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Quantitative Hepatic Perfusion Modeling using DCE-MRI with Sequential Breath-Holds

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Abstract

Purpose—To develop and demonstrate the feasibility of a new formulation for quantitative perfusion modeling in the liver using interrupted DCE-MRI data acquired during multiple sequential breath-holds.

Materials and Methods—A new mathematical formulation to estimate quantitative perfusion parameters using interrupted data was developed. Using this method, we investigated whether a second degree-of-freedom in the tissue residue function (TRF) improves quality-of-fit criteria when applied to a dual-input single-compartment perfusion model. We subsequently estimated hepatic perfusion parameters using DCE-MRI data from 12 healthy volunteers and 9 cirrhotic patients with a history of hepatocellular carcinoma (HCC); and examined the utility of these estimates in differentiating between healthy liver, cirrhotic liver and HCC.

Results—Quality-of-fit criteria in all groups were improved using a Weibull TRF (two degrees-of-freedom) versus an exponential TRF (one degree-of-freedom), indicating nearer concordance of source DCE-MRI data with the Weibull model. Using the Weibull TRF, arterial fraction was greater in cirrhotic versus normal liver ($39 \pm 23\%$ vs. $15 \pm 14\%$, $p=0.07$). Mean transit time (20.6 ± 4.1 s vs. 9.8 ± 3.5 s, $p=0.01$) and arterial fraction ($39 \pm 23\%$ vs. $73 \pm 14\%$, $p=0.04$) were both significantly different between cirrhotic liver and HCC, while differences in total perfusion approached significance.

Conclusion—This work demonstrates the feasibility of estimating hepatic perfusion parameters using interrupted data acquired during sequential breath-holds.

Keywords

DCE-MRI; Quantitative Perfusion MRI; Hepatic Perfusion Modeling; Tumor Perfusion Modeling; Hepatocellular Carcinoma

Introduction

Significant alterations in hepatic perfusion accompany the pathological changes of cirrhosis in addition to focal malignancies such as hepatocellular carcinoma (HCC) (1,2). In cirrhosis, repeated cycles of hepatocellular injury and scarring lead to progressive fibrosis of normal liver parenchyma. This increases resistance to hepatic perfusion, and results in a decreased ratio of portal venous to hepatic arterial flow (1). Meanwhile, HCC are highly vascularized tumors that draw the majority of their blood supply from branches of the hepatic artery (3). The neoangiogenic process characteristic to these lesions significantly reduces the fraction of blood flow received from the portal vein relative to normal liver.

Unfortunately, perfusion alterations that occur in cirrhosis cannot be assessed using liver biopsy, and are difficult to assess using qualitative imaging methods such as cross-sectional MR or CT. While many HCC can be identified using contrast-enhanced MR/CT imaging, little can be learned about these lesions' perfusion characteristics from qualitative methods alone. More accurate quantitative methods are therefore needed to develop further insight into the relationship between hepatic perfusion changes and the spectrum of chronic liver disease from fibrosis to cirrhosis. MR-based quantitative perfusion assessment has the potential to improve characterization of HCC as well as other hepatic malignancies known to have distinct patterns of contrast enhancement, such as metastatic neuroendocrine tumors and colorectal cancer.

Furthermore, quantitative measures of hepatic perfusion have significant potential to be used as non-invasive biomarkers of HCC response to anti-angiogenic drug therapy. For example, multifocal and metastatic HCC are increasingly treated with small-molecule VEGF antagonists that have been shown to prolong overall survival in patients with advanced HCC (4). These agents are thought to act by disrupting neoangiogenesis of the arterial blood supply to HCC lesions. Unfortunately, quantification of the treatment response is challenging, since anti-angiogenic therapy often does not cause tumor regression by RECIST criteria (5). Non-invasive quantification of blood flow to HCC holds promise as a means to evaluate anti-angiogenic therapy response, and may enable targeting of this intervention to patients most likely to benefit.

Qualitative MRI methods – primarily multiphase dynamic contrast-enhanced MRI (DCE-MRI) – remain the most accurate means for detection and characterization of focal liver lesions including HCC(6). Unfortunately, current implementations of multiphase DCE-MRI suffer from limited temporal resolution (12–20s / frame (7)) and an inability to consistently match acquisitions to the desired phases of enhancement. Recent advances in acquisition methods have resulted in several DCE-MRI sequences capable of acquiring whole liver volumes with high temporal and spatial fidelity (8–10). These sequences provide sub-centimeter spatial resolution to aid the identification of nascent hypervascular masses, while reducing the per-frame temporal footprint to improve visualization of enhancement dynamics (11). In addition to simplifying radiological diagnosis of HCC, the improved spatiotemporal resolution afforded by these sequences has direct application to hepatic perfusion modeling.

Perfusion modeling of hepatic DCE-MRI data has proven challenging for several reasons. These include the dual vascular inputs to the liver as well as the heterogeneous fibrotic changes that occur in hepatic sinusoids in cirrhosis. Characterizing the effects of fibrosis and cirrhosis on hepatic perfusion requires a mathematical model capable of reflecting the significant alterations in parenchymal architecture which may occur in diseased liver. Moreover, determination of absolute contrast concentration has proven difficult due to a variety of sequence-specific (12) and sequence-independent factors that introduce

nonlinearities in the relationship between MR signal and contrast concentration. Finally, relatively high SNR is necessary to generate accurate estimates of hepatic perfusion parameters (12), which may be difficult to achieve due to aforementioned spatial and temporal resolution requirements. Major progress towards these requirements has been made in accordance with the acquisition methods described above, as well as novel approaches to image reconstruction (13).

Artifacts from respiratory motion also remain a major barrier to accurate determination of hepatic perfusion parameters. Correction for respiratory motion using navigators has been attempted (14). Unfortunately, the liver undergoes non-rigid deformation during free-breathing (15). For this reason, local measurement of diaphragm position is unreliable for whole-liver motion correction. Retrospective motion correction through view-ordering has also been previously investigated (16). However, rapid wash-in and wash-out of contrast restricts the temporal range over which reordering is reliable. This limits the applicability of view-ordering methods in patients with hypervascular lesions such as HCC.

