Glomerular filtration rate measurements by dual-injection MR renography

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Dynamic contrast-enhanced MR renography, analyzed with appropriate tracer kinetic models [1], is a promising technique for the non-invasive assessment of glomerular filtration rate (GFR). Dual-injection measurements, such as before and after administration of an angiotensin-converting-enzyme (ACE) inhibitor, have been proposed as an improved diagnostic marker of renovascular disease [2]. Technical challenges associated with dual-injection measurements during the same exam include (a) optimization of the injected doses for each of the two measurements and (b) appropriate analysis of the second renography dataset given residual tracer from the first injection. We performed Monte Carlo simulations to determine the optimal distribution of dose for two injections and evaluated the precision of the two GFR values estimated by a 3-compartment tracer kinetic model. A patient study was done to assess reproducibility of GFR measurements after ACE-inhibitor in subjects without renal artery stenosis (RAS).

Method

In a Monte Carlo simulation, an overall dose ($d_0$) of 12 ml Gd-DTPA (500 mM/L) was split for two injections, based on a preliminary study which showed that 6 ml is an optimal single-injection dose [3]. For an arbitrary dual injection experiment using doses $d_1$ and $d_2$, and separated by inter-injection time delay $t_i$, the arterial input is given by $A(t) = (d_1/d_0) A_0(t) + (d_2/d_0) A_0(t-t_i)$ [4], where a noise-free input function $A_0(t)$, reflecting two injections, was obtained by averaging aortic input of our dual-injection subjects after aligning the time axes to match the time of arterial peaks. Tracer concentration vs. time curves for renal cortex and medulla were constructed by convolving $A(t)$ with impulse retention functions (IRF) [1] based on a 3-compartment model (Fig. 1). After addition of random 5% noise, curves were separated into the first and the second data set and subjected to parameter-fitting. Compartmental residues at the beginning of the second study were computed by convolving the compartmental IRFs determined in the first fitting and extrapolation of the tail of the first aortic curve. In fitting the second data set, these compartmental residues were treated as the initial state. Each simulation scenario includes one functional status ($GFR_1 = GFR_2 = 60$ ml/min and $GFR_1 = GFR_2 = 25$ ml/min), and one of the five combinations of $d_1$ and $d_2$ ($2+4, 4+8, 6+6, 8, 10+2$ ml). Based on 1000 trials, the standard deviation (SD) for the difference $GFR_1 - GFR_2$, computed as an indicator of precision.

Twenty-three patients (40 kidneys without RAS) underwent dual-injection MRR. For every experiment, serial coronal 3D spoiled GRE images were acquired at 1.5 T (Avanto, Siemens): TR/TE/flip angle = 2.84 ms/1.05 ms/12°, field of view $400 \times 400 \times 100$ mm, voxel size $1.6 \times 1.6 \times 2.5$ mm, acquisition time 3 s. Doses of 4ml and 8ml were used for the first and the second study. Images were obtained over 10 min following each injection.

During the interval (about 10 min) between the two studies, i.v. enalaprilat (ACE inhibitor 0.04 mg/kg, up to 2.5mg) was administered. GFR$_1$ and GFR$_2$ for a same kidney as estimated by the 3 compartment model were compared using correlation plot and linear regression, and their differences were evaluated by histogram.

Results and Discussion

Fig.2 (a) shows that, with overall dose of 12 ml for both injections, optimal dose for the first injection is 4-6 ml with a dose of 6-8 ml for the second injection. With dose of 4ml, SD of GFR$_1$-GFR$_2$ was 5.1 ml/min for true GFR of 60 ml/min, and 3.5 ml/min for true GFR of 25 ml/min, which indicated that GFR change of more than 7-10 ml/min (1.96SD) in a dual-injection study can be regarded as a significant change.

For patients without RAS, GFR$_1$ and GFR$_2$ have a reasonably high correlation coefficient, $R^2 = 0.81$ (Fig. 3(a)). The slope of the regression line, 0.65, is lower than 1 most likely because of the few outliers with much higher GFR$_1$ than GFR$_2$. Fig. 3(b) shows that for 30 cases (out of 40) the difference (GFR$_1$ – GFR$_2$) was within [-10, 10] ml/min. The higher difference between GFR$_1$ and GFR$_2$ in patient study than in the simulation could be attributed to additional sources of errors not reflected in our simulations, such as signal-to-concentration conversion, aortic input, or to physiologic effect of ACE.

Our results suggest that both intrinsic noise and measurement errors cause reduction in precision of GFR in a dual-injection experiment. For the detection of true physiologic changes between first- and second-injection MRR using the current techniques, thresholds of GFR changes must exceed at least 7-10 ml/min to be considered meaningful.