# Detection of skeletal muscle perfusion differences with DCE-MRI: contrast agent and pharmacokinetic model

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## Introduction

The introduction of neovascularization therapies in patients with peripheral arterial disease requires functional monitoring of vascular responses.[1] DCE-MRI combined with pharmacokinetic modeling is a promising technique to obtain information on and tissue perfusion and microvasculature.[2,3] However, further optimization of the technique is needed to enable detection of subtle functional vascular responses. Simulation studies show that medium-sized contrast agents such as Gadomer (apparent molecular weight 32 kDa [4]) provide more reliable pharmacokinetic parameter estimation[5] and might therefore be a better choice than small contrast agents such as Gd-DTPA (molecular weight 0.5 kDa).

In this study we investigated whether Gadomer is superior in detecting (patho-) physiological perfusion differences. For both contrast agents, the pharmacokinetic model optimally describing the data was chosen among three two-compartment models.

## Methods

*Animal model:* Eight New Zealand White rabbits underwent ligation of the right femoral artery. At days 14 and 21 post ligation an MRI examination was performed on a clinical 3.0 Tesla MR system with a 5-element phased-array cardiac coil. The animals were intubated and ventilated with 2 – 3 % isofluorane in oxygen. Each animal was administered a different contrast agent (Gadomer 0.1 mmol/kg or Gd-DTPA 0.15 mmol/kg) on either day.

*MRI:* The DCE-MRI protocol was adjusted to the temporal requirements of each contrast agent, resulting in a higher spatial resolution for Gadomer, at the cost of temporal resolution (table 1).

*Image analysis:* Regions of interests were drawn in the soleus (red) and tibialis (white) muscle in both the control and ischemic hind limb. Signal curves were converted to tissue concentration time curves ($C_t$), using a linear approximation. Three two-compartment tracer kinetic models were used to fit the $C_t$. For all models a fixed biexponential plasma concentration time curve ($C_p$), as measured from blood samples in a previous study [5], was used as arterial input function. The extended generalized kinetic model[6] described the data in terms of the transfer constant $K^{trans}$, fractional interstitial space $v_e$, and fractional blood plasma space $v_p$:

$$C_t(t) = v_p C_p + K^{trans} \int_0^t C_p(u) \cdot e^{-\frac{K^{trans}}{v_e}(t-u)} du$$

This model can be simplified to 2 two-parameter models. In the original generalized kinetic model[7] (GKM) the contribution of $v_p$ is ignored, and in the Patlak model[8] reflux is neglected (i.e. $K^{trans}/v_e = 0$).

For each model the mean fit error (*FE*) was calculated:

$$FE = 100\% \cdot \sqrt{\sum (C_{t,fit} - C_t)^2 / \sum C_t^2}$$

Fit errors of the different models were tested to define the most appropriate model. Paired Student's t-tests were used to test the differences between red and white, and ischemic and control muscle tissue for $K^{trans}$ estimated with the optimal model.

*Table 1: DCE-MRI Acquisition parameters*

| | Gadomer | Gd-DTPA |
|---|---|---|
| Matrix | 304 × 304 × 60 | 128 × 128 × 30 |
| Voxel size (mm³) | 0.8 × 0.7 × 1.3 | 2.0 × 1.6 × 2.5 |
| Repetition time (ms) | 7.7 | 6.1 |
| Echo time (ms) | 2.0 | 1.0 |
| Flip angle (°) | 20 | 20 |
| Acquisition time per phase (s) | 22.3 | 3.9 |
| Number of dynamic phases | 60 | 220 |

