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Vascular Input Function Correction of Inflow Enhancement for Improved Pharmacokinetic Modeling of Liver DCE-MRI

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Abstract

Purpose—To propose a simple method to correct the vascular input function (VIF) due to inflow effects and to test whether the proposed method can provide more accurate VIFs for improved pharmacokinetic modeling.

Methods—A spoiled gradient echo sequence based inflow quantification and contrast agent concentration correction method was proposed. Simulations were conducted to illustrate the improvement in the accuracy of VIF estimation and pharmacokinetic fitting. Animal studies with dynamic contrast-enhanced (DCE) MR scans were conducted before, one week and two weeks after portal vein embolization (PVE) performed in the left portal circulation of pigs. The proposed method was applied to correct the VIFs for model fitting. Pharmacokinetic parameters fitted using corrected and uncorrected VIFs were compared between different lobes and visits.

Results—Simulation results demonstrated that the proposed method can improve the accuracy of VIF estimation and pharmacokinetic fitting. In animal study results, pharmacokinetic fitting using corrected VIFs demonstrated changes in perfusion consistent with changes expected after PVE, while the perfusion estimates derived by uncorrected VIFs showed no significant changes.

Conclusion—The proposed correction method improves the accuracy of VIFs and therefore provides more accurate pharmacokinetic fitting. This method may be promising in improving the accuracy of perfusion quantification.

Keywords

vascular input function; inflow enhancement quantification; dynamic contrast-enhanced imaging; pharmacokinetic fitting

Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with pharmacokinetic modeling is an important method to assess the liver perfusion (1) and function (2). It has been applied to the detection (3) and characterization (4) of malignancy, classification of fibrosis stage (5,6), and identification of cirrhosis (7). The liver is a complex organ with two vascular sources, the hepatic artery, and portal vein. In the pharmacokinetic analysis of liver DCE-MRI, arterial input function (AIF) and portal venous input function (PIF) are both critical for accurate model fitting (1). Any significant deviation from the real vascular input function (VIF) can result in unreliable fitting results (8).

Usually, due to the limits in imaging spatial resolution, AIF and PIF are commonly extracted from the abdominal aorta as a surrogate of the hepatic artery, and the main portal vein, respectively, where the blood flow velocities are relatively high. In 3D T_1 -weighted spoiled gradient echo (SGRE) sequence, which is widely used in routine DCE protocols, axial excitation slabs are an efficient means to provide 3D volumetric coverage of the liver and the most commonly used strategy for liver imaging. However, as a result, unsaturated spins in fresh blood entering the excitation volume from above (aorta) or below (portal circulation) will lead to inflow enhancement due to the time of flight effect.

Many researchers have attempted to acquire accurate VIF/AIF or provide alternatives when a reliable AIF is difficult to obtain. Phase-based AIF methods (9) measure the phase accumulation due to the susceptibility changes and transform the phase signal into the concentration of contrast agent. This method can avoid the magnitude saturation problems. However, it suffers from phase wrapping, flow-induced phase shift or extended scan time due to a prolonged repetition time (TR). Moreover, the phase-based VIF/AIF extraction method is sensitive to signal to noise ratio (SNR). A standard population-averaged AIF (10) has also been proposed based on empirical equation fitting. This method is useful when a reliable AIF cannot be measured, and it can provide stable fitting results. The disadvantage of the population-average AIF approach is that it ignores the inter-subject variance of cardiac output of different patients, which may introduce additional error. Saturation or inversion preparation pulses before acquisition (11) were commonly used to address the inflow problem, as well. However, saturation and inversion pulses may reduce SNR performance and prolong scan time.

