

Blood plasma Gd-DTPA concentration derived from skeletal muscle is comparable with a direct measurement from the aorta

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Introduction: For the quantitative analysis of DCE-MRI data, an estimate of blood plasma contrast agent (Gd-DTPA) concentration is required. Usually, reported plasma concentration curves derived from direct measurements of contrast agent concentration in a representative population are used, but, more recently, methodologies using reference tissues such as skeletal muscle have been developed [1,2]. This study aimed to compare plasma concentration curves derived from direct measurement in the aorta with curves derived from a reference tissue approach.

Methods and Materials: *Aorta measurement ($C_{p,aorta}(t)$):* Gd-DTPA plasma curves from six patients were derived by digitally tracing, interpolating and combining whole-blood data published by Fritz-Hansen *et al.* [3], acquired by measuring aortic concentration using DCE-MRI. These data were subsequently scaled by $1/(1-Hct)$, where Hct is the haematocrit fraction (assumed to be 0.45), to account for the cellular fraction of whole blood. To model long-duration plasma contrast agent kinetics (at time points greater than 120s following peak enhancement), data published by Weinmann *et al.* [4] were appended to the curve. A bi-exponential function of the form $C_p(t) = a_1 \exp(-m_1 t) + a_2 \exp(-m_2 t)$ was iteratively fitted to characterise the curve from peak enhancement onwards. These data constitute $C_{p,aorta}(t)$.

Muscle-derived plasma concentration ($C_{p,muscle}(t)$): DCE-MRI data were acquired axially from 25 male patients, centred on the lower abdomen, using a FLASH sequence with TE/TR/ $\alpha = 6.8\text{ms}/30\text{ms}/30^\circ$ and a reference PDw measurement using $\alpha=5^\circ$. Gd-DTPA was injected at 5ml/s. Each image acquisition lasted 0.96s and a total of 285 dynamic images were acquired. The dynamic data were converted to Gd-DTPA concentration using the method of Hittmair [5]. ROIs corresponding to the right gluteus maximus muscle were defined in each patient and the mean tissue Gd-DTPA concentration curve ($C_t(t)$) within the ROI was calculated. Plasma concentrations were estimated from these tissue uptake curves by fitting a bi-exponential function of the form $C_t(t) = S(\exp(-r_1 t) + \exp(-r_2 t))$, rearranging the modified Kety equation ($dC_t(t)/dt = k_{ep} C_p(t) - K^{trans} C_t(t)$) for $C_p(t)$ and substituting $C_t(t)$ for $g(t)$, giving:

$$C_{p,muscle}(t) = \left(\frac{m_1}{K^{trans}} - \frac{1}{v_e} \right) S e^{-r_1 t} + \left(-\frac{m_2}{K^{trans}} + \frac{1}{v_e} \right) S e^{-r_2 t} = a_1 e^{-m_1 t} + a_2 e^{-m_2 t}$$

where $C_{p,muscle}(t)$ is the muscle-derived Gd-DTPA plasma concentration curve, K^{trans} is the vascular exchange constant and v_e is the fractional extra-vascular, extra-cellular volume. We assume K^{trans} and v_e in skeletal muscle equals 0.07/min and 0.14, respectively [6].

Results and Discussion: The aortic plasma Gd-DTPA concentration is shown in Figure 1, with standard deviation error bars at each point and a bi-exponential fit from peak enhancement onwards overlaid. The mean muscle-derived plasma curve is also shown with equivalent error bars. The parameter values that define these curves are shown with their associated least-squares sigma uncertainties in Table 1. Parameters defining $C_{p,muscle}(t)$ have a greater uncertainty than those in $C_{p,aorta}(t)$, which could be due to greater noise in the muscle measurement or natural variation in either the plasma concentration or the muscle K^{trans} and/or v_e . Such variation could be caused by a number of physical or physiological sources such as a variation in cardiac output. However, it is clear from Figure 1 and Table 1 that, over the entire patient cohort, $C_{p,muscle}(t)$ is similar to $C_{p,aorta}(t)$, indicating that gluteus maximus or other major muscles can be used to estimate $C_p(t)$ in quantitative DCE-MRI analysis of the lower abdomen. Peak enhancement is slightly lower in $C_{p,muscle}(t)$, which is why the corresponding a_1 and m_1 are smaller than those for the aorta measurement. Both curves converge, however, following peak enhancement. Figure 2 shows maps of K^{trans} from a rectal carcinoma, processed using each plasma curve. The similarity of the histograms in Figure 2 illustrate the equivalence of each curve when used for quantification.

