Comparison of the arterial input function measured at low and high contrast agent doses in prostate cancer patients

Shiyang Wang[1], Gregory S. Karczmar[1], Xiaobing Fan[1], Federico Pineda[1], Milica Medved[1], Ambereen Yousuf[1], and Aytek Oto[1]
[1]*Radiology, University of Chicago, Chicago, IL, United States*

Target audience: Researchers who focus on quantitative DCE-MRI, pharmacokinetic modeling, prostate cancer diagnosis.

Purpose: Dynamic contrast enhanced MRI (DCE-MRI) is an important tool in the diagnosis of prostate cancer. Correct measurement of the arterial input function (AIF) is critical for accurate measurements of [K^{trans}] and [Ve] from DCE-MRI. The inter- and intra-person variability in AIFs is large, and if not properly accounted for can lead to large errors in pharmacokinetic analysis. The AIF is frequently measured directly from an artery. However, direct measurements are subject to large systematic errors at standard doses of MRI contrast agents, due to 'shutter speed' and T2* effects. These effects are much smaller at lower doses of contrast media. Therefore, we compared directly measured AIFs for a low dose (AIF_{LD} =0.015 mmol/kg) and a high (standard) dose (AIF_{HD} =0.085 mmol/kg) administered 5 mins after the low dose. This allowed assessment of the errors at high doses of contrast media and accurate measurement of the true shape of the AIF (AIF_{LD}).

Methods: Twenty-two patients with prostate cancer underwent preoperative MRI scans and prostatectomy. DCE-MRI was acquired on a Philips Achieva 3T scanner using an mDixon sequence with TR/TE1/TE2 = 4.8/1.69/3.3ms; flip angle=10°, in-plane resolution:1.25x1.75x3.5mm^3; temporal resolution = 8.3 seconds/scan. Contrast agent (Multihance, Bracco) was injected I.V. at a low dose (LD) of 0.015 mmol/kg, and a speed of 0.32–0.35 mL/s. Images were acquired for 3.5 mins, with 25 dynamic scans post contrast. The 2nd DCE-MRI scan was performed 5 minutes after the completion of 1st DCE-MRI, with 85% of the total contrast dose ('HD'; 0.085 mmol/kg) delivered at a rate of 2.0 mL/s, with 60 dynamic scans, for 8.3 mins post injection. The duration of the two injections was the same, so that the curve shapes could be directly compared. The AIF was measured directly from the external iliac artery for both injections. Pixels with less than 20% enhancement were treated as non-enhanced and filtered out of images. Contrast concentration in the artery was calculated from signal enhancement [1], TR, flip angle, and contrast agent relaxivity, using established methods. Because AIF_{LD} included sharp first-pass and second-pass peaks, an AIF-empirical mathematical model (AIF-EMM) was used to fit both passes of the low dose contrast bolus (Figure 1, left). The low dose AIF-EMM is given by:

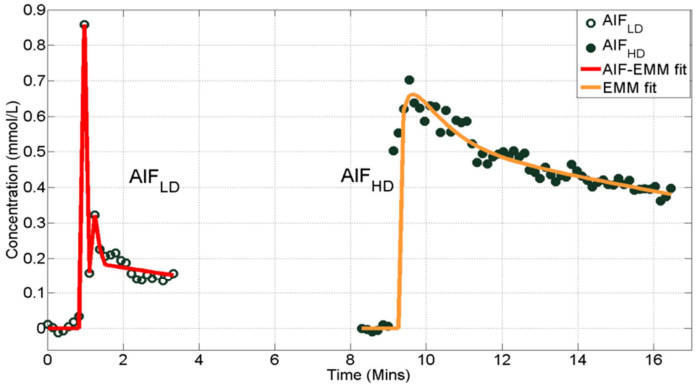

Figure 1 Concentration vs. time for low dose and high dose AIFs of a typical patient

Table 1 Double injection parameter comparison

Dose	Max Signal Enhancement(%)	Max Contrast concentration (mM)	Uptake Rate(α) (mM/s)	Washout(β) Rate(mM/s)
Low	33±9	0.68±0.23	1.58±1.35	0.4±0.32
High	29±1	0.87±0.31	1.79±0.79	0.038±0.026

$$C(t) = A * (1 - e^{-\alpha t}) * e^{-\beta t} * \left(b + c * e^{-\gamma t} + d * e^{-\theta(t-t0)^2}\right) \quad [Eq.\,1]$$

where, A is the upper limit of tracer concentration, α is the rate of contrast uptake (mM/s), β is the overall washout rate (mM/s), the term $b + c * e^{-\gamma t}$ controls the relationship between the 1st and 2nd passes, d and θ determine the peak and enhancement rate of the 2nd pass, and t0 is the time of the 2nd pass. A published EMM was used to fit AIF_{HD} (Figure 1, right) [2].

Results: Figure 1 compares AIF_{LD} vs. AIF_{HD} of a typical patient. Table 1 shows maximum signal enhancement, maximum contrast media concentration, uptake and washout rates determined from the EMM's for the low and high doses. Directly measured percent enhancement and maximum concentration are comparable for the low and high doses. However, when these parameters are normalized to the injected dose of contrast agent, the enhancement and max concentration is 6.45 times larger for the small dose than the large dose ($p<1e-4$). The large difference in enhancement and max concentration, as well as in washout rates is due to the fact that the first pass peak is completely absent in AIF_{HD}. AIF_{LD} also includes a clearly defined second pass peak of the contrast media bolus in 14 out of 22 scans (64%), but this second pass is never seen in AIF_{HD}.

Discussion and Conclusion: When AIF_{HD} and AIF_{LD} are normalized to the injected dose of contrast, the measured maximum enhancement and maximum contrast concentration are over 6.45 times larger for the small dose. The peak of the contrast media bolus cannot be detected following the large dose. This is consistent with the 'shutter speed' effect [3] and decreased T2* due to high plasma concentrations of contrast media. As a result enhancement is 'compressed' during the first pass of the contrast agent bolus. AIF_{LD} is much sharper than AIF_{HD} and includes a peak due to the second pass of the bolus. Due to the very significant under-estimate of arterial enhancement produced by a standard dose of contrast agent, direct arterial measurement of the AIF will produce large systematic errors in pharmacokinetic parameters. In addition, AIF_{HD} measured directly from the artery does not accurately represent the true shape of the AIF. Other methods, e.g. 'Reference Tissue Methods' [4] have potential to produce more accurate AIF's. AIF_{LD} provides an approximate gold standard that can guide development of methods for calculating the AIF.

References:[1]Schabel, Phys Med Biol.53(9):2345-73(2008) [2] Fan, MRM.51:487–494(2004) [3] Yankeelov, MRM.50:1151-69 (2003) [4] Yang, MRM. 61(4):851-9 (2009).