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Comparison of Models and Contrast Agents for Improved Signal and Signal Linearity in Dynamic Contrast-Enhanced Pulmonary MRI

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Abstract

Motives—To compare pulmonary blood flow (PBF) measurements acquired with three previously published models (low dose "single bolus", "dual bolus", and a "non-linear correction" algorithm) for addressing the non-linear relationship between contrast agent concentration and MR signal in the arterial input function (AIF), and to compare both lung signal and PBF measurements obtained using Gd-DTPA (Magnevist) with those obtained using the high-relaxivity agent Gd-BOPTA (Multihance).

Materials and Methods—Ten out of twelve healthy humans were successfully scanned on two consecutive days at 1.5T. Contrast-enhanced pulmonary perfusion scans were acquired with a 3D spoiled gradient echo pulse sequence and interleaved variable density k-space sampling with a 1s frame rate and 4×4×4 mm³ resolution. Each day, two perfusion scans were acquired with either Gd-DTPA or Gd-BOPTA; the order of the administered contrast agent was randomized. ROI analysis was used to determine PBF based on indicator dilution theory. Linear Mixed Effects Modeling was used to compare the AIF models and contrast agents.

Results—With Gd-DTPA, no significant differences were observed between the mean PBF calculated for the "single bolus" (323 ± 110 ml/100ml/min), "dual bolus" (315 ± 177 ml/100ml/min), and "non-linear correction" (298 ± 100 ml/100ml/min) approach. With Gd-BOPTA, the mean PBF using the "dual bolus" approach (245 ± 103 ml/100ml/min) was lower than with the "single bolus" (345 ± 130 ml/100ml/min, $p < 0.01$) and "non-linear correction" (321 ± 115 ml/100ml/min, $p = 0.02$). Peak lung enhancement was significantly higher in all regions with Gd-BOPTA than with Gd-DTPA ($p < 0.01$).

Conclusion—The “dual bolus” approach with Gd-BOPTA resulted in a significantly lower PBF than the other combinations of contrast agent and AIF model. No other statistically significant differences were found. Given the much higher signal in the lung parenchyma using Gd-BOPTA, the use of Gd-BOPTA with either single bolus or the non-linear correction method appears most promising for voxel-wise perfusion quantification using 3D dynamic contrast enhanced pulmonary perfusion MRI.

Keywords

dynamic contrast enhanced MRI; quantitative pulmonary perfusion; arterial input function

INTRODUCTION

Quantification of pulmonary perfusion is desired to detect progressive fibrotic and obstructive lung diseases, to monitor treatment response longitudinally, or to quantify the rate of disease progression [1–6]. However, quantification of pulmonary perfusion using the common dynamic T1-weighted contrast-enhanced MRI is challenging due to both the nonlinear relationship between signal and contrast agent (CA) concentration and the lungs' low baseline signal. The non-linear relationship of signal to CA concentration most often results in an underestimation of the CA concentration near the peak of the arterial input function (AIF), conventionally measured in the pulmonary artery, resulting in an overestimation of pulmonary blood flow (PBF) measurements.

Three alternative AIF models have been proposed in the literature to better compensate for the tradeoff between non-linear arterial signal with high CA concentration and signal to noise in the lung parenchyma. The first, and arguably the easiest to implement in a clinical setting, is a low-dose “single bolus”, following the strategy of Nikolaou et al. [7,8]. Ohno et al. concluded that 5 mL should be administered at 5 mL/sec at concentrations of 0.3 mmol/mL for patients < 70 kg and 0.5 mmol/mL for patients >70 kg. This is equivalent to roughly 0.020–0.025 mmol/kg – approximately ¼ of the package label standard dose. The second proposed strategy, the “dual bolus” approach, has been adapted to the lung from cardiac perfusion by Risse et al., and has been implemented in a clinical setting by others [2,9]. Prior to a “normal” contrast bolus adequate for generating sufficient lung signal, a low dose “pre-bolus” acquisition is performed and used solely for the AIF determination. Assuming a linear and time-invariant system, the “true” AIF signal-time curve is constructed by scaling and shifting the pre-bolus to match the second “normal” dose bolus. Although not compared directly to SPECT, the approach showed promising results when compared to prior MRI and SPECT literature values. However, it requires two perfusion scans with some intervening delay to allow for sufficient washout of the “pre-bolus” injection. The third method focuses not on the contrast injection protocol itself but instead on a post-processing algorithm to correct for the non-linearity and obtain an accurate AIF signal-time course curve [10]. Despite using a low dose of 0.025 mmol/kg, Neeb et al. showed that assuming a linear relationship between signal and CA concentration was not valid for all pulse sequence parameters. Their “non-linear correction” method is based upon the use of a calibration curve derived from the MR signal equation to account for the specific pulse sequence parameters and contrast agent relaxivity. Notably, this method has the advantage that it does

