HOMologous Black-Bright-Blood and Flexible Interleaved Imaging Sequence (HOBBI) for Dynamic Contrast-Enhanced MRI of the Vessel Wall

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INTRODUCTION

Atherosclerosis is the primary cause of heart disease and stroke. It is known to be accompanied by a chronic inflammatory condition that can lead to acute clinical events such as plaque rupture and thrombosis (1). Inflammation of the vessel wall has been associated with atherosclerotic plaque initiation (2), progression, and rupture (3). Consequently, inflammation has become an emerging therapeutic target and potential biomarker to assess the therapeutic response in novel agent development (4). Thus, in vivo quantitative measurement of inflammation in atherosclerotic plaques is important.

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) with pharmacokinetic analysis has been used to noninvasively characterize inflammation in atherosclerotic vessel walls (5–9). To accurately quantify pharmacokinetic parameters, however, two competing factors, temporal and spatial resolutions, make the acquisition technically challenging (10). Currently, most studies rely on “bright-blood” techniques (5–7,9,11,12), which can acquire the arterial input function (AIF) from bright-blood images directly. However, the temporal resolution of these techniques is usually insufficient to accurately extract the AIF in such studies because they have to be acquired in a higher resolution for vessel wall delineation. More significantly, the vessel wall region proximal to the lumen can be difficult to quantify reliably, due to contamination from high luminal signals. Especially in early lesions, bright-blood DCE-MRI often fails to delineate the wall boundary, and is overshadowed by the high-intensity of the lumen. Recently, Calcagno et al. developed a novel interleaved dual-imaging DCE sequence, SHILO (13), to acquire AIF at a high temporal resolution and produce a high spatial resolution for vessel wall. However, it still suffers from signal contamination of the vessel wall using bright-blood imaging.

To solve the problem that the bright-blood techniques cannot evaluate the thin vessel wall, “black-blood” DCE-MRI techniques have been proposed, which image the thin vessel wall by suppressing blood signal (8,14,15). However, AIF cannot be directly measured from black-blood DCE-MRI. Thus, two-competing factors, temporal and spatial resolutions, make the acquisition technically challenging (10). Currently, most studies rely on “bright-blood” techniques (5–7,9,11,12), which can acquire the arterial input function (AIF) from bright-blood images directly. However, the temporal resolution of these techniques is usually insufficient to accurately extract the AIF in such studies because they have to be acquired in a higher resolution for vessel wall delineation. More significantly, the vessel wall region proximal to the lumen can be difficult to quantify reliably, due to contamination from high luminal signals. Especially in early lesions, bright-blood DCE-MRI often fails to delineate the wall boundary, and is overshadowed by the high-intensity of the lumen. Recently, Calcagno et al. developed a novel interleaved dual-imaging DCE sequence, SHILO (13), to acquire AIF at a high temporal resolution and produce a high spatial resolution for vessel wall. However, it still suffers from signal contamination of the vessel wall using bright-blood imaging.

To solve the problem that the bright-blood techniques cannot evaluate the thin vessel wall, “black-blood” DCE-MRI techniques have been proposed, which image the thin vessel wall by suppressing blood signal (8,14,15). However, AIF cannot be directly measured from black-blood techniques. Many existing investigations (16–19) therefore choose to use the area under the enhancement-versus-time curve (AUC) (14) instead of direct pharmacokinetic modeling to avoid the negative impact from lacking AIF. However, area under the enhancement-versus-time curve (AUC) lacks physiological interpretation as well as self-normalization. Other studies have used a reference-region (RR) model to perform pharmacokinetic

Purpose: To present a HOMologous Black-Bright-blood and flexible interleaved imaging (HOBBI) sequence for dynamic contrast-enhanced magnetic resonance imaging (MRI) of the vessel wall.

Theory and Methods: A HOBBI sequence is proposed to acquire high-spatial-resolution black-blood and high-temporal-resolution bright-blood dynamic contrast-enhanced images in an interleaved fashion. Black-blood imaging allows for thin vessel wall evaluation, whereas bright-blood imaging obtains the arterial input function accurately. A simulation was performed to assess the accuracy of the pharmacokinetic parameters [transfer constant ($K_{\text{trans}}$)] and fractional plasma volume ($v_p$)] generated from HOBBI. In vivo evaluation was also used to validate HOBBI in an animal model of aortic atherosclerosis.