In this work, we formulate a novel approach to hepatic perfusion modeling designed to exclude motion-corrupted data acquired between sequential breath-holds. We subsequently utilize this method to determine whether an additional degree of freedom in the tissue residue function (TRF) improves fitting of the perfusion model to the raw data. Lastly, we perform a pilot study to evaluate the performance of resultant quantitative perfusion parameters – as well as two semi-quantitative measures of perfusion requiring less computational effort – for differentiating between normal liver, diseased (cirrhotic) liver and HCC.

Materials and Methods

Theory

For hepatic perfusion analysis, a dual-input single-compartment model of the liver was utilized (17). This model accounts for the two vascular inputs to the liver (hepatic artery and portal vein). It assumes that contrast agent in the intravascular space (hepatic sinusoids) rapidly equilibrates with the extravascular extracellular space (EES, i.e.: Space of Disse). This model has previously been validated in animal studies acquired using radiolabeled microspheres (12). Mathematically, the model is described by the equation:

$$\frac{dC_L(t)}{dt} = k_a[C_a(t - \tau_a)] + k_p[C_p(t - \tau_p)] - k_2C_L(t) \quad [1]$$

where $C_L(t)$, $C_a(t)$ and $C_p(t)$ represent contrast concentrations in a unit volume of liver parenchyma, hepatic artery and portal vein, respectively. k_a and k_p are the arterial and portal venous inflow rate constants (s^{-1} ; analogous to K^{trans}), while k_2 is the outflow rate constant from the liver compartment. τ_a and τ_p represent the transit times of contrast between the hepatic artery/portal vein and liver parenchyma. The ratio of k_a to $k_a + k_p$ (arterial fraction) serves as an indicator of the relative contributions of hepatic artery and portal vein to total perfusion, and is frequently altered in disease.

Previous work has demonstrated that the values of τ_a or τ_p are small – typically 1–2s (18) – when ROIs are placed in the aorta and the portal vein near the liver hilum. This agrees with our observations that intrahepatic arterial and portal venous branches enhance rapidly after contrast arrival. Fixed values of 2s for τ_a and τ_p were therefore utilized during modeling, which allows Eq. 1 to be simplified as:

$$\frac{dC_L(t)}{dt} = k_a C_{a-\tau a}(t) + k_p C_{p-\tau p}(t) - k_2 C_L(t) \quad [2]$$

Eq. 2 is typically rewritten as a convolution to account for the fact that the impulse response of the unit tissue volume (residue function) is not instantaneous, and cannot be modeled as delta function, i.e.:

$$C_L(t) = [k_a C_{a-\tau a}(t) + k_p C_{p-\tau p}(t)] \otimes R_L(t) \quad [3]$$

where $R_L(t)$ is the residue function of the unit volume, or tissue residue function (TRF). Previous theoretical work has demonstrated that $R_L(t)$ is well modeled as an exponential distribution ($e^{-k_2 t}$), provided that mixing between the vascular bed and EES compartment is rapid and complete (19). This may be a reasonable approximation in a healthy liver that possesses wide endothelial fenestrae, allowing for rapid exchange of gadolinium contrast between the intravascular and EES compartments. However, the exponential model imposes significant constraint on the shape of the residue function. In diseased hepatic parenchyma, dysplastic lesions and HCC, the shape of the residue function likely deviates from an exponential distribution. By adding a single additional degree of freedom to the residue function and constraining it to the form of a Weibull distribution:

$$R(t) = e^{-\left(\frac{t}{a}\right)^b} \quad [4]$$

, where a and b are scale and shape parameters, a variety of behaviors ranging from exponential decay to step-like decay can be modeled (20). Permitting this range of shapes can be highly advantageous, as residue functions corresponding to diseased liver parenchyma and focal hepatic lesions are likely to differ significantly from normal liver.

Study Population

For this IRB-approved HIPAA-compliant prospective study, 12 healthy volunteers (7 men, 5 women, average age 30.1 years, range 21–59 years) and 9 subjects with hepatic cirrhosis and known solitary HCC (5 men, 4 women, average age 59.8 years, range 44–68 years) were imaged after obtaining informed consent between July 2009 and August 2012. The etiology of HCC in most patients was either alcoholic cirrhosis (4 patients), chronic hepatitis C infection (6 patients) or a combination thereof. One patient developed cirrhosis due to hereditary hemochromatosis, another due to primary biliary cirrhosis, and one patient had co-existing hepatitis B and hepatitis C infection. We were also fortunate to be able to recruit one patient who was undergoing sorafenib therapy for multifocal HCC. This patient was imaged at three time points: one day before, three days after, and two months after starting sorafenib.

Subjects with contraindications to MRI (pacemaker, metallic implants, claustrophobia) determined by safety screening were excluded from the study. Prisoners and mentally disabled individuals were not recruited. Individuals with known renal disease ($GFR < 60$) and pregnant women were not enrolled. Subjects were instructed not to enroll if they did not believe they could hold their breath for 30 seconds. Subjects were also instructed to fast for at least four hours before imaging per routine abdominal MRI protocol at our institution. This was important to standardize and minimize the effects of meal related perfusion changes in the liver.

Image Acquisition

All imaging was performed on a clinical 3.0T scanner (Discovery MR750, GE Healthcare; Waukesha, WI) using a 32-channel torso coil (Neocoil; Pewaukee, WI). A previously described, multi-echo 3D radial spoiled gradient-echo (SPGR) sequence was used to acquire data continuously for 3 minutes (8,21) and reconstructed with a true 4s footprint. A real-time display returned low-resolution images every second to permit breath-hold coordination with contrast arrival. Subjects were instructed to conduct a 10s pre-contrast breath-hold at mid-expiration, followed by intravenous injection of gadobenate dimeglumine (0.1mmol/kg at 2.0mL/s) followed by 30mL of saline chaser at the same injection rate. Subjects were subsequently instructed by the scan operator to perform a 20–25s breath-hold upon contrast arrival in the right heart, capturing the arterial phase of hepatic enhancement. Subjects were then instructed to perform two additional breath-holds during the portal-venous and delayed phases approximately 20s after the conclusion of the previous breath-hold.

