Pharmacokinetic Modelling of Delayed Gadolinium Enhancment in the Myocardium

B. R. Knowles[1], P. G. Batchelor[1], V. Parish[1], M. Ginks[1], S. Sinclair[1], S. Plein[2], R. Razavi[1], and T. Schaeffter[1]

[1]Division of Imaging Sciences, King's College London, London, United Kingdom, [2]Academic Unit of Cardiovascular Medicine, University of Leeds, Leeds, United Kingdom

Introduction. Contrast Enhanced Magnetic Resonance Imaging (CE-MRI) is a clinical tool for the determination of cellular viability following myocardial infarction. Due to the histological changes during ischemia, contrast enhancement in MR images can be seen a few minutes post contrast agent administration. This phenomenon, known as late enhancement, has been shown to be an indicator of eventual cellular necrosis [1]. Quantification of this process has so far been unexplored using MRI. In this work we present the first results on a new model of pharmacokinetics of late enhancement.

Theory. It can be considered that the mechanism of late enhancement involves a trapping of contrast agent in the extracellular space. This trapping can be modelled as a compartment with a fractional volume v_{trap} and transfer K^{trap}. We extended a well established two compartment model [2], which contains a blood volume and an extracellular space to include this third compartment (figure 1).

In pharmacokinetics, the rate of change of concentration in the extracellular and trapping compartments is described by two differential Kety equations [3] (equations 1 and 2). The standard solution to equation 1 is the convolution of $C_p(t)$ with an impulse response function. For the purpose of this model however, it is assumed $C_p(t)$ has a bi-exponential form [4] (equation 3), where D is the contrast agent dose per kg of body weight. This is not a valid assumption for first pass perfusion imaging; however for late enhancement modelling we are imaging over a longer time period. The solution to equation (1) under this condition is a three-exponential function [1]. Using this function for $C_e(t)$, the solution to equation (2) is a four-exponential function. The complete model describing the kinetics of late enhancement is the sum of the product of the concentration of contrast agent in each compartment with the respective fractional volume (equation 4). Equation 5 shows the complete late enhancement model, where d_1, d_2, d_3 and d_4 are known functions of K^{trans}, K^{trap}, v_e and v_{trap}, and m_3 and m_4 are K^{trans}/v_e and K^{trap}/v_{trap} respectively.

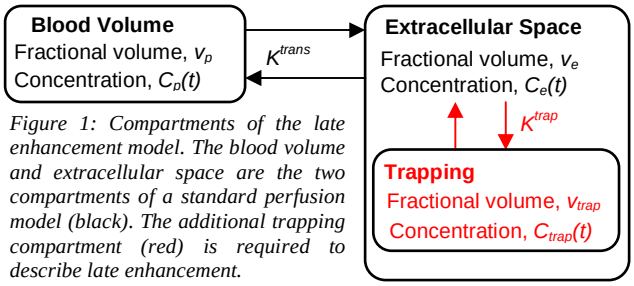

Figure 1: Compartments of the late enhancement model. The blood volume and extracellular space are the two compartments of a standard perfusion model (black). The additional trapping compartment (red) is required to describe late enhancement.

$$\frac{dC_e(t)}{dt} = K^{trans}\left(C_e(t) - C_p(t)\right) \quad (1)$$

$$\frac{dC_{trap}(t)}{dt} = K^{trap}\left(C_{trap}(t) - C_e(t)\right) \quad (2)$$

$$C_p(t) = D[a_1 e^{-m_1 t} + a_2 e^{-m_2 t}] \quad (3)$$

$$C_t(t) = v_p C_p(t) + v_e C_e(t) + v_{trap} C_{trap}(t) \quad (4)$$

$$C_t(t) = D\left[d_1 e^{-m_1 t} + d_2 e^{-m_2 t} + d_3 e^{-m_3 t} + d_4 e^{-m_4 t}\right] \quad (5)$$

Figure 2: Equations used in late enhancement model derivation.

Methods. Five patients post myocardial infarct (4 chronic, 1 acute) undergoing MRI were imaged using a 1.5T Philips Achieva MR system (Philips, Best, The Netherlands) with a prototype 32 channel coil (Invivo, USA) or 5 channel Philips cardiac coil. A dynamic imaging sequence was created to provide large coverage of the ventricles. The imaging sequence was an ECG triggered, 3D inversion recovery turbo field echo (IR-TFE) imaging sequence, with an inversion time of 270ms with up to 10 slices. Resolution was approximately 1.3x1.3x10mm. Images were acquired during breath hold; of approximately 15 seconds. On occasion, SENSE was employed at a factor of 2 if increased coverage of the infarct was required. Patients were administered with 20ml Gd-DTPA and were imaged in the short axis view at intervals of 1 minute for a time period of up to 20 minutes. Between 12 and 17 minutes a high resolution late enhancement image was acquired for comparison.