Results: In the simulation test, the estimated $K_{\text{trans}}$ and $v_p$ measured by HOBBI were more accurate than those from black-blood dynamic contrast-enhanced-MRI. In the animal model testing, $K_{\text{trans}}$ and $v_p$ also demonstrated good interscan reproducibility ($K_{\text{trans}}$: ICC = 0.77, $v_p$: ICC = 0.72, respectively). Additionally, $K_{\text{trans}}$ showed a significant increase from 1 month (0.026 ± 0.013 min⁻¹) to 2 months (0.069 ± 0.018 min⁻¹) in animal model plaque progression after balloon injury.

Conclusion: The proposed HOBBI sequence was demonstrated to be feasible and accurate in estimating the pharmacokinetic parameters of the atherosclerotic vessel wall, and has potential to become an early screening tool for atherosclerosis disease. Magn Reson Med 000:000–000, 2014. © 2014 Wiley Periodicals, Inc.
analysis (8). However, the assumed perfusion characteristics of reference regions may introduce bias, especially for clinical studies with large variance among subjects.

In this study, we propose a HOmologous Black-Bright-blood and flexible Interleaved imaging sequence (HOBBI), which can acquire black-blood and bright-blood images in a temporally interleaved fashion. The spatial and temporal resolution of these two images can be adjusted flexibly according to the requirements of pharmacokinetic analysis on different targets. Both computer simulation and in vivo experiments in an animal model were used to determine its feasibility and advantages for atherosclerotic lesion imaging.

**THEORY**

HOBBI is composed of two interleaved imaging modules (20): the black-blood and bright-blood imaging, as shown in Figure 1a. A two-dimensional (2D) \( T_1 \) weighted spoiled gradient echo (SPGR) was used for data acquisition in both modules. In image acquisition, a low-high phase encoding order was used to fill the k-space center with desired contrast. The two modules can be acquired with different spatial/temporal resolutions based on different imaging targets.

**Black-Blood Imaging Module**

The black blood prepulse contains a nonselective saturation-recovery (SR) pulse and a quadruple inversion-recovery (QIR) pulse sequence (21) (Fig. 1a). The \( T_1 \) weighted contrast is generated by both the SR pulse and QIR sequences. The longitudinal magnetization of inflowing blood and in-plane vessel wall is also shown. A high-spatial-resolution black-blood image (H1) is acquired in eight black-blood imaging modules (M1–M8) with a low-high phase encoding order, and each one of the low-spatial-resolution bright-blood images (L1–L4) is acquired in two bright-blood imaging modules (m1–m2) with a low-high phase encoding order. In each dynamic scan, one black-blood image with four bright-blood images is acquired.

**Bright-Blood Imaging Module**

The bright-blood imaging module uses the same SR pulse to generate \( T_1 \) weighted bright-blood contrast. To assure
that signals of static tissue between the two imaging modules are comparable, four nonselective inversion-recovery pulses are placed after SR with the same timing as the QIR sequence in the black-blood imaging module (Fig. 1a). Conversely, the flowing blood experiences all four inversion pulses are placed after SR with the same timing as the QIR rules are comparable, four nonselective inversion-recovery pulses are placed after SR with the same timing as the QIR sequence in the black-blood imaging module (Fig. 1a). Conversely, the flowing blood experiences all four inversion recovery prepulses after the SR, with a net effect approximating SR, and generating a $T_1$ weighted signal.

**Interleaved Timing Diagram**

As shown in Figure 1b, a temporally interleaved segmented acquisition was designed to obtain black-blood and bright-blood images simultaneously during contrast-enhanced imaging. The spatial/temporal resolution of each imaging segment can be adjusted based on the imaging targets and the need for pharmacokinetic modeling. For atherosclerotic vessel wall imaging, the targeted vessel wall is typically small and thin; and its contrast enhancement process is relatively slow. Thus, a high spatial resolution is preferable to the temporal resolution in black-blood images. Conversely, the typical artery lumen in AIF acquisition is much larger, so the temporal resolution in bright-blood imaging to the typical artery lumen in AIF acquisition is much larger, so the temporal resolution in bright-blood imaging is four times higher than that of the bright-blood imaging, while the temporal resolution of the bright-blood imaging is four times higher than that of the black-blood imaging (Fig. 1b). To restrain the motion artifacts and minimize the average effect of changing signal during the acquisition for bright-blood imaging, the HOBBI sequence is interleaved in blocks of two in this study, as two imaging blocks can acquire a whole bright-blood phase.