Specific scan parameters included: TR=2.7ms, TE_{1,2,3}=0.4/1.0/1.7ms, flip angle=12° to balance SNR performance with signal linearity (22), bandwidth=±250kHz, FOV=48cm spherical with 256³ matrix, and a readout length of 224 points for 2.1mm isotropic spatial resolution. 180 time frames were reconstructed (centered) at 1s intervals with 4s true temporal resolution using an iterative SENSE algorithm (23). For scans performed after September 2011, two 3D–SPGR Cartesian acquisitions, one using the 32-channel and the other using the body coil were also performed to generate a coil sensitivity map. Scan parameters for the coil sensitivity scans included: TR/TE = 1.2/0.6 ms, flip angle=12°, BW = ±125 kHz, FOV = 48 × 48 × 40cm, and matrix = 256×256 with 1cm slice thickness. Scan

time was 16s for each acquisition. Resultant coil sensitivity maps ($\frac{body}{coil}$) were interpolated onto coordinates of the radial acquisition.

Post-Processing

Breath-hold periods were retrospectively identified using data obtained from a respiratory bellows, or from the time-signal curve of the *k*-space origin (24) if bellows data were unavailable. It was assumed that hepatic motion was negligible during breath-hold periods (25). To minimize the effect of shifts in liver position between breath-holds, four time-averaged image volumes incorporating frames from precontrast, arterial, portal venous and delayed-phase breath-holds were generated and registered using the Insight Toolkit (26), implemented with rigid (affine) transformation and gradient descent using mutual information. The mutual information metric was chosen because of temporal changes in signal intensity resulting from the administration of contrast agent. Using the three transformation matrices obtained from these registrations, each frame from the arterial, portal venous and delayed phase breath-holds was subsequently registered to the initial (pre-contrast) breath-hold (Figure 1). Timeframes acquired during free-breathing were excluded from further analysis due to intra-frame motion corruption that could not be corrected through registration.

After registration, image volumes were weighted using the coil sensitivity map (available in 10 of 21 scans) to correct for non-uniform receiver sensitivity. To further reduce the effect of spatial signal inhomogeneity, signal values at each voxel were divided by their pre-

contrast averages (S_0) to convert the data to enhancement ratios, i.e.: $\Delta S = \frac{S - S_0}{S_0} - 1$. For subsequent pharmacokinetic modeling, it was assumed that the relationship between enhancement ratio and contrast concentration was linear. This has been shown to be a reasonable approximation for the range of concentrations typically encountered in the liver (27,28). Although this approximation may contribute to errors in absolute perfusion

measurements, perfusion parameters that reflect the temporal behavior of the contrast bolus (e.g.: mean transit time) should be relatively unaffected.

Input Function Determination

To generate hepatic arterial and portal venous input functions, an aortic ROI roughly at the level of the celiac artery and a portal venous ROI at the liver hilum (each 1cm thick) were manually segmented using thresholding and morphologic erosion (Matlab; Mathworks, Natick, MA). The aortic ROI was positioned near the center of the excitation volume in order to minimize inflow effects. Time-signal curves for voxels in the aortic and PV ROIs were averaged to generate the arterial input function (AIF) and portal venous input function (PVIF). Because continuous input functions are required for pharmacokinetic modeling, the PVIF during free breathing periods was approximated using piecewise cubic interpolation. The aorta is retroperitoneal and does not move significantly during free breathing; motion corruption of the AIF was therefore negligible and interpolation was not required. To investigate whether interpolation of the PVIF accurately reproduces the true input function, two volunteers were instructed to hold their breath for as long as possible on initiation of the arterial-phase breath-hold. These data were used to conduct PVIF interpolation during simulated breath-holds.

Perfusion Model Fitting

Using the series of registered image volumes, time-signal curves were generated for each voxel within the hepatic parenchyma after segmenting a large rectangular ROI containing the whole liver. Motion-corrupted data from free-breathing periods were excluded from further analysis, and only data acquired during breath-hold periods were used for perfusion model fitting.

Pharmacokinetic analysis using both exponential and Weibull tissue residue functions (TRFs) was performed for time-signal curves corresponding to voxels within the liver. Data were fitted to the perfusion model (Eq. 3) using a weighted iterative nonlinear least-squares minimization based on a trust-region reflective algorithm (lsqcurvefit; Matlab; Mathworks, Natick, MA). Weights were set so that only data corresponding to breath-hold periods were utilized during fitting. No interpolation of time-signal curves in the tissue parenchyma was performed.

For each time-signal curve, the parameters k_a and k_p , as well as the scale/shape parameters a and b (Weibull TRF, Eq. 4) and the time constant k_2 (exponential TRF) were fit. To initiate the iterative calculation, values of k_a and k_p were first set to reflect the perfusion characteristics of normal liver (75% of perfusion from portal vein; 25% of perfusion from hepatic artery). The initial value of b was set to one so that the initial shape of both TRFs was identical.

Resultant best-fit values of k_a , k_p , a , b and k_2 were used to calculate four quantitative perfusion parameters:

1. total hepatic perfusion $\frac{mL}{min \cdot 100g}$, assuming a small vessel hematocrit of 0.25 (27,29)
2. the arterial fraction = $k_a / (k_a + k_p)$
3. the contrast mean transit time (MTT)
4. the volume of distribution (V_D)

Voxel-wise parametric maps were generated for each exam to visualize the spatial distribution of these four parameters throughout the liver. Note that the portal venous fraction ($= k_p / (k_a + k_p) = 1 - \text{arterial fraction}$) can also be calculated, but for the sake of brevity will not be shown or discussed further.