not require prior knowledge about the pre-contrast T1 and T2* values on the tissue for the calibration curve.

The majority of prior work related to pulmonary perfusion quantification has used gadopentetate dimeglumine (Gd-DTPA, Magnevist; Schering AG, Berlin, Germany). However, gadobenate dimeglumine (Gd-BOPTA, Multihance; Bracco Imaging SpA, Milan, Italy) has a higher relaxivity. It therefore has the potential to improve signal in the lung parenchyma in contrast-enhanced pulmonary perfusion MRI. This is particularly important in the anterior non-dependent portions of the lungs in supine individuals where lung tissue density (and therefore signal) is even lower than in the dependent portions of the lung.

Our purpose, therefore, was two-fold: 1) to directly compare pulmonary blood flow measurements obtained using the three proposed models (low-dose "single bolus", "dual bolus", and "non-linear correction") for addressing the non-linear relationship between signal and contrast agent concentration, and 2) to compare lung parenchyma signal and quantitative measures of pulmonary blood flow obtained using Gd-BOPTA with those obtained using Gd-DTPA.

MATERIALS AND METHODS

MR Protocol

In this HIPAA compliant and Institutional Review Board (IRB) approved study, twelve healthy human subjects (7F, 5M, age: 37 ± 13 yrs, weight: 71 ± 11 kg) were each scanned on two consecutive days, using Gd-BOPTA on one day and Gd-DTPA on the other, in a randomized order. Scans were performed on a 1.5T scanner (SignaHDxt, GE Healthcare, WI) with a commercial 8-channel cardiac phased array coil. Dynamic contrast-enhanced perfusion MRI was performed using a 3D spoiled gradient echo pulse sequence and interleaved variable density k-space sampling at end-expiration [11]. Two perfusion datasets were obtained each day: a "pre-bolus" acquisition using 0.01 mmol/kg of contrast agent and a "bolus" acquisition using 0.025 mmol/kg. A wait time of 20 minutes between scans was allowed for CA washout. The injection was performed at 3.5 mL/s and was followed by 35 mL of saline. Relevant parameters were: TR/TE = 2.12/0.70 ms, flip = 30° , 75% fractional echo, acquired spatial resolution = isotropic 4 mm, FOV = 40 (S/I) $\times$ 28 (A/P) $\times$ 40 (L/R) cm³, BW = ± 125 kHz, parallel acceleration 2 $\times$ 2, and acquired temporal resolution of 1 second with 22 time frames. Images were reconstructed using a k-space adaptive filter as a temporal view-sharing method. This filter has a width of 1 s at the center of k-space and linearly increased to 7 s to the edge of k-space for a temporal footprint of 7 s.

Image Analysis and Measurements

Image measurements were performed using MATLAB (The Mathworks Inc.; Natick, MA, USA). Signal-time courses were determined in seven regions: the main pulmonary artery (AIF) and in three regions of each lung. The signal-time course within the AIF was determined by a semi-automatic process. A 3D box was manually centered on the pulmonary artery (excluding the pulmonary veins) and 30 pixels with the highest signal intensity during the entire pixel time course were selected to avoid partial volume effects.