**METHODS**

**Sequence Optimization**

To develop a theoretical model for the black- and bright-blood phase, the signal evolution of the blood was separately considered for the two imaging modules:

1. Inflowing blood in the black-blood imaging module experiences:

$$90^\circ - T_s - 180^\circ - T_{I1} - 180^\circ - T_{I2}.$$  

The longitudinal magnetization of the inflowing blood before the SPGR acquisition part can be expressed as:

$$M_z^{\text{Black-blood}} = M_0^z \{1 - 2 \exp[-(T_{I2}/T_1)] + 2 \exp[-(T_{I1} + T_{I2})/T_1] - \exp[-(T_s + T_{I1} + T_{I2})/T_1]\},$$  

where $M_0^z$ is the longitudinal magnetization of blood in the black-blood imaging module, $T_s$ is the saturation delay time, and $T_{I1}$ and $T_{I2}$ are the inversion delay time intervals (Fig. 1a). By minimizing longitudinal magnetization of blood during contrast-enhanced dynamic acquisition, the optimal parameters $T_s$, $T_{I1}$, and $T_{I2}$ can be found to provide sufficient blood suppression in a wide range of $T_1$:

$$[T_s, T_{I1}, T_{I2}] = \arg \min_{T_{I1}, T_{I2}} \int_{T_{I2}}^{T_{I\text{max}}} \left( M_z^{\text{Black-blood}} \times (T_s, T_{I1}, T_{I2}, T_1) \right) \, dT_1$$

where $T_{I\text{max}}$ and $T_{I\text{min}}$ are the maximal and minimal $T_I$ of blood during DCE imaging [$T_{I\text{max}} = 1550$ ms and $T_{I\text{min}} = 200$ ms were used in this study (21)].

The maximal thickness of the imaging slice determines the blood suppression efficiency of the sequence. To achieve a good black-blood effect, the following condition should be met,

$$v_{\text{mean}} \times T_{I2} > \text{maximal imaging slice thickness},$$  

where the mean velocity of the rabbit aorta $v_{\text{mean}} = 146$ mm s$^{-1}$ (23). Equation [2] demands that the blood inside the imaging slice in the prepulse duration should not be residual at the time of imaging.

2. Inflowing blood in the bright-blood imaging module experiences:

$$90^\circ - T_s - 180^\circ - 180^\circ - T_{I1} - 180^\circ - 180^\circ - T_{I2}.$$  

Ignoring the $T_1$ relaxation between the two very closely placed inversion pulses in QIR sequence, the longitudinal magnetization $M_z^{\text{Bright-blood}}$ of the inflowing blood before the SPGR acquisition part can be approximated as:

$$M_z^{\text{Bright-blood}} = M_0^z \{1 - \exp[-(T_s + T_{I1} + T_{I2})/T_1]\}.  

**Simulation Test**

Before application in in vivo imaging, simulations were carried out to compare the accuracy of pharmacokinetic parameters derived from both HOBBI and RR-based pharmacokinetic analysis (8). The simulations were performed using MATLAB (MathWorks, Natick, MA) based on a rabbit atherosclerosis model (8). First, the AIF was simulated using MATLAB (MathWorks, Natick, MA) based on a rabbit atherosclerosis model (8). First, the AIF was simulated using a biexponential equation (24):

$$C_0(t) = \begin{cases} 
0, & t < t_1 \\
D[a_1 \exp(- (t - t_1)/\tau_1) + a_2 \exp(- (t - t_1)/\tau_2)], & t \geq t_1 
\end{cases}$$  

where the dose $D = 0.1$ mmol kg$^{-1}$ (mmol Gadolinium/kg body weight), the amplitudes $a_1 = 22$ kg L$^{-1}$, $a_2 = 9.7$ kg L$^{-1}$, the time constants $\tau_1 = 2.5$ min, $\tau_2 = 75$ min, the arrival time of contrast agent $t_1 = 16$ s (24). Considering the hematocrit of blood, the concentration of contrast agent in the blood was determined by $C_a = C_0 \times (1 - \text{Hct})$, with an assumed hematocrit value (Hct) of 0.4 (24). Meanwhile, according to the AIF, the nominal uptake curves of the vessel wall and muscle were generated by the Patlak model (25): $C(t) = v_p C_0(t) + K^{\text{trans}} \int_0^t C_0(\tau) \, d\tau$ (25). First, with
fixed signal-to-noise ratio (SNR), the pharmacokinetic parameters of the vessel wall were set as: $K_{\text{trans}}$ from 0.02 to 0.2 min$^{-1}$ in steps of 0.02 min$^{-1}$; $v_p$; while $v_p$ from 0.01 to 0.1 in steps of 0.01. $K_{\text{trans}}$ = 0.1 min$^{-1}$. The SNR was defined as signal/noise, where the signal was determined by the mean signals of delayed phases (140–180 s after contrast arrival), and the noise was defined as the standard deviation of zero mean Gaussian noise. The fixed SNR of vessel wall and muscle was 22, whereas the SNR of blood was set as 96 (comparable with in vivo experiments, see the “In vivo animal model test results” part). Moreover, different SNR levels ranged from 15 to 30 in step of 1 for vessel wall and muscle were simulated with fixed $K_{\text{trans}} = 0.1$ min$^{-1}$ and $v_p = 0.05$. The SNR of AIF was set to four times of the vessel wall SNR to account for the different spatial resolution. A normal distribution was assumed for kinetic parameters in the reference region (26) (muscle in this study); $K_{\text{trans}} = 0.0244 \pm 0.0022$ min$^{-1}$ (mean ± standard deviation), $v_p = 0.0240 \pm 0.0073$.