Roberts et al quantitatively evaluated the influence of inflow effect and B_1 inhomogeneity on the AIF and the kinetics fitting using a flow phantom (12). Recently, Ivancevic et al. proposed a method to fit a calibration equation which describes the relationship between contrast agent concentration and signal intensity using a flow phantom (13). This method is limited in clinical application since it requires the use of a calibration experiment with flow phantom for any individual imaging protocol. Wang et al. also proposed a method that assumes a peak of AIF, and interpolates the AIF using a cubic spline, and optimizes the AIF using a two-input one compartment model (1) with least square method (8). In addition, the extended RF excitation volume in the superior-inferior direction used with coronal or sagittal excitations may saturate the inflowing spins more effectively. However, with the

considering of the balance between the spatial resolution and scan time, the axial acquisition is the most commonly used since it can minimize the partial volume effect in vascular input function extraction (12).

In this study, we propose a simple method to quantify the inflow enhancement effect from an SGRE-based DCE-MRI study and develop a method to correct the VIF for inflow effects, thereby providing more accurate pharmacokinetic modeling for liver DCE-MRI.

Theory

Figure 1 shows examples of inflow enhancement effects in abdominal aorta (Fig. 1a) and portal vein (Fig. 1b) in the pre-contrast phase of the DCE-MR image of a pig. Such inflow enhancement will affect the contrast agent concentration estimation of VIFs, thus resulting in inaccurate pharmacokinetic parameter estimation. The protons in the hepatic arteries and portal veins must pass through the capillary bed in the liver before reaching the hepatic veins. Since the liver is fully included in the field of view, it is reasonable to assume that blood in the small branch of the hepatic vein has experienced a sufficient number of RF pulses and reached the steady state M_z^{SS} . Supporting Figure S1 gives the enhancements of aorta, portal vein and hepatic vein observed on the in-vivo DCE scan, which also can serve as an evidence of this assumption. Thus, the equilibrium magnetization M_z^0 can be calculated using the SGRE steady state equation (14,15):

$$M_z^{SS} = \frac{M_z^0(1 - e^{-TR/T_1})}{1 - \cos(\alpha)e^{-TR/T_1}} \quad [1]$$

where TR is the repetition time, α is the flip angle. On the other hand, due to the high blood velocity, the blood in the abdominal aorta and the main branches of portal vein may only experience a limited number of pulses and not reach the SGRE steady state. In the phases before contrast agent injection, the number of pulses the blood spins have experienced, N_p , can be estimated (15) using the equation:

$$M_z^{(N_p)} = M_z^0(1 - e^{-TR/T_1}) \frac{1 - (\cos(\alpha)e^{-TR/T_1})^{N_p-1}}{1 - \cos(\alpha)e^{-TR/T_1}} + M_z^0(\cos(\alpha)e^{-TR/T_1})^{N_p-1} \quad [2]$$

where $M_z^{(N_p)}$ is the magnetization of spin. As it can be seen from Eq. [2], N_p is derived directly from the equation without knowing of the flow pattern or flow speed. N_p is a quantitative parameter to describe the inflow enhancement. Please see the Appendix for the complete derivation of Eq. [2].

Smaller N_p occurs when a spin moves very fast or is near the border of an imaging volume to experience an insufficient number of pulses for the magnetization to approach the steady state, resulting in significant inflow enhancement. While larger N_p means a spin flows

slowly or is far away from the margin of FOV, thus having milder inflow enhancement effect. Since the temporal resolution of the liver DCE-MRI is usually much lower than cardiac pulsation, it is reasonable to assume that inflow enhancement effects are independent of cardiac phase, and we note that portal flow is non-pulsatile and therefore independent of cardiac pulsatility. Thus, the T_1 of blood after contrast agent injection can be estimated phase by phase using Eq. [2] if M_z^0 and N_p are known or can be measured.

The aorta and portal vein can be approximated as straight within the imaging volume, therefore the distance the blood inside these vessels has traveled can be considered as straight as well. Hence, the mean velocity of the flowing spin can be approximated as:

$$v_{\text{SGRE}} = \frac{D}{N_p \text{TR}} \quad [3]$$

where D is the travel distance of a flowing spin, which can be measured from the images directly. Figure 2 is the flowchart of the proposed correction method using the PIF as an example.