The lung signal-time course was determined by selecting a coronal slice in the anterior, middle, and posterior regions using local anatomy as landmarks in order to be consistent through the subject population. Regions of interest (ROIs) were manually drawn to exclude large vessels in both the right and left lung. All relative signal-time courses were then calculated using $S_{rel}(t) = [S(t) - S(0)]/S(0)$, where $S(0)$ was the average signal over the first three time frames before arrival of the contrast bolus.

The CA concentration time course for the AIF was related to pulmonary vascular signal using the following equations for each of the three models:

1. "Single Bolus" [8]:

The relative signal-time course was determined using the "bolus" acquisition, and converted to the CA concentration time course by assuming a linear relationship between signal and CA:

$$C_{AIF}(t) = S_{rel}(t) \quad \text{Eq. 1}$$

2. "Dual Bolus" [9]:

The AIF was constructed using data from the "pre-bolus" acquisition as previously published by Risse et al.:

$$C_{AIF}(t) = \sum_{q=0}^{V/V_{pre}} S_{rel,pre}(t + q\tau); \quad \text{Eq. 2}$$

where V is the "bolus" volume, V_{pre} is the "pre-bolus" volume, $S_{rel,pre}$ is the "pre-bolus" signal-time course for the "pre-bolus", and τ is the duration of the "pre-bolus" injection. Therefore the new C_{AIF} is constructed by adding up the "pre-bolus" volume until it matches the volume of the "bolus" injection, while being shifted to achieve the correct kinetics of the "bolus" injection.

3. "Non-linear Correction" [10]:

Normalized $S_{rel}(t)$ in the AIF from the "bolus" acquisition was corrected to $C_{AIF}(t)$ according to its appropriate calibration curve using the method described by Neeb et al. and the signal equation for an SPGR sequence:

$$S_{SPGR}(c) = M_0 \cdot \exp(-TE \cdot R_2^*) \cdot \sin(\alpha) \cdot \frac{1 - \exp(-TR \cdot R_1)}{1 - \cos(\alpha) \cdot \exp(-TR \cdot R_1)} \quad \text{Eq. 3}$$

where signal, S_{SPGR} , is a function of concentration, c ; M_0 is the equilibrium longitudinal magnetization; α is the flip angle; and R_i ($i = 1, 2$) is the relevant relaxation rate for the CA administered. Equation 3 can be solved by using the appropriate pulse sequence parameters and relaxivity values ($r_1 = 4.1$ L/mmol/s for Gd-DTPA; 6.6 L/mmol/s for Gd-BOPTA, and $r_2^* = 22$ L/mmol/s for Gd-DTPA; 28 L/mmol/s for Gd-BOPTA) from the literature [10,12,13].

The calibration curve relating pulmonary vascular signal and CA concentration has three regions, the boundaries of which are determined to minimize the expected error. Region I includes concentrations for which the linear approximation is reasonable, Region III includes concentrations which are determined solely from the analytical MR signal equation, and Region II is a smooth transition zone (centered on a concentration c_{norm} as determined using methodology described in Ref [10]) in which concentration is calculated as a linearly-weighted combination of the methods used for Region I & III. Figure 1 shows the calibration curves that were used for both Gd-DTPA ($c_{\text{norm}} = 0.75$ mM) and Gd-BOPTA ($c_{\text{norm}} = 1$ mM).

For all three AIF models, we assumed that the CA concentration in the lung parenchyma during the “bolus” acquisition was low enough for the linear assumption to hold true and thus CA concentration-time courses were simply proportional to the relative signal-time courses. The corrected AIF concentration as a function of time was then used to determine pulmonary blood flow (PBF) in each of the six parenchymal lung regions using a truncated singular value decomposition (SVD) deconvolution (0.3 eigenvalue threshold) and the well-known techniques of indicator dilution theory [14,15]:

$$C_{\text{lung}}(t) = \text{PBF} [C_{\text{AIF}}(t) \otimes R(t)] \quad \text{Eq. 4}$$

where $R(t)$ is the residue function. Finally, the global PBF was calculated as the mean of the six regional PBF measurements for each subject.

In addition to PBF, two other parameters were recorded. Relative peak AIF and peak signal in the lung parenchyma were defined as the maximum value of the signal in each respective location divided by the baseline pre-contrast signal. The peak AIF signal was used as a qualitative proxy for the amount of signal saturation, while peak signal in the lung ROI's were used to compare the relative signal enhancement within the lung parenchyma between the two different contrast agents.