After generating the concentration curves for blood, vessel wall, and muscle, their changing $T_1$ values were calculated, according to the relationship between concentration and $T_1$ values (27):

$$r_{\text{Gd}} = 1/T_1 - 1/T_{1,0}.$$  

where $r_{\text{Gd}}$ = 3.3 L mmol$^{-1}$ s$^{-1}$, and $[\text{Gd}]$ represents the contrast agent concentration, and $T_{1,0}$ is the initial value of $T_1$ before the contrast agent arrives. In this study, the $T_{1,0}$ of blood was set to 1550 ms (28), and $T_{1,0}$ of vessel wall and muscle was set to 1150 ms (29). Based on the sequence protocols of HOBBI and black-blood + RR technique (8), signal curves of blood, vessel wall, and muscle were obtained from the changing $T_1$ values. Each simulation was repeated 5000 times with independent zero-mean standard normal distribution noise (standard deviation = signal/SNR) added separately for every signal curve. Then, these simulated curves were converted back to concentration curves based on Eq. [4] and the assumed $T_{1,0}$ of blood, vessel wall, and muscle. For the HOBBI technique, the $K_{\text{trans}}$ and $v_p$ were calculated by the Patlak model (25) using a simulated AIF and vessel wall curve. For black-blood + RR technique, pharmacokinetic modeling was done with simulated muscle curve and vessel wall curve (8).

According to the optimized timing diagram of the HOBBI sequence, we assumed each imaging segment takes 0.5 s. Then, each black-blood and bright-blood imaging module can be acquired in 4 and 1 s, corresponding to a temporal resolution of 8 and 2 s after factoring in the interleaved acquisition pattern (Fig. 1b). With regards to the prepulse durations of black-blood + RR technique (8), the temporal resolution was set as 5 s by considering the big difference in acquisition efficiency between these two methods. The duration time after contrast arrival in all simulations was set to 180 s (8).

### Data Analysis

The mean and standard deviation of the estimated $K_{\text{trans}}$ and $v_p$ were used to compare the two methods. The coefficient of variation (CV) and root mean square error (RMSE) were used to evaluate the precision and accuracy of the estimated $K_{\text{trans}}$ and $v_p$ of the vessel wall.

$$CV = \sqrt{\frac{\sum_{j=1}^{N} (P_{\text{est}} - P_{\text{true}})^2/(N - 1)}{P_{\text{true}}}}$$

$$RMSE = \sqrt{\frac{\sum_{j=1}^{N} (P_{\text{est}} - P_{\text{true}})^2/(N - 1)}{P_{\text{true}}}}$$

$P_{\text{true}}$, $P_{\text{est}}$, and $P_{\text{true}}$ are the parameter’s simulated true values, estimated values, and mean value of the estimated

### Table 1: HOBBI Scan Parameters

<table>
<thead>
<tr>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip angle</th>
<th>SPGR factor</th>
<th>$T_1_s$</th>
<th>$T_1_l$</th>
<th>$T_2_l$</th>
<th>FOV</th>
<th>Slice thickness$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>3.7</td>
<td>30°</td>
<td>20</td>
<td>110</td>
<td>170</td>
<td>60</td>
<td>80 x 80 mm$^2$</td>
<td>6 mm</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>Temporal resolution</td>
<td>Number of dynamic scans</td>
<td>Spatial resolution</td>
<td>Temporal resolution</td>
<td>Number of dynamic scans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 x 0.5 mm$^2$</td>
<td>7.88 s</td>
<td>25</td>
<td>0.5 x 2.0 mm$^2$</td>
<td>1.97 s</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$One slice.
values, respectively. N is the number of repeated tests (N = 5000 in this case).