Methods

Simulation Study

To test whether the proposed method can estimate the inflow enhancement and effectively correct the contrast agent concentration of VIFs for more accurate pharmacokinetic analysis, a numerical phantom consisted of an aorta, portal vein, and static liver tissue was designed (Fig. 2). The diameters of aorta and portal vein were set to 17 mm (16) and 11 mm (17), respectively. Since both the aorta and portal vein are large vessels with a diameter larger than 5 mm, plug flow pattern was simulated for both vessels (18-20). Though the velocity of the aorta is pulsatile, the temporal resolution of each DCE-MRI time frame is generally much lower than the cardiac cycle, so the velocity of the aorta was set as the mean velocity of diastole and systole, and that was 0.5 m/s (21,22). While the velocity of the portal vein is relatively stable along time (23,24), a constant velocity was set to 0.3 m/s (17).

The concentration curve of AIF was simulated using the empirical equations (25)

$$\text{AIF} = \sum_{n=1}^2 \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(-\frac{(t - t_n)^2}{2\sigma_n^2}\right) + a \exp(-bt) / (1 + \exp(-s(t - \tau))) \quad [4]$$

As for the PIF, the second term of the empirical equation

$$\text{PIF} = a \exp(-bt) / (1 + \exp(-s(t - \tau))) \quad [5]$$

was used because it is not the first pass of contrast agent. The equation parameters for VIFs were fitted with a set of real patient DCE data (26). The parameters for AIF were: $A_1 = 1.6 \text{ mM/min}$, $A_2 = 50.4 \text{ mM/min}$, $t_1 = 0.38 \text{ min}$, $t_2 = 20.0 \text{ min}$, $\sigma_1 = 0.08 \text{ min}$, $\sigma_2 = 0.38 \text{ min}$, $\sigma_2 = 5.41 \text{ min}$, $a = 3.19 \text{ /min}$, $b = 0.12 \text{ /min}$, $s = 679 \text{ min}$, $\tau = 0.38 \text{ min}$. The parameters PIF were: $a = 3.41 \text{ /min}$, $b = 0.21 \text{ /min}$, $s = 96.34 \text{ min}$, $\tau = 0.45 \text{ min}$. The curve of liver tissue was generated by a dual-input one-compartment model (1) with arterial perfusion $F_a = 41 \text{ mL/100mL/min}$, portal venous perfusion $F_p = 138 \text{ mL/100mL/min}$ (5). The arterial fraction (AF) was calculated as $F_d/(F_a + F_p)$. The concentration curve $C(t)$ was converted to T_1 using equation

$$\frac{1}{T_1(t)} - \frac{1}{T_1^{\text{pre}}} = r_1 C(t) \quad [6]$$

where T_1^{pre} is the T_1 value before contrast agent injection, which was set to 1932 ms for blood and 812 ms for liver tissue (27), respectively. A typical R1 relaxivity, r_1 , of a gadolinium contrast agent was set to 4.5 /mM/s (28) at 3.0T in this simulation.

The imaging parameters of SGRE for simulation were: $\text{TR} = 4 \text{ ms}$; $\alpha = 12^\circ$. The blood will reach 99% of the steady state when N_p is larger than about 200 based on Eq. [2] assuming these parameters. The true N_p of vessel pixel was calculated by the flow velocity and distance of inflow using Eq. [3]. The corresponding signal intensity can be calculated using Eq. [2] phase by phase. Complex random noise of 50 dB was added to the raw Cartesian k-space before image reconstruction. The definition of SNR used for these

simulations was $\text{SNR} = 10 \log_{10} \frac{P_{\text{sig}}}{P_{\text{noise}}}$, where P_{sig} is the mean power of k-space signal and P_{noise} is the mean power of noise.

The proposed method was employed to quantify the N_p of the flowing spins from the reconstructed images. To evaluate the accuracy of inflow quantification of the proposed method, mean and standard deviation of the estimated N_p errors of all the pixels with the same value of true N_p were calculated. To evaluate the improvement of the proposed method on T_1 and contrast agent concentration estimation, the mean and standard deviation of estimation errors of both methods were calculated and compared with paired Student's t-test.