Statistical Analysis

Statistical analysis was done with R (R Development Core Team, Vienna, Austria) and the nlme package (Pinheiro et al. 2012). Continuous variables were summarized as mean $\pm$ 1 standard deviation (SD). Linear mixed effect models [16] were used to model PBF as a function of contrast agent and AIF model (fixed effects) with a subject-dependent intercept (random effects). The models were fitted by maximum likelihood and were based on complete data. A likelihood ratio F test was used to assess whether inclusion of the contrast agent by AIF model interaction term significantly improved the model fit. Relative peak lung enhancement was compared between CA using paired Student's t-test. A p-value 0.05 (two sided) was the criterion for statistical significance.

RESULTS

Of the 12 subjects recruited, 10 completed the exams successfully at both time points for all models resulting in 10 complete datasets for analysis. Two of the 12 subjects (both female) had adverse reactions (both reported "tingling" and "burning" sensations) to the "pre-bolus"

(0.01 mmol/kg) acquisition with Gd-DTPA and refused the "bolus" (0.025 mmol/kg) acquisition. The contrast agent by AIF model interaction term (derived from the likelihood ratio F test) was included in both the PBF ($p = 0.01$) and the AIF model ($p = 0.06$). The latter was done despite being only marginally significant to facilitate comparisons between models. The average peak AIF values and PBF measurements for each method are illustrated with box plots in Figure 2. For all AIF models, the average peak AIF was greater using Gd-BOPTA than with Gd-DTPA (Figure 2a). For a given contrast agent, the peak AIF increased for both the "dual bolus" and "non-linear correction" models compared to the "single bolus", although not all comparisons reached statistical significance. The "dual bolus" method, however, differed significantly between the two contrast agents used ($p < 0.01$) and compared to the "single bolus" ($p < 0.01$) and "non-linear correction" ($p = 0.01$) models when used with Gd-BOPTA. The mean peak AIF signal value for the "dual bolus" correction method with Gd-BOPTA was the greatest (21 ± 6 relative to baseline).

The mean PBF values over the whole lung with Gd-DTPA were 323 ± 110 ("single bolus"), 315 ± 177 ("dual bolus"), and 298 ± 100 ("non-linear correction") ml/100ml/min (Figure 2b, Table 1). Similarly, mean PBF values over the whole lung with Gd-BOPTA were 345 ± 130 ("single bolus"), 245 ± 103 ("dual bolus"), and 321 ± 115 ("non-linear correction") ml/100ml/min (Figure 2b, Table 1).

Statistical results from the linear mixed effects model used to assess differences in PBF across both contrast agent and AIF modeling method are presented in Table 1. The PBF values calculated from all models with Gd-DTPA did not differ significantly from each other (all p -values $\gg 0.05$). However, using Gd-BOPTA, the "dual bolus" method produced significantly lower PBF values than both the "single bolus" ($p < 0.01$) and "non-linear correction" models ($p = 0.02$). Only the "dual bolus" AIF method resulted in significantly different PBF values when using different contrast agent agents ($p < 0.01$) – lower PBF values were observed using Gd-BOPTA. In fact, the only significant differences when combining the effects of both contrast agent and AIF model was for the "dual bolus" method. "Single bolus" and "non-linear correction" models did not significantly differ, regardless of the contrast agent used.

Lung enhancement was greater with Gd-BOPTA compared with Gd-DTPA (Table 2), regardless of location (anterior, middle, or posterior), shown visually in Figure 3.

DISCUSSION

Quantification of pulmonary perfusion using dynamic contrast-enhanced MRI requires accurate modeling of contrast agent concentration. In order to maintain adequate signal in the lung parenchyma, there is a limit to how low the dose of the bolus can be made because of the very large dynamic range between the high signal in the main pulmonary artery (where the AIF is measured) and the low tissue density in the lung parenchyma. Using a simple model that assumes a linear relationship between signal intensity and CA concentration in the main pulmonary artery can result in an underestimation of the peak of the AIF concentration time course. This error then propagates into the determination of PBF and other quantitative metrics. In this study, we compared three different previously

published AIF models for minimizing this non-linear effect using both Gd-DTPA, the contrast agent most frequently used in the pulmonary perfusion MRI literature and a newer contrast agent with a higher relaxivity, Gd-BOPTA.