In Vivo Test on Experimental Animal Model

After institutional animal care and use committee approval, atherosclerotic plaques were induced in the aorta of 10 New Zealand white male rabbits (mean weight = 2.3 ± 0.2 kg; Keyu Animal Breeding Center, Beijing). Rabbits were fed a high cholesterol diet (1% cholesterol, 5% lard, and 1% egg yolk) beginning 1 week prior to the surgical balloon injury. The balloon injury was performed as follows. Anesthesia was induced by an injection of 2.4–2.7 mg kg⁻¹ 3% sodium pentobarbital through a marginal ear vein. Blunt dissection of thigh muscles was made to expose the femoral artery, so that a size 3 × 15 mm² Fogarty balloon catheter (VOYAGER, USA) could be introduced through the femoral artery. When the catheter tip reached the proximal abdominal aorta, the catheter balloon was inflated with sterile saline to a pressure of 8 atm, and then drawn back for a length of about 15 cm to the iliac bifurcation. The catheter balloon tip was deflated and the injury procedure was repeated three times. Closure of the surgical wound was accomplished by stitching the fascia and the skin layer with an absorbable suture. After the balloon injury, all rabbits remained on the cholesterol-enriched diet.

The rabbits were randomly divided into two groups (five rabbits each, defined as Group 1 and Group 2). At 1 month after the balloon injury, rabbits in Group 1 received two DCE-MRI scans on two consecutive days before being sacrificed and histologically evaluated. The rabbits in Group 2 were scanned once at 1 month, twice at the 2 months follow-up, and were then sacrificed. An illustration of the experimental design is detailed in Figure 2.

All rabbits were scanned on a 3.0 T MR system (Achieva, TX, Philips) using an eight-channel knee coil. The MRI protocol included: (1) a gradient echo 2D time-of-flight sequence to identify the location of the aorta-iliac bifurcation, with slice thickness of 3 mm and totally 27 slices; (2) a T₁ weighted double-inversion-recovery sequence to estimate Ktrans and vp between two methods, HOBBI (red triangle line): one black-blood and four bright-blood images interleaved with temporal resolution of 2 s for AIF, and temporal resolution of 8 s for vessel wall uptake curve; and RR technique (blue circle line): only black-blood images with time resolution of 5 s for vessel wall and muscle uptake curves. After contrast arrival, all durations were set to 180 s. All simulations were done without considering some acquisition related issues, such as the flow pattern, and segmented k-space view ordering. (please also see the fourth paragraph of “Discussion and Conclusions”). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
black-blood sequence (30), with delay time \( t_d = 340 \text{ ms} \), field-of-view \( FOV = 110 \times 110 \text{ mm}^2 \), matrix \( M = 220 \times 220 \), echo time \( TE = 7 \text{ ms} \), echo train length \( ET = 16 \), slice thickness \( T_s = 3 \text{ mm} \), and a total of 20 slices; and a T2 weighted fast spin echo sequence with field-of-view \( FOV = 110 \times 110 \text{ mm}^2 \), matrix \( M = 220 \times 220 \), TR = 6000 ms, echo time \( TE = 85 \text{ ms} \), echo train length \( ET = 16 \), slice thickness \( T_s = 3 \text{ mm} \), and a total of 20 slices to locate atherosclerotic plaques; (3) a HOBBI sequence to acquire DCE-MRI images at the location with the largest plaque. At the beginning of the third acquisition of the black-blood dynamic protocol, 0.17 mmol kg\(^{-1}\) of contrast agent (Gd-DTPA) was injected through the marginal ear vein at a rate of 2 mL s\(^{-1}\) followed by 15 mL 0.9% saline solution flush. The scan parameters of HOBBI are shown in Table 1.

**MRI Analysis**

In black-blood DCE images, vessel wall and reference region (psoas muscle) contours were manually drawn on each frame to calculate the signal curves by an expert reader using a custom-designed image analysis software (CASCADE) (31). The reader was blinded to the scan time and group. In the bright-blood images, 8–10 pixels were selected within the aorta on each image to acquire the signal curve of blood. For the HOBBI protocol, assuming that the blood and vessel wall both have the fixed \( T_1 \) values \( T_{1, \text{blood}} = 1550 \text{ ms} \) (28) and \( T_{1, \text{vessel wall}} = 1150 \text{ ms} \) (29), concentration curves of the vessel wall and blood were calculated using Eq. [4]. Then, AIF \( (G_p) \) was calculated by \( G_p = G_0/(1 - Hct) \) with \( Hct = 0.4 \) (24) considering the hematocrit of blood. Pharmacokinetic analysis was performed using the Patlak model (25) with vessel wall concentration curve from black-blood images and AIF from bright-blood images of HOBBI. As a comparison, the black-blood images generated by HOBBI were used to generate pharmacokinetic parameters using the RR method (8) without AIF from the bright-blood images. Also, the SNRs of blood, vessel wall, and muscle were measured for the animals, with the signal determined by the mean signals of delayed phases (140–180 s after contrast arrival) in previous described regions of interest, while the noise was defined as the standard deviation of a peripheral air region in the same phases.