To further explore the impact of inflow enhancement of VIFs on the pharmacokinetic model analysis and test the performance of the proposed method, the pharmacokinetic parameters were fitted using the tissue curves and VIFs with different N_p values. With the plug flow setting in this simulation, the N_p can be converted to the location selected for VIF extraction (the distance to the edge of FOV in the inflow side) using Eq. [3], which is more intuitive in practical DCE analysis. In this simulation, only N_p values less than 200 were tested since the blood can be considered as reaching the steady state when N_p is larger than about 200. The mean ratios of errors of pharmacokinetic parameters including arterial perfusion, portal venous perfusion, and arterial fraction, fitted by VIFs with and without correction were calculated, respectively.

In vivo Experiments

In vivo animal experiments were performed after approval of institutional animal care and use committee (IACUC). Thirteen domestic pigs (all female, mean weight 54 kg) were studied. Portal vein embolization (PVE) of the left lateral and left middle branches of the portal vein was performed using non-spherical polyvinyl alcohol (NSPVA) particles via a transcutaneous, transhepatic approach. For each pig, embolization was performed until complete stasis of flow under fluoroscopy flow in the catheterized branches was achieved.

All pigs were then imaged using a 3.0T clinical MRI system (Discovery MR750, GE Healthcare, Waukesha, WI) using a 32-channel phased array torso coil (Neocoil, Pewaukee, WI) under anesthesia. Imaging was performed before (visit 1), one week (visit 2) and two weeks (visit 3) after PVE. DCE imaging was conducted using a respiratory navigator triggered dual-echo differential subsampling with Cartesian ordering (DISCO) sequence (29) with the following imaging parameters: TR/TE1/TE2 = 4/1.5/3 ms, $\alpha = 12^\circ$, bandwidth (BW) = ± 127 kHz, FOV = 358×358 mm², slice thickness = 4.0 mm, number of slices = 60, and axial slab excitation. In-plane matrix size was 256×256 , spatial resolution was interpolated to 1.4×1.4 mm² via sinc interpolation. Dual-echo acquisition was used to facilitate fat suppression via standard Dixon water-fat separation as part of the DISCO application. Respiratory gating was performed using a 2D pencil beam navigator was put on the right liver dome, with the acceptance window was set to 30%. View sharing was performed with a temporal resolution of 7.0 s. After the pre-contrast mask acquisition, 0.03 mmol/kg of gadofosveset trisodium (Ablavar, Lantheus Medical, North Billerica, MA) was injected through the marginal ear vein at a rate of 2 mL/s followed by 15 mL 0.9% saline solution flush injected at the same rate. A total of 20 dynamic phases were acquired during the dynamic scan over approximately 2.3 minutes.

In addition, 4D-flow MRI of the portal vein was also performed on 6 pigs at each of the three visits using radially undersampled phase contrast acquisition (PC-VIPR) (30) with retrospective ECG-gating. Imaging parameters were: TR/TE = 6.3/2.4 ms, $\alpha = 10^\circ$, BW = ± 125 kHz, velocity-encoding gradient = 60 cm/s, FOV = $360 \times 360 \times 360$ mm³, spatial resolution = $1.4 \times 1.4 \times 1.4$ mm³. Data were reconstructed to 14 time-frames per cardiac cycle.

Image Analysis

DCE images were reformatted into the coronal plane for better visualization of the aorta and portal vein. A Gaussian filter with a kernel size of $3 \times 3 \times 3$ and standard deviation of 0.65 was applied to all the phases of DCE images for smoothing (31). Next, a region of interest (ROI) containing about 10 pixels was drawn in the right branch of the hepatic vein on the pre-contrast phase by free hand, for M_z^0 calculation. The mean signal intensity of ROI of the pre-contrast dynamic phase, M_z^{SS} , was used to calculate M_z^0 assuming a pre-contrast blood T_1 value of 1932 ms (27) by Eq. [1]. ROIs for AIF and PIF extraction were then selected in the abdominal aorta and portal vein at the level of porta hepatis, respectively, which are distal of the vessels and should have the largest N_p . The N_p was calculated from the pre-contrast image for the ROIs of AIF and PIF with Eq. [2]. The ROIs for AIF and PIF were copied and

pasted to all phases and the corresponding T_1 curve after contrast agent injection was calculated using Eq. [2] with the N_p value estimated from the previous steps. The approximate inflow distance of blood, D , in the abdominal aorta or portal vein was measured from the DCE images. The SGRE-based flow velocity v_{SGRE} can be calculated using Eq. [3].