Both contrast agents' peak reconstructed AIF were greater with the non-linear method than the single bolus, suggesting that some signal saturation occurs in the AIF even with a 1/4-standard (0.025 mmol/kg) bolus. Despite the suggestion of signal saturation in the AIF, however, the PBF measurements did not differ significantly between “non-linear” and “single bolus” models, possibly related to the small sample size.

The peak AIF was greater with Gd-BOPTA than with Gd-DTPA when using the “dual bolus” method, which may influence the observed lower PBF with Gd-BOPTA compared with Gd-DTPA. Unlike Gd-DTPA, the relaxation rate of Gd-BOPTA is not linear across CA concentrations and actually starts to plateau at higher CA concentrations [12]. This will result in lower signal intensity at higher CA concentrations than predicted for a constant relaxivity. It is possible that the pulmonary capillaries may reach high enough concentrations that the non-constant relaxivity of Gd-BOPTA could lead to erroneously low PBF calculations.

The well-known physiological gravitational gradient in lung parenchyma density along anterior/posterior direction for the supine subjects was seen using both Gd-DTPA and Gd-BOPTA; however, the lung enhancement was greater with Gd-BOPTA, likely due to its higher relaxivity than Gd-DTPA. This is especially important when attempting quantitative pulmonary perfusion measurements due to the improved linearity of signal to concentration when smaller contrast doses and higher flip angles than the Ernst angle are used. Also, when performing 3D perfusion assessment, the importance of maintaining adequate signal in the non-dependent regions of the lung becomes more important than when performing 2D assessments in a mid-coronal plane.

This study has limitations. Four of our p-values were at the 0.05 threshold of statistical significance. Our small sample size may have contributed to this. Also potential real differences could be masked by the variability of PBF measurements due to lung inhomogeneity combined with the ROI analysis that was used. Furthermore, possible variation in breath hold volumes are known to affect PBF measurements [17,18] and could have confounded these results. Prior work has shown reasonable intra-observer reproducibility for PBF measurements [19]. Therefore, the same observer placed all the ROIs for this region based analysis. To minimize the effects of differing lung volumes on our results, we used end-expiratory breath holds that have been shown to be more reproducible than inspiration breath holds [20,21]. Additionally, we assumed that the pulmonary artery remained unaffected by slightly different breath hold positions between the “pre-bolus” and “bolus” acquisitions. Furthermore, no reference standard of pulmonary blood flow (e.g. positron emission tomography) was obtained. Thus, while we have shown that the “dual bolus” technique with Gd-BOPTA produced results at odds with the other models; we have not shown which of the models produces the most accurate estimate of actual pulmonary blood flow. Future work will be needed to directly compare the use of these AIF models when using Gd-BOPTA with a true reference standard. It is also possible that no differences were

observed between the single bolus and the nonlinear correction method due to our specific pulse sequence parameters. High flip angles and short TR/TE times, like those used in our pulse sequence, will improve the linearity between signal and contrast agent concentration making it less necessary to correct for nonlinear relationships. However, when high flip angles and short TR/TE times are not feasible, the nonlinear correction method might improve these situations, as was seen in the original paper by Neeb et al., in which a 15 degree flip angle was used during acquisition [10].