Residue Function Comparison

To ascertain whether the Weibull TRF affords an improved fit to time-signal data compared to the exponential TRF, average time-signal curves from two 1cm^3 liver ROIs (right and left lobes) and an HCC ROI (in tumor patients) were measured in all subjects. To assess the goodness-of-fit for each TRF, the total sum of squared residuals (SOS_{Res}) and the bias-corrected Akaike information criterion (30) (AIC) were calculated for both models. Lower values of SOS_{Res} and AIC indicate more accurate fitting.

Perfusion parameters corresponding to these ROIs were subsequently calculated for both models using the fitting procedure outlined above, and results from the right and left liver ROIs were averaged. Differences between the fitted parameters of each model corresponding to normal liver, cirrhotic liver and HCC were compared using Student's two-tailed t-test. Measurement errors for the ROI-averaged parameters were based on the variance of the distribution of voxel-wise parameters within the ROIs.

Semiquantitative Perfusion Parameters

Two semiquantitative perfusion parameters – contrast time-to-arrival (TTA) and arterial phase area under curve (AUC_{APh}) – were also calculated for voxels within the whole-liver ROI. These parameters are model-free relative indicators of tissue perfusion that require less computational effort and may be less sensitive to noise than model-based quantitative perfusion parameters (31).

Time-to-arrival was defined as the time after aortic enhancement at which a voxel reaches 80% of its maximum signal. The aortic enhancement time was obtained by averaging TTAs within the aortic ROI. After calculating hepatic TTAs using this arrival criterion, voxels whose TTAs fell at the beginning or end of a breath-hold period were identified. The time-signal data for each of these voxels were subsequently interpolated using cubic Hermite polynomials, and TTAs were re-calculated using the interpolated data.

Arterial-phase area-under-curve (AUC) was defined as the area under the time-signal curve during the arterial-phase breath-hold (AUC_{APh}). AUC_{APh} was determined by summing the signal at each voxel during the arterial phase breath-hold using the trapezoidal rule. By utilizing only timeframes from the arterial phase breath-hold when calculating AUCs, differences between normal liver and arterially perfused lesions are emphasized. Because of inter-patient variations in breath-hold length and cardiac output, AUC_{APh} values for each exam were normalized to the AUC of the aortic ROI averaged over the breath-hold period ($\text{AUC}_{\text{APh}} = \text{AUC}_{\text{Voxel}} / \text{AUC}_{\text{Aorta}}$).

Quantitative and Semiquantitative Perfusion Parameter Comparisons

Differences in quantitative and semi-quantitative perfusion parameters were investigated across the spectrum of hepatic disease represented in this study. Values of the quantitative perfusion parameters in ROIs corresponding to normal liver, cirrhotic liver and HCC were determined using both the exponential and Weibull TRF models. In the only patient with multifocal HCC lesions, perfusion parameters from three tumors of similar qualitative appearance were averaged to avoid biasing the study towards this patient. Resultant group-wise perfusion parameter estimates were then generated by averaging across all patients in the two study groups (healthy volunteers and cirrhotic patients) as well as all HCC lesions.

Two-tailed t-tests assuming non-uniform variances of perfusion parameter means within the study groups (32) were used to assess differences in perfusion parameter means between the normal and cirrhotic groups; as well as between fibrotic liver and tumor within the cirrhotic group.

Results

Perfusion Modeling using Sequential Breath-Holds

The S-I translations required to register sequential 1s timeframes from the three post-injection breath-holds to the pre-contrast average ($BH1_{Av}$, Figure 1) in a normal volunteer are plotted in Figure 2. Within each breath-hold, variation in the magnitude of S-I translation required for registration is minor (sub-voxel). However, shifts of 2–3 voxels between breath-holds were typically required. These shifts are significant and were corrected with rigid registration. Significant translations (>1 voxel) in the A–P direction were also required for registration in some subjects. Corrections for translation in the L–R direction and rigid rotation were typically negligible, but could easily be corrected using this approach. Details of registration requirements within and between breath-holds have been described elsewhere (25).

In a small number of cases (4/21), rigid registration did not accurately align the portal venous ROI across the four sequential breath-holds. When this occurred, the transformation matrix was manually adjusted to ensure that the position of the portal vein was consistent with the location of the ROI.

Segmented aortic and portal venous ROIs from a healthy volunteer can be seen in Figures 3a and 3b, while Figure 3c shows the aortic and portal venous input functions corresponding to these ROIs. This volunteer was instructed to conduct a single 60s breath-hold during the arterial and portal venous phases of enhancement, allowing a motion-free PVIF to be obtained over the entire interval. As can be seen in Fig. 3c, the AIF is a rapidly-changing function during the breath-hold interval which possesses an initial peak and a second peak corresponding to systemic re-circulation of contrast agent. However, as expected the PVIF changes more slowly and smoothly, reflecting contrast dilution and widening of the contrast bolus during transit through the capillary beds of the gut before arrival in the portal vein. An interpolated PVIF assuming 15s of missing data – roughly the duration of free breathing allowed between the arterial and portal venous phase breath-holds – can also be seen in Figure 3c. Because of the aforementioned characteristics of the PVIF, interpolation is shown to approximate the actual input function quite well over this interval.

The largest dimension of HCC in the study averaged 1.8 cm, with a range of 1.3 to 2.5 cm. Plots of representative average time-signal curves of liver and HCC ROIs in a cirrhotic patient – as well as the result of fitting these data to the perfusion model in Eq. 3 – can be seen in Figure 4. Although there are gaps in the raw data due to free breathing, the fitted time-signal curves closely approximate these data during the breath-hold intervals. As expected, significant differences in liver and HCC ROI enhancement patterns exist during the arterial phase. Although the HCC ROI reaches peak signal (due to high arterial fraction) and starts to decline, the liver ROI only begins enhancing in the late arterial phase. The liver ROI presumably reaches peak signal between arterial and PV phase breath-holds, and starts to decline during the PV phase breath-hold.