For each visit of all pigs, ROIs of left (embolized side) and right (control side) lobe were selected on the DCE images to evaluate local perfusion parameters. ROIs of tissue were manually drawn to avoid large vessels and bile ducts. The T_1 values of liver tissue of dynamic phases after contrast agent injection were calculated using Eq. [1]. Assuming an intrinsic liver tissue pre-contrast T_1 value of 812 ms (27), the contrast agent concentration curves of liver tissue can be converted using Eq. [6]. In this study, r_1 of gadofosveset trisodium was set as $5.3 \text{ mM}^{-1}\text{s}^{-1}$ on 3T (28). The same dual-input one compartment model (1) was employed to fit the in vivo tissue curves along with the AIF and PIF curves with and without correction. The nonlinear least square algorithm was adopted for the model fitting. The fitted perfusion parameters using both the corrected and uncorrected VIFs were compared with paired Student's t-test to determine whether the two methods provided significantly different results. For fitted results of both methods, the perfusion parameters were compared between left and right lobes and each two different visits using paired Student's t-test to inspect whether the perfusion parameters changed due to PVE surgery, as well.

Flow measurements from 4D-flow MRI were performed in EnSight (CEI, Apex, NC) using manual placement of cut-planes in the vessel of interest. The mean velocities, $v_{4D-flow}$, of 6 pigs, totally 18 visits were analyzed for comparison. The intraclass correlation coefficient (ICC) was employed to compare the consistency of v_{SGRE} and $v_{4D-flow}$.

Results

Simulation Study

The mean and standard deviation of the error of estimated N_p are shown in Fig. 3(a). When N_p was relatively small, the error of estimated N_p was almost zero; while N_p was larger, the error of estimated N_p by the proposed method became evident. Roughly, the mean and standard deviation increased with increasing N_p . The mean and standard deviation of the estimated T_1 and contrast agent concentration errors with different N_p values are shown in Fig. 3(b) and (c), respectively. With increasing N_p , both the mean and standard deviation of estimated T_1 error decreased. On the other hand, the absolute mean T_1 estimation error of uncorrected method was larger than that of the corrected method ($P < 0.001$); the standard deviation of estimated T_1 error of the uncorrected method was also larger than the corrected method ($P < 0.001$). Regarding the concentration estimation error of the two methods, the absolute mean and standard deviation of the estimated concentration error were larger than the corrected concentration ($P < 0.001$). In general, the uncorrected method underestimated the contrast agent concentration by a considerable amount, while the proposed method provided more accurate (mean error 0.13 mM versus -1.43 mM of the uncorrected method), although slightly overestimated, contrast agent concentration.

Figure 4 plots the ratio of error of the fitted pharmacokinetic parameters using the corrected and uncorrected VIFs of different N_p values. Regarding arterial and portal venous perfusion, the absolute error of both methods decreased when the N_p increased, while the estimations with corrected VIFs had a lower absolute error than the uncorrected in all the tested circumstances. Regarding the arterial fraction, the absolute error of the proposed method was also relatively lower than the uncorrected results, in general. It is worth noting that the estimated AF was less affected when the inflow enhancement effects of aorta and portal vein were close. When the N_p of the aorta was much smaller than the portal vein, the AF was overestimated in the uncorrected VIFs. Otherwise, the AF was underestimated.

In vivo Experiments

Examples of estimated N_p and along the aorta and portal vein are shown in Fig. 5. In the in vivo results, the mean N_p of the selected ROIs was 80 for AIF and 100 for PIF, respectively, which was the largest we can obtain in the vessels.