Post processing was performed offline, using in-house software written using MATLAB (Mathworks, USA). Initially, images were manually registered to compensate for in-plane translational motion. Regions of interest (ROIs) were defined around the myocardium and the left ventricular blood pool. Signal intensity within these ROIs was converted to contrast agent concentration, [Gd], by means of a T_1 calculation as an intermediate step. T_1 was calculated by numerically solving the short tau inversion recovery equation [5]. This is a similar method as used by Nielson *et al* [6]. The AIF was determined by fitting a bi-exponential function (equation 3) to the average [Gd]-time data in the ventricular blood pool to determine the a_1, a_2, m_1, and m_2 parameters. The late enhancement model was then fitted to the [Gd]-time data in the myocardium on a pixel by pixel basis for each slice. Parameter maps of K^{trans}, K^{trap}, v_e, v_{trap} and v_p were created.

Results and Discussions. Figure 3 shows maps of the pharmacokinetic parameters and the corresponding late enhancement image. It can be seen that there is a reduction in K^{trans} within the area of scarring and microvascular obstruction (MVO). There is also a reduction of v_e in the area of the MVO. When comparing healthy tissue to infarcted tissue, the K^{trap} parameter on average showed a fivefold increase in infarcted tissue. The v_{trap} parameter was also found to increase threefold. The increase in both K^{trap} and v_e suggests a trapping of contrast agent in the extracellular space. It can be seen there is a high degree of noise in the parameter maps from the areas of healthy tissue. This has arisen due to the signal suppression of the healthy tissue from the inversion pulse of the imaging sequence.

The interpretation of the K^{trap} and v_{trap} parameters seems to be dependent on the age of the infarct. In acute infarctions, there is a rupturing of the cellular membrane, causing a free transfer across the membrane boundary [7]. In chronic infarctions, it is likely that the increased volume of extracellular space causes a trapping of contrast agent.

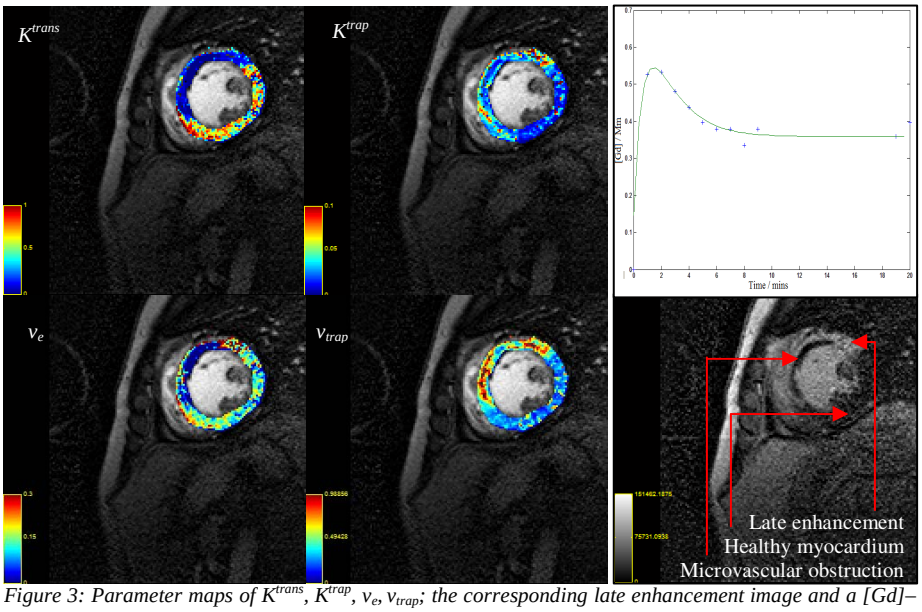

Figure 3: Parameter maps of K^{trans}, K^{trap}, v_e, v_{trap}; the corresponding late enhancement image and a [Gd]–time curve with model fit.

Conclusions. This new three compartment model, unlike a standard two compartment model, accurately describes the trapping of contrast agent in the extracellular space commonly observed in myocardial scarring, providing a useful tool in quantification of such scars.

References. **1** Kim *et al.* Circulation. 1999;100(19):1992-2002. **2**. Tofts and Kermode Magn Reson Med. 1991;17(2):357-67. **3**. Kety Pharmacol Rev. 1951;3(1):1-41. **4.**Weinmann *et al.* AJR Am J Roentgenol. 1984;142(3):619-24. **5.** Fleckenstein *et al.* Radiology. 1991;179(2):499-504. **6** Nielson *et al.* J Magn Reson Imaging. 2004;20(3):403-10. **7** Mahrholdt *et al.* Eur Heart J. 2002;23(8):602-19.