It is acknowledged that the model used in this analysis does not account for water exchange or fractional blood volume, both of which could be included in future analysis. Furthermore, the upslope of the aorta measurement is assumed to be negligible, which, for measurements of this duration, seems to be reasonable. The source of the variation in $C_{p,muscle}(t)$ could be evaluated by comparing each curve with direct measurements of plasma concentration in each patient, such as from a nearby artery, which was not possible in the current study due to arterial in-flow effects.

Conclusion: Across a large patient cohort, plasma concentrations derived from gluteus maximus muscle is equivalent to a direct measurement from the aorta. This approach can therefore be used to estimate plasma contrast agent concentration in quantitative DCE-MRI analysis of the lower pelvis, using fixed values of muscle K^{trans} and v_e . It also has the significant advantage over reported or 'standard' plasma curves that it is representative of individual patient physiology and of Gd-DTPA injection characteristics.

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References: [1] Kovar D.A. et al, *J Magn Reson Imag* **8**(5), 1126-1134 (1998) [2] Yankeelov T.E. et al, *Magn Reson Imag* **23**, 519-529 (2005), [3] Fritz-Hansen T., *MRM* **36**(2): 225-31 (1996), [4] Weinmann H.J., *Physiol Chem Phys Med NMR* **16**(2): 167-72 (1984), [5] Hittmair K., *MRM* **31**(5): 567-71 (1994), [6] Levett D. *BMC Pharmacology* **3**(3) (2003).

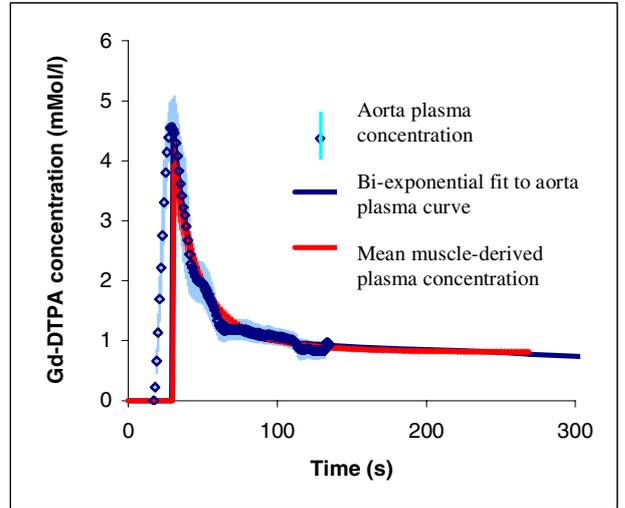


Figure 1: Mean aortic plasma concentration and bi-exponential fit ($C_p(t)$), with the mean muscle-derived plasma concentration overlaid. Error bars represent the standard error in each point.

	a_1 (mMol/l)	m_1 (/min)	a_2 (mMol/l)	m_2 (/min)
$C_{p,aorta}(t)$	3.6 ± 0.1	4.9 ± 0.1	1.3 ± 0.1	0.08 ± 0.04
$C_{p,muscle}(t)$	2.8 ± 0.6	3.2 ± 1	0.9 ± 0.3	0.05 ± 0.1

Table 1: Parameters defining $C_p(t)$ and $C_{p,muscle}(t)$ according to the function $C_p(t) = a_1 \exp(-m_1 t) + a_2 \exp(-m_2 t)$.

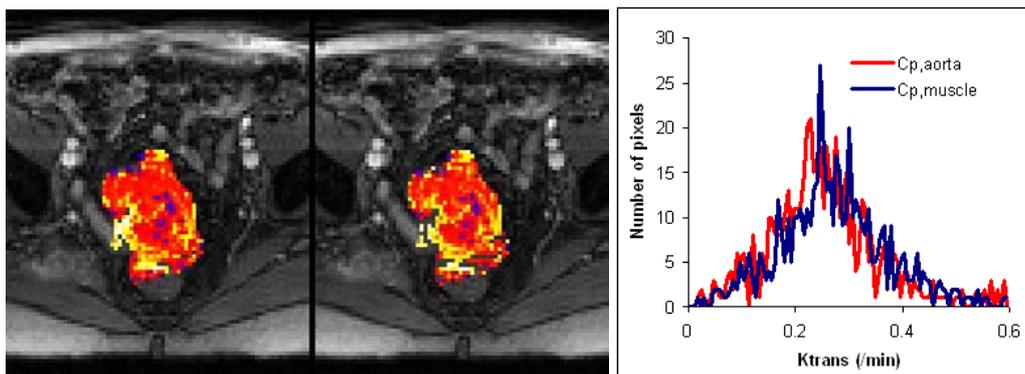


Figure 2: a) and b) K^{trans} maps from a rectal carcinoma, using $C_{p,aorta}$ and $C_{p,muscle}$, respectively. Histograms of these two maps in c) show the equivalence of the two plasma curves.