A typical example of AIF and PIF with and without correction of the in vivo experiments is shown in Fig. 6. Even though the flow velocity derived with the correction method vary considerably in the portal vein, the contrast concentrations along the portal vein vary to a far lesser extent (as shown in Supporting Figure S2, which is available online). The corrected AIF and PIF by the proposed inflow quantification and correction method were much higher for the uncorrected curves. Notably, the uncorrected PIF had a higher peak than uncorrected AIF, which might be caused by the higher N_p in the aorta. This non-physiologically possible observation disappeared after correction.

The paired Student's t-tests comparing in vivo fitted perfusion parameters (arterial perfusion (Fig. 7a), portal venous perfusion (Fig. 7b) and arterial fraction (Fig. 7c)) of all the lobes and visits, between the results with correction and without correction are shown in Fig. 7. The arterial perfusion and portal venous perfusion fitted by the uncorrected VIFs were non-physiologically high (larger than 1000 mL/100mL/min). The arterial and portal venous perfusion parameter estimates were much more reasonable using the proposed corrected VIF method (around 65 mL/100mL/min for arterial perfusion, 358 mL/100mL/min for portal venous perfusion). The arterial fraction estimated using corrected VIFs was also higher than the corrected one, similar to the simulation results.

Figure 8 shows the results of comparing the perfusion parameters of left and right lobes of pigs among different visits. Regarding the results of the proposed method, the portal venous perfusion of left lobe decreased ($P < 0.001$) after PVE, while the arterial fraction increased ($P < 0.001$) from baseline (visit 1) compared to one week after PVE (visit 2). The data from visit 2 (one week after PVE) showed that the corrected portal venous perfusion of left lobe was lower than the right lobe ($P = 0.016$), while the corrected arterial fraction was higher than right lobe ($P < 0.001$). The arterial fraction significantly decreased ($P = 0.003$) from one week after PVE (visit 2) to two weeks after PVE (visit 3). However, there was no significant difference found between the left lobe and right lobe or each two different visits from the result of the uncorrected VIFs.

Regarding the portal vein velocity comparison between v_{SGRE} and $v_{4D-flow}$, the ICC of two measurements was 0.855. Figure 9 is the scatter plot of velocities of portal vein measured from the pre-contrast of DCE images and the 4D-flow MRI images. Good consistency of two measurements could be observed from the results.

Discussion

In this study, a new method that corrects the vascular input function of inflow enhancement method was proposed to improve the accuracy of perfusion quantification using DCE-MRI of the liver. Based on simulations and study of pigs that have undergone portal vein embolization, the proposed method appears to alleviate the effects of inflow enhancement. This method is compatible with routine DCE acquisition protocols, without any need for complex calibration steps or other post-processing. In addition, the proposed method has the potential to apply to many scenarios where the imaging volume is limited and contains large vessels.

The simulations of conventional T_1 and concentration estimation showed that without correction for partially saturated spins can lead to underestimation of the apparent gadolinium concentration, resulting in the subsequent overestimation of arterial and portal venous perfusion. Furthermore, differences of inflow enhancement in the aorta and portal vein would lead to the error in the estimation of AF. In both simulations and the animal experiments, the proposed method effectively corrected VIFs with different inflow enhancement effects and provided more accurate estimates of AF. The T_1 and concentration estimations of the proposed method performed very well except for $N_p = 1$. This is because when $N_p = 1$, the signal intensity is less T_1 dependent, the contrast is proton density weighted, such that it is not possible to reliably estimate contrast agent concentration. However, the case when $N_p = 1$ is likely of no practical consequence because this case only affects pixels 1.2-2 mm away from the edge of the imaging volume.

The in vivo experiments further validated the simulation results. The arterial and portal venous perfusion calculated using the uncorrected VIFs were unrealistically high, which likely resulted from the marked underestimation of the contrast agent concentration. The overestimation of the arterial fraction may result from the different levels of inflow enhancements due to the different flow velocities in aorta and portal vein. The proposed method corrected the underestimation of the VIF curves and lead to perfusion parameter estimates within a reasonable physiological range (5,32). Furthermore, the consistency of portal vein velocities measured from the pre-contrast DCE images using the proposed method and the 4D-flow MRI results served as a side evidence for the quantitation accuracy of the proposed method.