Dual vs. Single Degree-of-Freedom Residue Functions

Figure 5 shows plots of the average time-signal curve corresponding to an HCC ROI in a second cirrhotic patient, with fitted time-signal curves generated using the exponential TRF (a) and Weibull TRF (b) overlaid. As can be seen in the plots, perfusion modeling using the

Weibull TRF affords improved concordance between the fitted time-signal curve and the raw data during initial contrast uptake. Quantitative quality-of-fit indicators including the bias-corrected Akaike information criterion (AIC) and sum-of-squares residuals (SOS_{Res}) are correspondingly improved. Figure 5c shows plots of the exponential and Weibull TRFs corresponding to the estimated time-signal curves in Figs. 5a/b. The shape of the residue functions is quite different: the Weibull TRF has adopted more step-like behavior compared to the exponential TRF. The extra degree of freedom available to the Weibull TRF has evidently resulted in a significantly different estimate of the underlying perfusion characteristics of the HCC ROI in this patient.

A comparison of quality-of-fit indicators and estimated perfusion parameters determined using exponential and Weibull TRFs in normal volunteers (healthy liver), patients (cirrhotic liver) and HCC can be seen in Table 1. The bias-corrected AIC, as well as the sum-of-squares residuals are considerably lower for the Weibull distribution compared to the exponential distribution in all groups. This indicates that perfusion modeling using the Weibull TRF affords improved correspondence to the raw data despite the potential instability introduced by increasing the number of degrees-of-freedom.

With respect to perfusion parameter estimates, there is a statistically significant difference in the average mean transit time between the TRFs for healthy liver. This difference is marginally significant in cirrhotic liver and in HCC. There are also differences in total perfusion across the three groups, although significance is achieved only in healthy liver. Given these differences in addition to improved quality-of-fit indicators, it is possible that the Weibull TRF more accurately estimates quantitative perfusion parameters compared to the exponential TRF.

Quantitative and Semiquantitative Perfusion Modeling

Rapid changes during the time course of lesion enhancement in a patient with multifocal HCC are visualized in Figure 6. As can be seen in Fig. 6b, the HCC lesions quickly take up contrast, but become isointense with surrounding hepatic parenchyma at 15s (Fig 6d) with subsequent washout during the portal venous phase (Fig. 6e).

Voxel-wise parametric maps of this patient's liver corresponding to perfusion, MTT, arterial fraction and V_D , as well as the two semiquantitative parametric maps of TTA and AUC_{Aph} are shown in Figure 7. Both the quantitative perfusion and semiquantitative AUC_{Aph} maps in Figs. 7a and 7b depict increased perfusion to regions coinciding with the tumors in Figs. 6b and 6c. The MTT and TTA maps in Figs. 7c and 7d also distinguish the tumors from surrounding cirrhotic parenchyma; the tumors are seen to have shorter MTTs and more rapid contrast times of arrival, respectively. The arterial fraction map in Fig. 7e demonstrates decreased portal flow to the HCC lesions, while the volume of distribution map in Fig. 7f does not depict significant differences in the V_D of lesions and normal liver.

Figures 8a-c show coronal reformats depicting the enhancement pattern of an HCC lesion in a second cirrhotic patient. At 35s after contrast injection, the lesion is visible as an enhancing region (arrowhead, Fig. 8a), which becomes isointense with surrounding liver parenchyma at 45s (Fig. 8b). However, during the portal venous phase the lesion exhibits washout and capsular enhancement (Fig. 8c), features known to be specific for HCC. Figures 8d-f show MTT, arterial fraction and TTA maps corresponding to the coronal reformats in Figs. 8a-c. The HCC lesion does not demonstrate significantly decreased MTT versus background liver, though the capsular rim shows increased MTT (Fig. 8d, black arrowhead). The arterial fraction of the HCC is significantly increased (Fig. 8e), and the TTA of this region is correspondingly reduced (Fig. 8f).

Statistical Comparisons of Perfusion Parameters

A comparison of ROI-averaged quantitative and semiquantitative perfusion parameters corresponding to regions of healthy liver in normal volunteers and cirrhotic, tumor-free liver in patients can be seen in Table 2a. Relative to volunteers, patients demonstrate decreased total perfusion, increased mean transit time, increased arterial fraction, and insignificant changes in volume of distribution. The increase in arterial fraction is marginally significant under both the Weibull and exponential TRF models, while changes in perfusion and MTT are not significant. Nevertheless, there is considerable difference in the mean values of these parameters between the two groups, and these differences would likely achieve significance with a larger sample size. Of the semiquantitative parameters, TTA is significantly increased in the patients versus the healthy volunteers, while AUC_{APh} is not significantly different between the two groups.

Table 2b shows a comparison of ROI-averaged quantitative and semiquantitative perfusion parameters between cirrhotic liver and tumor (HCC) within the patient group. Average results from HCC in seven patients are reported due to difficulty in segmenting small satellite lesions in two patients whose primary lesions were treated with radiofrequency ablation. Statistically significant differences in MTT and arterial fraction are detected between cirrhotic liver and tumor using both the Weibull and exponential TRFs. These differences are consistent with tumors receiving primarily hepatic arterial perfusion. Large differences in total perfusion are also detected using both TRFs. These differences are marginally significant, due to considerable variance of the mean perfusion in the tumor group (possibly resulting from lesion heterogeneity). Both semiquantitative perfusion parameters demonstrate significant differences between cirrhotic liver and tumor, with more rapid arrival times and increased AUC_{APh} in the ROIs corresponding to tumors.

For the patient with metastatic HCC treated with sorafenib, plots depicting the effect of sorafenib on both semiquantitative and quantitative (Weibull TRF) HCC perfusion parameters are shown in Figure 9. In this patient, perfusion parameters of three HCC ROIs corresponding to distinct lesions were calculated and averaged for each scan (pre-drug; 3 days and 2 months post-drug). Figures 9a and 9b show the effect of therapy on total perfusion and AUC_{APh} . Sorafenib decreased perfusion in the lesions according to both the quantitative and semiquantitative indicators of blood flow. Figures 9c and 9d show the effect of sorafenib therapy on MTT and TTA; both the contrast arrival time and transit time of contrast through the HCC are increased. Figure 9e plots the arterial fraction, which decreased slightly after initiation of therapy; while Fig. 9f shows a plot of V_D , which is significantly decreased by sorafenib therapy.