Statistical analysis for all data was performed in SPSS (version 16.0, Chicago, IL). The SNRs of blood, vessel wall, and muscle were reported as mean ± standard deviation. The reproducibility of \( K^{\text{trans}} \) and \( v_p \) generated from the repeated scans (from Group 1 and Group 2) of the HOBBI sequence with AIF and the RR method without AIF were evaluated by the intraclass correlation coefficient (ICC; one-way random, single measure) defined as (32):

\[
\text{ICC} = \frac{s_r^2}{s_r^2 + s_e^2},
\]

where \( s_r^2 \) is the variance of \( K^{\text{trans}} \) and \( v_p \) between rabbits, and \( s_e^2 \) is the variance of measurement error between repeated scans of the same rabbit. In this analysis, all the animals from Group 1 and Group 2 were included due to the limited sample size (\( N = 5 \)) in each group. Consequently, this ICC corresponds to a more heterogeneous population than either group alone.

The \( K^{\text{trans}} \) and \( v_p \) values generated from the HOBBI sequence at 1 month and average values at 2 months (defined as the average values in the two repeated scans)
in Group 2 were compared by the paired-sample t-test (two tailed) to evaluate plaque progression.

Histology Analysis

Immediately after imaging, the rabbits were euthanized and the aorta exposed. Using the aortic-iliac bifurcation as a guide, the segment scanned was marked to maintain orientation and position throughout excision. Corresponding to the imaging slice, the aorta was dissected out and a 6-mm thick segment was obtained. The specimens were fixed for 24 h in 10% neutral buffered formalin, then processed and embedded in paraffin. A 5-μm cross section for each specimen was obtained and stained with hematoxylin-eosin. Digital images of the stained sections were obtained. Morphometry was performed using CASCADE (31) to measure the maximal vessel wall thickness.

RESULTS

Optimization of $T_s/\text{TI}_1/\text{TI}_2$

Based on Eq. 2, a few sets of parameters were found to provide comparable blood suppression efficiencies as plotted in Figure 3: $T_s/\text{TI}_1/\text{TI}_2 = 110/170/60$ ms, $T_s/\text{TI}_1/\text{TI}_2 = 155/205/70$ ms, $T_s/\text{TI}_1/\text{TI}_2 = 240/285/90$ ms, with maximal imaging slice thickness 8.76, 10.22, 13.14 mm, respectively. The corresponding shortest $T_s$ values of blood that can be sufficiently suppressed are: 133, 159, and 183 ms, respectively. For the sake of improved imaging efficiency, $T_s/\text{TI}_1/\text{TI}_2 = 110/170/60$ ms were chosen as the optimal parameters to be used in the following experiments.

Simulation Test Results

As shown in Figure 4, the mean $K^{\text{trans}}$ values generated from HOBBI were closer to the true values than those of the RR technique (Fig. 4a); the CVs from HOBBI were much smaller than those from the RR technique (Fig. 4b); the RMSEs of HOBBI were also much smaller than those of RR technique, especially for high $K^{\text{trans}}$ values (Fig. 4c). The $v_p$ estimation showed similar results (Fig. 4d-f).

In simulation of different SNR levels (Fig. 5), the mean $K^{\text{trans}}$ values generated from HOBBI were closer to the true values than those of the RR technique for all SNR levels (Fig. 5a); the CVs and RMSEs of $K^{\text{trans}}$ were much smaller than those of the RR technique (Fig. 5b,c). Meanwhile, HOBBI overestimated the mean $v_p$ values over the RR technique; however, the CVs and RMSEs of the $v_p$ values generated from HOBBI were much smaller than those of the RR technique under different SNRs (Fig. 5e,f).

In Vivo Animal Model Test Results

All scans were successfully performed on all rabbits. Figure 6 shows an example of dynamic black-blood and bright-blood images acquired by HOBBI throughout the contrast injection process. Blood suppression was sufficient before and after contrast arrival. During contrast arrival, no obvious flow artifacts could be seen (Fig. 6f). The spatial resolution of black-blood images was high enough to delineate both the vessel lumen and wall. The bright-blood images (Fig. 6b–e,g–j,l–o) were produced with high temporal resolution. The concentration curves...
The SNR of blood in bright-blood images was 95.91 ± 18.49 (mean ± standard deviation); whereas the SNRs of vessel wall and muscle in black-blood images were 22.42 ± 4.59 and 21.78 ± 3.12, respectively. The ICC of $K^{\text{trans}}$ and $v_p$ generated from the HOBBI sequence between repeated scans of 10 rabbits were 0.77 and 0.72, respectively. The ICC of $K^{\text{trans}}$ and $v_p$ generated from RR method using black-blood images of HOBBI between repeated scans were 0.70 and 0.40. As shown in Table 2, in Group 2, the $K^{\text{trans}}$ of the HOBBI sequence increased significantly ($P < 0.05$) between the 1 month (0.026 ± 0.013 min$^{-1}$) and 2 month follow-ups (0.069 ± 0.018 min$^{-1}$).