More importantly, unlike the conventional perfusion estimation method, the inflow corrected method was able to detect physiologically feasible changes after portal vein embolization. Compared to baseline, the portal venous perfusion decreased one week after embolization in the left lobe, due to reduced blood flow in the portal vein branches. The arterial perfusion of left lobe increased, although not significantly, in visit 2, reflecting the known compensatory hepatic arterial buffer response of the liver (33). As one of the few organs with two

independent vascular supplies, the liver is able to upregulate perfusion of one vascular supply if the other one is compromised (34). As a result, the arterial perfusion increased after PVE in the embolized liver segments. Two weeks after PVE, portal venous perfusion and arterial perfusion reached almost baseline levels. This may be due to the recanalization of the embolized portal vein branches. As only particles have been used for embolization instead of a coil, the rate of recanalization is relatively high (35). On the other hand, with the uncorrected VIFs, the portal venous perfusion decreased but not significantly, while the arterial perfusion and arterial fraction of the embolized lobe decreased from visit 1 to visit 2, which was not consistent with the PVE procedure. This likely results from error related to the different inflow enhancement effects of aorta and portal vein. In addition, the portal venous flow might change after the PVE, which could further disturb the estimation of pharmacokinetic analysis.

There are also some limitations of this study. First, we recognize that the distribution of imaging flip angle may not be perfectly homogeneous within FOV, and variable flip angles near the edge of the imaging volume will introduce additional error (12). The impact of a non-uniform flip angle profile could be incorporated into refined correction methods, in principle, although was beyond the scope of this work. As the purpose of this work was to demonstrate the impact of inflow enhancement and the feasibility of inflow enhancement correction, the inhomogeneity of B_1 field was not taken into consideration in this study. Second, no ground truth of perfusion can serve as a reference for the in vivo perfusion parameter fitting. Thus, numerical simulations were used in this study to validate the proposed method, and the in vivo experiment with animals after PVE further indicated its feasibility. A flow phantom with true velocity information should further benefit the validation in future studies.

An additional limitation is that due to the lack of T_1 measurement, the pre-contrast T_1 values of arterial and venous blood were assumed the same value. This could have contributed to a systematic error in the estimation of concentration. The $\pm 20\%$ of T_1 error will finally cause 60%~30% of concentration error (reference T_1 was 1932 ms, N_p was 80, and concentration was 1 mM). Please note, the proposed method can only correct the underestimation of vascular input function due to the inflow. Incorporating T_2^* correction (36) or double injection methods (37,38), the saturation of vascular input function due to the both the high concentration of contrast agent and inflow may be improved.

In conclusion, the proposed vascular input function correction method of inflow enhancement is a relatively straightforward and efficient way to provide more reliable VIFs for improved pharmacokinetic modeling and perfusion quantification in the liver using DCE-MRI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix: Derivations of Equation [2]

The longitudinal relaxation principle of the n^{th} pulse is (15)

$$\begin{cases} M_z^{(n)}(0_-) = M_z^0(1 - e^{-\text{TR}/T_1}) + M_z^{(n-1)}(0_+)e^{-\text{TR}/T_1} \\ M_z^{(n-1)}(0_+) = \cos(\alpha) M_z^{(n-1)}(0_-) \end{cases} \quad [\text{A1}]$$

So Eq. [A1] can also be written as

$$M_z^{(n)}(0_-) = M_z^0(1 - e^{-\text{TR}/T_1}) + \cos(\alpha) M_z^{(n-1)}(0_-)e^{-\text{TR}/T_1} \quad [\text{A2}]$$

