Three-compartment Pharmacokinetic Modeling of Chronic Myocardial Infarction Gadolinium Kinetics

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Introduction: The primary mechanism behind late gadolinium-enhanced (LGE) chronic myocardial infarct (MI) imaging is widely thought to be an increased gadolinium (Gd) concentration due to fibrotic tissue. Several groups have utilized T1 measurements to measure the blood-tissue partition coefficient (calculated as the ratio of tissue to blood Gd-concentrations) using a two compartment model (1,2). A three compartment model yields not only information about flow of the injected contrast agent from the vascular space to the myocardial tissue, but in the case of chronic MI to trapping fibrosis and in the case of acute MI into the myocytes themselves (3). With model inputs of the LV bloodpool and tissue Gd-concentrations, a three-compartment model (Fig 1A) yields transfer constants (K) between the compartments, compartment fractional volumes (v) and gadolinium concentrations curves for tissue blood plasma, the extravascular extracellular space and trapping fibrosis compartments (3-5). A detailed model may not only be useful to detect and characterize MI, but non-ischemic cardiomyopathies with global or diffuse fibrosis. The major aim of this study was to investigate the suitability of a three compartment pharmacokinetic model of late gadolinium-enhancement for chronic myocardial infarcts.

Materials and Methods: Twenty-five individuals (23 men and two women; age mean±std, 61.5±9.9 years) underwent MR imaging at 1.5T. All subjects in this study had a prior SPECT study as part of their routine medical care and the diagnosis of myocardial infarction. The infarct age ascertained from medical history was on average 11.6±10.1 years and ranged from 2 to 31 years. Single slice T1 measurements were performed before contrast administration and after injection of 0.2 mmol/kg of gadodiamide, approximately every two minutes using an inversion recovery CINE balanced steady-state free precession technique. Gd-concentrations of blood, viable, and infarcted myocardium were calculated and interpolated to one minute intervals and averaged across all subjects (Fig 1B). The blood concentration was modeled with a bi-exponential and tissue concentration with a three compartment model, including vascular (plasma), free and trapping compartments (Fig 1A). Fractional volumes for the three compartments and transfer constants into the compartments were fitted parameters of the model. The plasma (C_p) and tissue (C_t, for viable and infarcted myocardium) Gd-concentrations were modeled as:

$$C_p(t) = D\sum_i a_i e^{-m_i t} \quad \text{and} \quad C_t(t) = v_p\, C_p(t) + v_{free}\, C_{free}(t) + v_{trap}\, C_{trap}(t) \quad .$$

The transfer constants out of the compartments were fixed as $K2=K1/v_{free}$ and $K4=K3/v_{trap}$ to reduce the number of model parameters. The coefficient of determination (R^2) was calculated as ($1-SS_{err}/SS_{tot}$).

Results: Tissue gadolinium concentrations (Fig 1B) followed expected curves, with infarcted myocardium greater than viable myocardium and the infarcted myocardium curve crossing the LV-blood curve at 10 minutes. Calculated model parameters are listed in Tables 1 and 2. Gd-concentration curves of the three compartments for infarcted and viable myocardium are plotted in Fig 1C and D. The three-compartment model closely followed the measured data for blood, viable and infarcted myocardium, note the high R^2.The three-compartment model yielded markedly increased trapping volumes and decreased transfer constants of infarcted tissue when compared to viable myocardium. The fractional volume of the trapping compartment (v_{trap}) was larger in infarcted myocardium when compared with viable myocardium, while V_{free} and V_p were similar.

Table 1	a_1 (kg/l)	a_2 (kg/l)	m_1 (min^{-1})	m_2 (min^{-1})	R^2
Blood	4.48	4.06	0.36	0.02	1.00

Table 2	K_1 (min^{-1})	K_2 (min^{-1})	K_3 (min^{-1})	K_4 (min^{-1})
Infarcted Myocardium	1.35	2.27	0.23	0.54
Viable Myocardium	2.13	4.36	0.17	4.36
	V_{free}	V_{trap}	V_p	R^2
Infarcted Myocardium	0.59	0.42	0.02	0.99
Viable Myocardium	0.49	0.04	0.02	1.00

Three-compartment model parameters calculated for blood,, infarcted and viable myocardium. Note, the similar volumes of the free (v_{free}) and plasma (v_p) spaces and the larger volume of the trapped (v_{trap}) compartment in infarcted tissue.

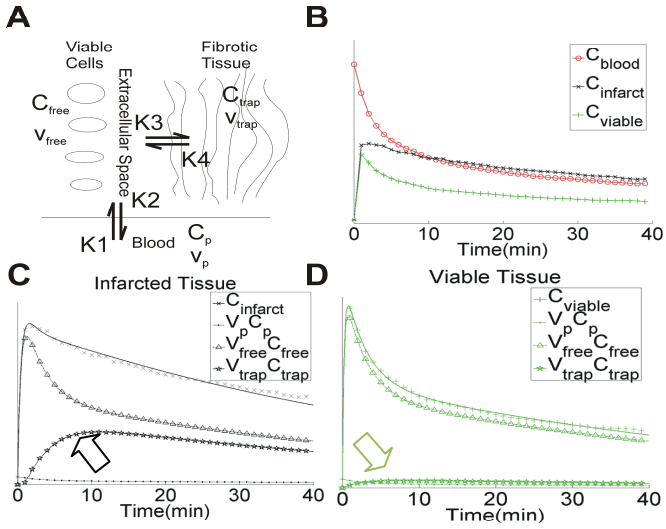

Figure 1 A) Three-compartment model; B) Measured blood and myocardial Gd-concentration; Modeled compartmental tissue concentration curves for C) infarcted and D) viable myocardium ; Note the increased concentration in the trapped compartment in infarcted tissue relative to viable tissue (arrows).

Conclusions: A three compartment model is suitable for detailed modeling of chronic MI Gd-pharmacokinetics. This model provides further justification that fibrotic tissue traps the Gd contrast agent while Gd-concentrations in the free extracellular matrix remain similar with viable myocardium. Further studies of individual subjects and the effects of fitting algorithms and sampling requirements are necessary.

1. Flacke SJ et al. Radiology 2001;218:703-710.
2. Jerosch-Herold M et al. Am J Physiol Heart Circ Physiol 2008;295:H1234-H1242.
3. Knowles BR et al. Magn Reson Med 2008;60:1524-1530.
4. Kety SS. Pharmacol Rev 1951;3:1-41.
5. Sokoloff L et al. J Neurochem 1977;28:897-916.