Histological analysis of the matched regions showed well-formed atherosclerotic lesions typical of induced rabbit plaques. Figure 8 shows an example of the aortic vessel wall obtained in the area scanned, containing many foam cells, macrophages, and inflammatory cells. The maximal vessel wall thickness measured from all rabbits was 0.69 ± 0.16 mm (mean ± standard deviation).

**DISCUSSION AND CONCLUSIONS**

In this study, the HOBBI sequence for DCE-MRI of atherosclerotic vessel walls was proposed. The traditional “bright-blood” and “black-blood” techniques were extended to a “black-bright-blood” technique with different spatial/temporal resolutions. Although DCE-MRI has been extensively used in oncology, it remains challenging to noninvasively quantify perfusion of atherosclerotic plaques, especially for early lesions, due to its requirements for high spatial resolution to visualize small vessel walls, and high temporal resolution to allow accurate analysis of pharmacokinetics. HOBBI is able to generate both high spatial resolution black-blood and high temporal resolution bright-blood images to fulfill the requirements at the same time.

HOBBI has unique advantages in perfusion imaging of atherosclerotic plaques, especially in early lesions. The traditional bright-blood method (5,9,12) suffers from vessel wall signal contamination due to the high intensity of the lumen. As a result, regions near the lumen are difficult to quantify reliably, and exclude its utilization in early lesions. Conversely, black-blood imaging without signal contamination has difficulties for pharmacokinetic analysis. Previously proposed solutions such as the RR method (8) for black-blood DCE-MRI may still introduce bias and variance. Recently Fan et al. proposed a saturation recovery + double inversion recovery (SR+DIR) (22) based method which also contain interleaved black-blood and bright-blood acquisitions. However, it may suffer from artifacts in black-blood images, because blood $T_1$ values can vary in a large range during DCE acquisition (24,33). The HOBBI sequence proposed here is designed to overcome those drawbacks. Simulation results indicate that the estimated pharmacokinetic parameters derived from the HOBBI have a high accuracy with lower RMSE than the traditional RR method. Furthermore, the smaller CV of HOBBI in simulation tests also suggests its better reproducibility than black-blood + RR method. Based on the experimental parameters settings in this study, the in vivo experiment also showed a higher ICC using HOBBI than black-blood + RR method.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value after 1 month$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness$^c$ (mm)</td>
<td>0.64 ± 0.15</td>
<td>0.72 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>$K^{\text{trans}}$ (min$^{-1}$)</td>
<td>0.028 ± 0.014</td>
<td>0.026 ± 0.013</td>
<td>0.069 ± 0.018</td>
</tr>
<tr>
<td>$v_p$</td>
<td>0.247 ± 0.084</td>
<td>0.263 ± 0.079</td>
<td>0.130 ± 0.029</td>
</tr>
</tbody>
</table>

$P \leq 0.05$ is considered as statistical significant, labeled in bold.

$^a$Data shown are means ± standard deviations, and measurements were the averaged values of repeated scans where reproducibility scans were available.

$^b$P value for change within Group 2 from 1 month to 2 months by paired t-test.

$^c$Measured by histology.

extracted from HOBBI are shown in Figure 7. The SNR of blood in bright-blood images was 95.91 ± 18.49 (mean ± standard deviation); whereas the SNRs of vessel wall and muscle in black-blood images were 22.42 ± 4.59 and 21.78 ± 3.12, respectively.

The ICC of $K^{\text{trans}}$ and $v_p$ generated from the HOBBI sequence between repeated scans of 10 rabbits were 0.77 and 0.72, respectively. The ICC of $K^{\text{trans}}$ and $v_p$ generated from RR method using black-blood images of HOBBI between repeated scans were 0.70 and 0.40. As shown in Table 2, in Group 2, the $K^{\text{trans}}$ of the HOBBI sequence increased significantly ($P < 0.05$) between the 1 month (0.026 ± 0.013 min$^{-1}$) and 2 month follow-ups (0.069 ± 0.018 min$^{-1}$).