Despite these limitations, this study is to our knowledge the first to directly compare the most promising models for addressing the non-linearity of signal to concentration for quantitative dynamic contrast enhanced 3D pulmonary perfusion MRI and to compare the conventionally used contrast agent (Gd-DTPA) with a higher relaxivity agent (Gd-BOPTA). We observed significant differences between PBF measurements when using the “dual bolus” method with Gd-BOPTA, possible due to the non-constant relaxivity with respect to CA concentration. Therefore we recommend not using the “dual bolus” method with Gd-BOPTA. Additionally, we observed that 1) the PBF measurements did not differ between contrast agents when using either of the other AIF determination models (“single bolus” or “non-linear correction”) and 2) the lung tissue signal is greater with Gd-BOPTA than with Gd-DTPA due to the higher relaxivity of Gd-BOPTA. Anticipating that Gd-BOPTA will provide improved quantitative dynamic 3D contrast enhanced pulmonary perfusion MRI, these results, in total, support the use of Gd-BOPTA in combination with either a “single dose” or the “non-linear correction” method although future work will be necessary to confirm these pilot study results in the setting of disease.

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Figure 1.

Calibration curves based on the analytical signal equation for normalized signal intensity and CA concentration for Gd-DTPA (dashed line) and Gd-BOPTA (dotted line) are shown. Higher signal intensity is seen for Gd-BOPTA due to its higher relaxivity compared to that of Gd-DTPA. The transitions from the linear approximation to purely analytic regions are indicated by $cnorm$ labels on the graph and are slightly different for each contrast agent ($cnorm = 0.75$ mM for Gd-DTPA; 1.0 mM for Gd-BOPTA).

Figure 2.

Average values of peak AIF (a) and pulmonary blood flow (b) are presented in box plots across each AIF model. The red boxes on the left are for Gd-DTPA, and the blue boxes on the right are for Gd-BOPTA. Mean values are denoted by solid circles. Median values are denoted by red lines. Observed statistical differences ($p < 0.05$) from linear mixed modeling are presented for both measurements. For Peak AIF, significant differences are presented with solid brackets. For PBF, solid brackets represent statistically significant differences, whereas the dashed brackets represent statistical differences near the 0.05 threshold (0.049 – 0.051).

Figure 3.
An axial and coronal time frame at peak lung enhancement for a typical subject is shown (Gd-DTPA on the left column, Gd-BOPTA on the right column). The lung parenchymal signal and known A/P gradient can be better appreciated with Gd-BOPTA.

P-value results from a linear mixed effects model to assess differences in PBF across both contrast agent and AIF determination method. Since the model included the CA by AIF model interaction, p-values for every possible pair-wise comparison of CA-AIF model combination are listed; note the matrix of p-values is symmetric. P-values 0.05 were considered statistically significant and are formatted in *italics*. P-values < 0.01 were considered to be highly statistically significant and are underlined in the table.

Table 1

	Gd-DTPA			Gd-BOPTA		
	Single Bolus	Dual Bolus	Non-linear	Single Bolus	Dual Bolus	Non-linear
PBF* (Mean ± 1 SD)	323 ± 110	315 ± 177	298 ± 100	345 ± 130	245 ± 103	321 ± 115
Gd-DTPA						
Single Bolus	--	0.83	0.47	0.85	<i>0.05</i>	0.98
Dual Bolus	0.83	--	0.61	<i>0.05</i>	<u>≤ 0.01</u>	<i>0.05</i>
Non-linear	0.47	0.61	--	0.98	<i>0.05</i>	0.87
Gd-BOPTA						
Single Bolus	0.85	<i>0.05</i>	0.98	--	<u>≤ 0.01</u>	0.45
Dual Bolus	<i>0.05</i>	<u>≤ 0.01</u>	<i>0.05</i>	<u>≤ 0.01</u>	--	<i>0.02</i>
Non-linear	0.98	<i>0.05</i>	0.87	0.45	<u>0.02</u>	--

* PBF units are ml/100ml/min

Table 2

Relative peak lung enhancement values, normalized to baseline pre-contrast signal with their corresponding p-values for Gd-DTPA and Gd-BOPTA are tabulated. Greater lung parenchymal tissue enhancement is seen with Gd-BOPTA than with Gd-DTPA.

	Gd-DTPA	Gd-BOPTA	<i>p-value</i>
Anterior:	2.1 ± 0.5	3.0 ± 0.8	<< 0.01
Middle:	2.1 ± 0.8	3.2 ± 1.0	<< 0.01
Posterior:	3.5 ± 1.0	4.9 ± 1.4	<< 0.01