Discussion

The purpose of this study was to formulate a method for hepatic perfusion modeling using interrupted data from sequential breath-holds, and to test its feasibility. Our results demonstrate that accurate modeling can be performed when data acquired during free-breathing is excluded from model fitting. By excluding this motion-corrupted data, quantitative perfusion parameters can be reliably estimated for 1–2 cm focal liver lesions such as HCC in addition to background liver parenchyma.

A second purpose of this work was to investigate whether the quantitative perfusion of normal and diseased liver can be more accurately modeled using a Weibull versus an exponential residue function. Our results show that in healthy liver, cirrhotic liver and tumor ROIs, the Weibull TRF provides a better fit of time-signal curves to the perfusion model. Our results also show that perfusion modeling using these TRFs results in differing estimates of quantitative perfusion parameters, particularly the mean transit time.

Importantly, these changes in perfusion parameter estimates are consistent with the Stewart-Hamilton relationship ($\text{flow} = V_D / \text{MTT}$). Given the improved fit to raw data afforded by the Weibull TRF, perfusion modeling using this residue function may generate estimates of hepatic perfusion parameters that are more accurate than those generated by the exponential TRF.

The final purpose of our work was to determine whether differences in quantitative perfusion parameters between healthy liver, diseased liver and HCC can be detected using this approach to perfusion modeling. Results from the comparison between volunteers and patients demonstrate that large differences in arterial fraction exist between normal and cirrhotic liver that approached statistical significance. This is consistent with the expected hepatic pathophysiology, as increased resistance to portal venous flow in cirrhotic liver is thought to increase the arterial fraction (33). Results from the comparison between cirrhotic liver and HCC (Table 2b) show significant differences in MTT and arterial fraction, as well as a large mean difference in total perfusion that also approached significance. The decreased MTT and increased arterial fraction of these lesions are consistent with the known pathophysiology of HCC, whose blood supply is thought to consist primarily of parasitized hepatic arterial branches resulting from neoangiogenesis (34). The difference in total perfusion did not achieve significance due to considerable tumor perfusion variation in different patients, possibly resulting from between-lesion heterogeneity.

Importantly, the semiquantitative perfusion parameters (TTA and AUC_{Aph}) also demonstrated significant differences between cirrhotic liver and HCC. The arrival time of contrast within HCC was more rapid compared to liver, as expected given their arterial blood supply. Moreover, AUC_{Aph} was greater in HCC, indicating that the tumors received more perfusion than surrounding hepatic parenchyma during the arterial phase breath-hold. Although differences in AUC_{Aph} between liver and HCC may be useful for identifying hypervascular lesions, it is likely this parameter is only useful as an indicator of relative perfusion within individual patients. Because AUC_{Aph} can vary greatly depending on cardiac output, the transit time of contrast through the gut, and the length of the arterial phase breath-hold, it is not specific to intra-hepatic perfusion changes. This makes between-subject comparisons of AUC_{Aph} challenging. TTA may be more useful for between-subjects comparisons as it has been normalized to the contrast arrival time in the aorta. However, because the TTA of liver is likely to vary with PV flow rate, this parameter may also be highly dependent on individual physiology.

While semiquantitative perfusion parameters may have limited utility for between-subjects comparisons, both quantitative and semiquantitative perfusion parameters demonstrated considerable changes in the patient who underwent treatment with sorafenib. Although the quantitative perfusion parameters exhibited alterations consistent with anti-angiogenic therapy (decreased perfusion, increased MTT) after three days, V_D was the only parameter to change considerably between the three-day and two-month time points. This is likely due to induction of necrosis within HCC lesions (5). Interestingly, the semiquantitative perfusion parameters TTA and AUC_{Aph} demonstrated large changes at both the three-day and two-month time points post-treatment. These parameters may therefore be useful for detecting relative changes in HCC blood flow within patients shortly after initiation of anti-angiogenic therapy.

The use of a real-time acquisition was extremely helpful to ensure that arterial and portal venous input functions could be generated for the full duration of scanning. In addition, we discovered during post-processing that the effect of respiratory motion on the aorta's input function was negligible. This is due to a relative lack of motion in this vessel resulting from its location in the retroperitoneum. Further, the aorta also did not suffer from phase-ghosting

caused by respiratory motion, likely due to our use of a 3D radial acquisition (35). Thus, the AIF can be determined directly from DCE-MRI data without the need for interpolation.

However, the PVIF must be approximated during motion-corrupted gaps in the data. We found that it was possible to interpolate gaps in the PVIF because the PV uptake curve is very smooth and well-behaved. However, the accuracy of the PVIF estimate relies on capturing the peak of PV enhancement during the arterial phase breath-hold. If the peak is not acquired, interpolation will incorrectly approximate the PVIF during the intervening free-breathing period, resulting in significant error in estimated perfusion parameters. In this study, breath-hold coaching was initiated with the arrival of contrast in the right heart as visualized on a real-time low-resolution display. This allowed for the enhancement peaks of both the aorta and portal vein to be captured within breath-holds as short as 20s in all subjects.

The comparison performed in this study to assess the feasibility of detecting differences in perfusion parameters of normal liver, cirrhotic liver and HCC was limited by sample size. Nevertheless, statistically significant differences were detected between cirrhotic liver and HCC with respect to MTT and arterial fraction. Importantly, values of the quantitative perfusion parameters reported in this study generally agree with those previously reported in the literature (27,36).