Histological analysis of the matched regions showed well-formed atherosclerotic lesions typical of induced rabbit plaques. Figure 8 shows an example of the aortic vessel wall obtained in the area scanned, containing many foam cells, macrophages, and inflammatory cells. The maximal vessel wall thickness measured from all rabbits was 0.69 ± 0.16 mm (mean ± standard deviation).

**FIG. 8.** a: A low power photomicrograph showing a slightly eccentric atherosclerotic plaque. b: A high power photo taken in the inset. The plaque is typical of rabbit lesions with many foam cells, macrophages, inflammatory cells, and neovessels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
In this study, HOBBI successfully evaluated rabbit aortic atherosclerotic vessel walls with a relatively small thickness (0.69 ± 0.16 mm by histology for all rabbits), which has comparable and even smaller thickness with important vascular beds in human, such as carotid and coronary. The high reproducibility shown in such thin vessel wall suggests its ability to image relatively early atherosclerotic lesions reliably. More significantly, HOBBI detected a K\text{trans} increase during the progression of atherosclerotic plaque despite the possible bias introduced by assumed constant precontrast T1, which agreed with the results by Chen et al. (8), indicating the feasibility of HOBBI for longitudinal studies and suggesting that HOBBI can be practical in clinical applications, such as the evaluation of therapeutic response (12). However, further study adding precontrast T1 measurement in DCE-MRI of vessel wall is still needed. Moreover, the key regions in advanced lesions (such as the fibrous cap and shoulder regions) where inflammation may lead to plaque rupture (1,34,35) have similar imaging challenges in DCE-MRI of early lesions. With the ability to quantitatively assess the relative thin wall without the drawbacks of luminal signal contamination or large bias/variance, the HOBBI sequence has great potential to quantify the perfusion characteristics in key regions of advanced plaques and may provide a new tool to predict the risk of plaque rupture (7,11).

To fulfill the requirements for spatial/temporal resolution and SNR, only one slice was imaged without 2D multislice implementation in the DCE-MRI of this rabbit model study. The main reason is that the interleaved acquisition scheme and long preparation time in HOBBI decrease acquisition efficiency. To overcome this limitation, further developments of fast imaging and reconstruction methods are underway, which utilize the redundant information provided by the same contrast and intensity (except for the blood) in bright-blood and black-blood imaging modules. A current drawback of HOBBI is its difficulty in larger coverage three-dimensional implementation, because the SR + QIR pre-pulse can only suppress the blood signal in a limited coverage (see the maximal imaging slice thickness in “Results—Optimization of T1/\text{T1}_1/\text{T1}_2” part). Another concern of the sequence is the elevated specific absorption rate compared to regular DCE scans, due to the addition of multiple adiabatic inversion pulses. In this study, however, the specific absorption rate value automatically calculated in this in vivo experiment was within the safety range even for potential human studies. For further application in human artery imaging in brain and neck, the specific absorption rate values of HOBBI automatically calculated by the clinically approved scanner are also within the safety range for a typical 70-kg subject. Then, the interleaved imaging scheme in black-blood imaging may potentially enhance the transient contrast effect in DCE acquisition. Further optimizing the k-space filling order and acquiring images in shorter time by utilizing fast imaging techniques can be carried out to reduce the transit contrast effect of HOBBI. In this study, the vP value was higher compared to other studies (8). The overestimation of vP in the Patlak model could be caused by the AIF-like signal contamination from the residual flow artifacts, generated by slow flow adjacent to the vessel wall in the black-blood images, especially during bolus arrival (as can be seen in Fig. 6f). Also, the partial volume artifacts introduced by relative larger slice thickness could be another reason. Another limitation is that the simulation is only intended to evaluate the potential advantages of HOBBI rather than predicting the real-world signal change, many potential secondary contributors to the signal change were not included in the simulation, such as the flow pattern, vessel wall motion, slice profiles, inversion efficiencies, transient SPGR signals, and segmented k-space view ordering.

Finally, as part of a larger on-going study, further histological lesion characterization is still pending. Future studies will include immunohistochemistry for microvasculature and cell identification as the need arises. Our confidence in the results of this study is based on the consistent size and morphology of the induced lesions. Previous studies have paved the way in establishing the relationship between the histological microvascular biomarkers and DCE-MRI parameters (3,8,36) by black-blood techniques using similar rabbit atherosclerosis models.

In conclusion, a HOBBI sequence was proposed to evaluate the perfusion of the atherosclerotic vessel wall with robust blood suppression. The simulation tests suggest its high accuracy and reproducibility. The feasibility and reproducibility of HOBBI were also demonstrated in vivo in a rabbit aortic atherosclerosis model. HOBBI may be a promising new tool used to assess the perfusion characteristics of early atherosclerotic lesions and in longitudinal studies.

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