Then, Eq. [A2] can be expanded

$$M_z^{(n)}(0_-) = (1 + \cos(\alpha)e^{-\text{TR}/T_1})M_z^0(1 - e^{-\text{TR}/T_1}) + M_z^{(n-2)}(0_-)(\cos(\alpha)e^{-\text{TR}/T_1})^2 \quad [\text{A3}]$$

until we obtain

$$M_z^{(n)}(0_-) = \sum_{k=0}^{n-2} (\cos(\alpha)e^{-\text{TR}/T_1})^k M_z^0(1 - e^{-\text{TR}/T_1}) + M_z^{(1)}(0_-)(\cos(\alpha)e^{-\text{TR}/T_1})^{n-1}$$

[A4]

where the term $M_z^{(1)}(0_-) = M_z^0$. Finally Eq. [A4] can be written as

$$M_z^{(n)} = M_z^0(1 - e^{-\text{TR}/T_1}) \frac{1 - (\cos(\alpha)e^{-\text{TR}/T_1})^{n-1}}{1 - \cos(\alpha)e^{-\text{TR}/T_1}} + M_z^0(\cos(\alpha)e^{-\text{TR}/T_1})^{n-1} \quad [\text{A5}]$$

which is the same form as Eq. [2].

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Figure 1.
Examples of a coronal reformatted images of an axially acquired T_1 weighted 3D-SGRE pre-contrast acquisition demonstrating inflow enhancements in abdominal aorta (a, white arrow) and portal vein (b, yellow arrow) in a pig. Note also the inflow enhancement of the inferior vena cava (arrowhead in a).

Figure 2.

The flowchart of proposed inflow correction method using PIF as an example. (a) Based on the assumption that the blood in the small branch of the hepatic vein has reached the steady state, the equilibrium magnetization M_z^0 can be calculated with the steady state signal M_z^{SS} measured from the pre-contrast image of the hepatic vein using Eq. [1]. The cyan point is the ROI where the hepatic vein was selected. (b) Using the M_z^0 calculated from the previous step, the N_p of the portal vein can be calculated using Eq. [2] based on the assumption that the blood in the portal vein and hepatic vein share the same pre-contrast T_1 and M_z^0 . Note the calculation is still based on the pre-contrast image. (c) Assuming the inflow effects are the same for the portal vein among different dynamic phase. The post contrast T_1 values of the portal vein can be calculated using Eq. [2] with the known N_p and M_z^0 . (d) Using Eq. [6], the concentration curve is derived with the T_1 curve. (e) Assuming the blood travel straightly along the vessel, the distance can be approximated from the image directly. Then, the SGRE sequence based blood velocity can be calculated using Eq. [3], since the effective flow time is about $TR * N_p$.

Figure 3. Simulated grayscale image demonstrating the inflow enhancement effect in the aorta and portal vein. The pre-contrast phase is shown, colorbar indicates the signal intensity.

Figure 4.

The error of N_p , estimated T_1 (a) and contrast agent concentration (b) of different N_p values. The result of the proposed method is shown in blue line and the result without correction is shown in red line as a comparison.

Figure 5. The error of fitted parameters a) arterial perfusion, b) portal venous perfusion and c) arterial fraction, using VIFs with the inflow correction (blue grid) and without correction (red grid).

Figure 6. Examples of N_p (a and c) and mean velocity (b and d) estimations of the abdominal aorta (a and b) and portal vein (c and d) of Fig. 1.

Figure 7.
Examples of AIF (red lines) and PIF (blue lines) with (solid lines) and without correction (dash lines).

Figure 8.

The comparisons of perfusion parameters including: a) the arterial perfusion, b) portal venous perfusion and c) arterial fraction fitted by VIFs with correction (blue bars) and without correction (red bars) using paired Student's t-test.

Figure 9.

The estimated arterial perfusion (a and b), portal venous perfusion (c and d) and arterial fraction (e and f) of 2 lobes and 3 visits using VIFs with (a, c and e) and without (b, d and f) correction for inflow enhancement. The significant different pairs using paired Student's t-test are marked with black bars.

Figure 10.

The Bland Altman plot of portal vein velocities measured from the pre-contrast DCE images using the proposed method and 4D-flow images.