Further, the accuracy of the perfusion parameters may be limited by several factors. The most significant of these is the use of signal enhancement ratios for perfusion modeling versus direct measurement of T_1 values. This is necessary due to the difficulty of performing rapid, high-resolution T_1 mapping in the abdomen. Although it is possible to acquire high-resolution full-liver T_1 maps during a single breath-hold using advanced relaxometry methods (37), pre-contrast T_1 mapping alone is insufficient to calibrate the MR signal to the dynamic T_1 values which occur during contrast passage (38). While bookend methods (39) may be a feasible means of improving T_1 calibration, the contrast uptake behavior of HCC lesions – which reach peak signal shortly after contrast injection – greatly limits their applicability, as arterial-phase signal in HCC would fall outside the bookend calibration range.

Several additional factors are likely to have influenced quantitative perfusion parameter accuracy. First, the MR signal saturates at high contrast concentrations – such as those occurring in the aorta during the first pass of a contrast bolus – when using fast, low flip angle T_1 -weighted sequences (12). However, due to T_2^* and susceptibility effects resulting from these high concentrations, it is unlikely that the signal-to- T_1 relationship of first-pass aortic blood would be linear even if a higher flip angle were used (40,41). Additionally, the reported measures of total hepatic perfusion are heavily dependent on the value of the small vessel hematocrit employed. This value determines the effective plasma fraction within the vascular compartments of the liver. Although the liver's small vessel hematocrit has been estimated previously (29), there may be variation between individuals. Moreover, because it has been shown that spins within RBCs can exchange with spins in plasma (42), the effective volume of the plasma compartment may be underestimated by the small vessel hematocrit, even if it is known exactly.

Lastly, our study is limited by the use of mutual information-based rigid registration. Although most of the shifts (translations) between breath-holds were corrected with registration, in 4/21 subjects the transformation matrices had to be manually adjusted to ensure that the PV ROI was appropriately situated over the vessel. Additionally, we did not account for non-rigid deformation of the liver during the respiratory cycle (15). Small lesions in different regions of the liver may undergo motion during free-breathing that

cannot be corrected through rigid registration methods. Fortunately, cirrhotic livers are very stiff, reducing hepatic deformation in comparison to normal liver. It is possible that non-rigid approaches to registration (43) may result in more accurate alignment of heterogeneously distributed HCC, but such approaches were not explored in this work.

Future work will focus on adding fat saturation to the acquisition by exploiting the different TEs of the four half-echoes to perform multipoint fat-water separation (44). Additionally, the relationship between SNR and perfusion parameter accuracy will be investigated to determine the minimum uncertainty of parameter estimates that can be achieved at a given spatial and temporal resolution. This will allow for optimization of scan parameters for hepatic perfusion MRI, balancing spatiotemporal resolution requirements with SNR.

In conclusion, this study has demonstrated the feasibility of perfusion modeling using interrupted data from sequential breath-holds. We have also shown that modeling the tissue residue function using a Weibull distribution improves fitting of raw data and permits more accurate estimation of hepatic perfusion parameters. Finally, we have shown that our perfusion quantification method is sensitive to differences in blood flow between normal liver, cirrhotic liver and HCC. Our results are encouraging, and demonstrate that perfusion modeling may have clinical utility for measuring anti-angiogenic treatment response in HCC. This approach to perfusion modeling should be applicable to other MR or computed tomography (CT) acquisitions that utilize interrupted data in multiple sequential breath-holds. This approach may also be useful for characterizing other focal hepatic lesions including metastatic disease. Whether decreased perfusion after anti-angiogenic therapy correlates with improved survival in patients with HCC or other malignant lesions remains an important but unanswered question that warrants further investigation.

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Figure 1.

Schematic representation of the acquisition and post-processing of DCE-MRI data for perfusion modeling. After contrast injection, a real-time display on the scanner console is used to coordinate breath-hold coaching with contrast arrival in the right heart. After scan completion, breath-holds are retrospectively identified, and average image volumes corresponding to arterial, PV and delayed phase breath-holds are generated. These breath-hold-averaged images are registered to the pre-contrast mask ($BH1_{Av}$), and the three resultant transformation matrices are used to register timeframes within each breath-hold to $BH1_{Av}$.

Figure 2.

Rigid registration-derived correction in S-I translation during a breath-hold is insignificant (sub-voxel), while translations between breath-holds are significant and must be corrected. After registering each 1s frame from the three post-contrast breath-holds to the pre-contrast average, S-I translation magnitudes were determined and plotted for each frame. As seen in the plot, variations in S-I translation correction *within* a breath-hold are negligible, but *between* breath-holds are 2–3 voxels in magnitude. Shifts of 5 voxels (1cm) between breath-holds occurred in some patients.

Figure 3.

Interpolation of the PVIF during free-breathing accurately reproduces the input function during motion-corrupted gaps in DCE-MRI data. **(a and b)** Arterial-phase axial and sagittal images of a healthy volunteer show aortic and portal venous ROIs (dotted lines) appropriately situated in the respective vessels (arrowheads). **(c, left)** Time-signal curves corresponding to the aortic and portal venous ROIs in a volunteer who conducted a 55s breath-hold during the arterial and PV phases of hepatic enhancement. The PVIF is interpolated between the end of this breath-hold and the beginning of the subsequent breath-hold at 105s. **(c, right)** Time-signal curves of the actual PVIF and the interpolated PVIF calculated over a simulated free-breathing period (generated by excluding 15s of data between presumed arterial and PV phase breath-holds) are shown.

Figure 4.

Excellent fitting of the quantitative perfusion model to raw data can be achieved even with gaps in the data during periods of free-breathing. An averaged time-signal curve in a liver ROI (points) is shown with fitted time-signal curve using the Weibull TRF overlaid. An average time-signal curve for an HCC ROI (triangles; fitted curve also overlaid) is shown for comparison. Note the early arrival of contrast in an HCC compared to adjacent liver parenchyma, as well as the relationship of these curves to the AIF (dashed line) and PVIF (dotted line). Also note that the PVIF reaches its peak before the end of the arterial phase breath-hold.

Figure 5.