*Table 2: Pharmacokinetic parameters and fit errors (mean ± standard error in the tibial muscle of the control limb for three models. GKM: Generalized kinetic model*

| | | Gadomer | Gd-DTPA |
|---|---|---|---|
| GKM | $K^{trans}$ ($10^{-3}$ min$^{-1}$) | 5.3 ± 0.3 | 65.7 ± 5.1 |
| | $v_e$ (%) | 17.2 ± 1.6 | 12.1 ± 0.5 |
| | fit error (%) | 12.3 ± 0.5 | 6.3 ± 1.2 |
| Patlak | $K^{trans}$ ($10^{-3}$ min$^{-1}$) | 3.6 ± 0.2 | 24.4 ± 0.9 |
| | $v_p$ (%) | 0.9 ± 0.1 | 2.4 ± 0.3 |
| | fit error (%) | 5.0 ± 0.6 | 11.1 ± 0.6 |
| GKM extended | $K^{trans}$ ($10^{-3}$ min$^{-1}$) | 3.8 ± 0.2 | 50.4 ± 3.2 |
| | $v_e$ (%) | 76.0 ± 8.9 | 12.3 ± 0.5 |
| | $v_p$ (%) | 0.9 ± 0.1 | 1.1 ± 0.3 |
| | fit error (%) | 5.3 ± 0.7 | 4.7 ± 0.6 |

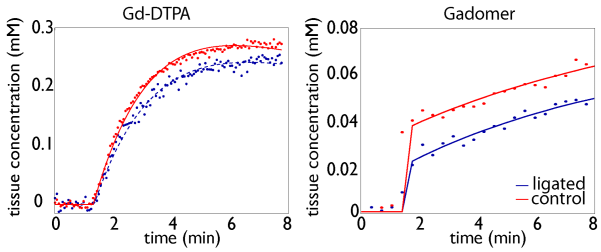


*Figure 1: Tissue concentration time curves for Gd-DTPA (left) and Gadomer (right) in the tibialis of the ligated (blue) and control limb)*

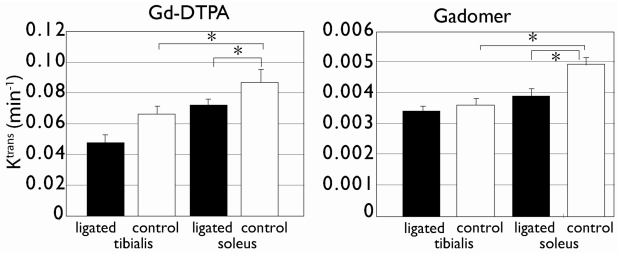


*Figure 2: $K^{trans}$ for Gd-DTPA (left) and Gadomer (right) in the tibialis and soleus of the ligated (black) and control limb (white)*

## Results

For Gadomer the Patlak model was the best two-parameter model ($p < 0.001$), whereas for Gd-DTPA the GKM gave the smallest fit errors ($p < 0.001$). Adding a third parameter, resulting in the extended GKM, gave no significant improvement for either contrast agent. For both Gd-DTPA and Gadomer, $K^{trans}$ was significantly higher in the tibialis compared to the soleus muscle. The difference between ischemic and control soleus muscle tissue was also significant ($p < 0.05$). In the tibialis the same trend was observed, but the differences were not significant ($p = 0.05$ and $p = 0.07$ for Gd-DTPA and Gadomer, respectively). Image quality was equal for both contrast agents ($SNR_{Gadomer} = 35 \pm 3.1$; $SNR_{Gd\text{-}DTPA} = 37 \pm 2.7$).

## Conclusion

For optimal estimation of $K^{trans}$ in skeletal muscle tissue, the pharmacokinetic model used should be adapted to the pharmacokinetic properties of the contrast agent. Apart from $K^{trans}$, the model should include $v_e$ for rapidly extravasating contrast agents such as Gd-DTPA and $v_p$ for larger agents such as Gadomer. Gadomer is equally successful in detecting physiological and pathophysiological perfusion differences as Gd-DTPA at a higher spatial resolution with equal image quality.

## References

[1] Simons M, Circulation 2005; 111:1556-1566

[2] Faranesh, AZ et al., MRM 2006; 55:1114-1123

[3] De Lussanet et al., NMR Biomed 2007; 20:717-725

[4] Misselwitz B et al., MAGMA 2001; 12:128-134

[5] Jaspers K et al., MRM 2009; 62:779-787

[6] Tofts PS et al., JMRI 1997; 7:91-101

[7] Tofts PS et al., JMRI 1999; 10:223-232

[8] Patlak et al., J Cereb Blood Flow Metab 1983; 3:1-7