIF's were $A_1 = 24.3$, $A_2 = 21.0$, $\sigma_1 = 1.29$, $\sigma_2 = 3.98$, $T_1 = 3.73$, $T_2 = 7.65$, $\alpha_1 = 1.82$ (1.75-1.86), $\alpha_2 = 0.80$, $\beta_1 = 0.0398$ (0.0373-0.0441),$s = 20.6$ (13.1-45.3), and $\tau = 5.25$. As explained above, β_2 was not fitted but held fixed at seven values to create the seven popAIF's. Minimum and maximum fit values are presented in parenthesis only for those parameters where the variation was >1% between the seven popAIF's. The measured $C_p(t)$ (black), and one of the popAIF curves (red, clearance half-life = 9 min) are plotted in fig. 1 together with the modelling equation. PopAIF$_{-20}$, and popAIF$_{+20}$ are plotted in green. DCE modelling of the eleven rat tumors with the popAIF resulted in reasonable quantitative values with low inter-animal variation (mean $K_{trans} = 0.46$ (SD = 0.08) min^{-1}, and mean $v_e = 0.18$ (SD = 0.02), individual values in table below). K_{trans} showed a strong dependence on the peak C_p concentration. Using the popAIF$_{-20}$/popAIF$_{+20}$ for modelling resulted in a mean relative deviation in K_{trans} of +8%/-8% respectively. The v_e dependence on the peak amplitude was much weaker (-2%/-2%).

Fig. 1



Animal #	Ktrans [1/min]	ve
1	0.55	0.21
2	0.41	0.16
3	0.40	0.18
4	0.41	0.16
5	0.40	0.17
6	0.48	0.17
7	0.49	0.19
8	0.65	0.21
9	0.50	0.21
10	0.38	0.16
11	0.42	0.18

Discussion

The bolus injected double dose of Gd-DTPA used here was enough to reliably detect the contrast agent dynamics in a rat aorta with high temporal resolution clinical CT. From this data a population based AIF was established for female Buffalo rats and successfully applied for one-compartment modelling of respective DCE-MRI data. It was also shown that an incorrect estimation of the peak amplitude of CA concentration could induce large errors in K_{trans}. In a real case, such variations could be the result of individual variation in specific rats. However, even though an individually acquired AIF during DCE-MRI could account for such variations, it would presumably induce even larger errors from underestimation of the peak due to low temporal resolution of the acquisition.

References: 1. Cheng H. et al, JMRI 28:736-743 (2008), 2. Parker et al MRM 56:993-1000 (2006), 3. Winkelmann S. et al. IEEE, 26:68-76 (2007), 4. Tofts P. et al JMRI 10:223-232 (1999)