The Weibull TRF affords improved fit of the perfusion model to the raw data versus the exponential TRF. Fitted time-signal curves generated using (a) exponential and (b) Weibull TRFs overlaid on raw data demonstrate significant differences, with the Weibull model more closely approximating data on visual inspection. Quality-of-fit indicators AIC and SOS_{Res} are improved for the Weibull versus the exponential residue function. (c) Plots of the fitted Weibull and exponential residue functions. The Weibull TRF takes on a significantly different shape, and is more step-like in appearance.

Figure 6.

Temporal behavior of HCC lesions relative to normal liver during a DCE-MRI scan.

Innumerable HCC lesions are not evident on the pre-contrast mask (**a**), but begin to enhance during the early arterial phase (**b**, **white arrow**). The lesions demonstrate obvious enhancement a few seconds later (**c**), but become difficult to distinguish from normal liver at the end of the arterial phase breath-hold (**d**). The lesions show washout during the portal venous phase breath-hold (**e**). Note that the arrow points to a single lesion on both axial and coronal reformats, demonstrating the isotropic spatial resolution of the radial acquisition.

Figure 7. Whole-liver maps of 2 mm voxel-wise quantitative and semiquantitative perfusion parameters depict significant differences between HCC and hepatic parenchyma. **(a and b)** Perfusion and AUC_{APh} maps show increased blood flow to HCC relative to background cirrhotic liver. **(c and d)** MTT and TTA maps show decreased transit times and more rapid arrival times of contrast to HCC lesions, respectively. **(e)** An arterial fraction map shows significantly increased arterial perfusion within HCC. **(f)** The volume of distribution of HCC is not significantly different from that of surrounding liver tissue.

Figure 8.

(a–c) Coronal reformats depicting progressive enhancement of an HCC lesion (arrowhead). The hepatic artery (a) and portal vein (b) can be seen (arrows). In (c), washout and capsular enhancement are noted, features very specific for HCC. (d–f) Coronal reformats with overlaid MTT, arterial fraction and TTA parametric maps. The HCC does not show decreased MTT in this patient, but the tumor capsule shows slightly increased MTT relative to background liver (d, arrowhead). The HCC does demonstrate increased arterial fraction (e) and decreased TTA (f).

Figure 9.

Quantitative and semiquantitative perfusion parameters corresponding to HCC lesions change in response to sorafenib therapy. **(a and b)** Plots of total perfusion and AUC_{A0} averaged over three HCC lesions in a patient before, three days after and two months after sorafenib treatment. Both the quantitative and semiquantitative parameters show decreased total perfusion. Normal liver is shown for comparison. **(c and d)** Plots of average mean transit time and time-to-arrival show increased MTT and TTA in HCC lesions after sorafenib therapy. **(e)** HCC show somewhat increased arterial fraction and **(f)** significantly decreased V_D in response to sorafenib therapy. Error bars represent SDs of averaged

perfusion parameters based on variances estimated by the fitting algorithm, and are suppressed for the liver ROI in (f).

Comparison of quality-of-fit indicators and quantitative perfusion parameters corresponding to Weibull and exponential residue functions.

Table 1

	Normal Liver (n = 12)				Cirrhotic Liver (n = 9)				HCC (n = 7)			
	Exponential	Weibull	p		Exponential	Weibull	p		Exponential	Weibull	p	
AIC	-303.38	-319.63			-267.17	-271.58			-203.39	-222.66		
SOS _{Res}	0.573	0.388			0.766	0.674			2.103	1.461		
Perfusion <i>I</i>	213 ± 20	175 ± 53	0.02		165 ± 28	140 ± 51	0.32		473 ± 44	383 ± 62	0.13	
MTT	12.3 ± 0.9 s	15.5 ± 4.2 s	0.01		14.8 ± 2.0 s	20.6 ± 4.1 s	0.07		7.8 ± 1.6 s	9.8 ± 3.5 s	0.09	
Art. Frac.	14 ± 8%	15 ± 14%	0.56		37 ± 16%	39 ± 23%	0.33		77 ± 17%	73 ± 12%	0.16	
V _b	30 ± 4%	31 ± 13%	0.63		29 ± 6%	31 ± 8%	0.46		27 ± 13%	28 ± 13%	0.28	

I
mL / min / 100 g

(a) Comparison of quantitative perfusion parameters corresponding to hepatic parenchyma between healthy volunteers and cirrhotic patients. Results using both exponential and Weibull TRFs are shown(b) Comparison of quantitative perfusion parameters between background (cirrhotic) hepatic parenchyma and HCC.].

Table 2

a	Exponential TRF				Weibull TRF			
	Norm. Liver	Cirr. Liver	p		Norm. Liver	Cirr. Liver	p	
Perfusion /	213 ± 20	165 ± 28	0.23		175 ± 53	140 ± 51	0.35	
MTT	12.3 ± 0.9 s	14.8 ± 2.0 s	0.22		15.5 ± 4.2 s	20.6 ± 4.1 s	0.16	
Art. Frac.	14 ± 8%	37 ± 16%	0.08		15 ± 14%	39 ± 23%	0.07	
V _D	30 ± 4%	29 ± 6%	0.79		31 ± 13%	31 ± 8%	0.98	
TTA	25.6 ± 4.2 s	37.7 ± 11.2 s	0.01					
AUC	0.13 ± 0.04	0.12 ± 0.05	0.90					

b	Exponential TRF				Weibull TRF			
	Cirr. Liver	HCC	p		Cirr. Liver	HCC	p	
Perfusion /	165 ± 28	473 ± 44	0.08		140 ± 51	383 ± 62	0.09	
MTT	14.8 ± 2.0 s	7.8 ± 1.6 s	0.01		20.6 ± 4.1 s	9.8 ± 3.5 s	0.01	
Art. Frac.	37 ± 16%	77 ± 17%	0.03		39 ± 23%	73 ± 12%	0.04	
V _D	29 ± 6%	27 ± 13%	0.80		31 ± 8%	28 ± 13%	0.71	
TTA	37.7 ± 11.2 s	15.5 ± 6.1 s	<0.01					
AUC	0.12 ± 0.05	0.29 ± 0.11	0.02					

/ mL / min / 100 g