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Time-Resolved Angiography Using InfLow Subtraction (TRAILS)

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Abstract

Purpose—A novel pseudo-continuous arterial spin labeling based angiographic method called Time-Resolved Angiography using InfLow Subtraction is introduced and used to acquire time-resolved whole-head angiographic data sets in healthy volunteers in a clinical feasible scan time of less than 5 min.

Methods—Using this new method, in conjunction with a sliding window reconstruction, a temporal resolution of 7.2 ms with a low temporal footprint of 432 ms can be achieved.

Results—Excellent vessel delineation compared to a time-of-flight MRA was demonstrated. Normal variations of the vascular system including the Circle of Willis (CoW) were identified using Time-Resolved Angiography Using Inflow Subtraction. Signal intensities were measured in various vascular segments to quantify the blood transit time.

Conclusion—In this feasibility study, we showed that Time-Resolved Angiography using InfLow Subtraction can be used to acquire hemodynamic information of the whole head in healthy volunteers with a high temporal and spatial resolution. Further studies in patients that suffer from vascular diseases to explore various flow patterns including longer transit time are needed.

Keywords

angiography; SPGR; arterial spin labeling; noninvasive; time resolved; noncontrast enhanced; 4D; MRA

The gold standard for time-resolved intravascular angiography is digital subtraction angiography (DSA) (1,2). It is a dynamic study, providing information about cerebral hemodynamics. DSA provides high spatial and temporal resolution information about the cerebral vasculature, and allows selective interrogation of intracranial arteries, which is important for delineating the specific arterial supply of intracranial vascular lesions. However, DSA is an invasive method associated with certain risks, such as strokes, adverse reactions to iodized contrast agents, exposure to ionizing radiation, and risks associated with arterial puncture. Also, during a DSA exam, the injected tracer volume and pressure may modify the regular intravascular flow pattern and change the appearance of certain vascular

structures, which ultimately could lead to a distorted representation of a vessel and blood-flow properties (3–5).

Time-of-flight MRA (TOF-MRA) is performed widely for noninvasive assessment of the intracerebral vascular abnormalities including arterial stenosis, dissections, aneurysms, and arteriovenous malformations or fistulas (6,7). However, it is not a dynamic study: it does not provide any temporal information, which is important for the diagnosis of delayed flow and arteriovenous shunting. While hemodynamic information can be extracted from phase-contrast MRA velocity data, this technique has not gained wide acceptance clinically due to its long acquisition times.

During the last decade, time-resolved, contrast-enhanced (CE)-MRA has been introduced as a lower resolution but minimal-invasive alternative to DSA. It has the advantage over DSA of providing cross-sectional anatomical information from structural MRI sequences performed during the same examination (8). However, the temporal resolution (usually in the order of seconds) of CE-MRA is constrained by the intravascular dynamics of the first pass of the contrast agent, as well as the short arterio-venous transit time that leads to early venous enhancement. In addition, CE-MRA requires intravenous injection of gadolinium-based contrast agents, which is contraindicated in patients with poor renal function due to the risk of nephrogenic systemic fibroses (9).

Hence, a fast non-CE time-resolved MRA technique is desired as a noninvasive and nonionizing alternative to DSA. Until now such methods were either limited by long acquisition times or the use of exogenous, gadolinium-based contrast agents, precluding their use in patients with significant renal impairment. A nascent MR angiographic method that addresses these needs utilizes arterial spin labeling (ASL) principles to provide time-resolved imaging of the intracranial vasculature without the need for an exogenous contrast agent. The ASL-based angiographic image formation is usually based on two magnetization preparation states, in which blood magnetization is either inverted (“label” state) or left unperturbed (“control” state). Previously, various static ASL-based angiography methods have been proposed for imaging of the cerebral vasculature using fast readout methods, such as echo planar imaging (EPI), TrueFISP, or fast spin echo (FSE), which follow the magnetization preparation module to image the tagged blood while it is still in the arteries (10–13).

Recently, pseudo-continuous arterial spin labeling (PCASL)-based time-resolved magnetic resonance angiography (MRA) strategies have been presented in which the preparation module is followed by a multiphase readout, allowing one to extract important hemodynamic information such as blood arrival and transit times. Alternatively to a multiphase readout, one can use multiple acquisitions subsequent to preparation modules with varying tagging durations or varying posttagging delays to retrieve hemodynamic information (14–22). Depending on the readout and labeling strategy, targeting of a specific vessel of interest for angiographic purposes is also possible. In theory, the spatial or temporal resolution of PCASL-based angiography is only restricted by the scan time or TR unlike CE-MRA. However, in practice due mostly to scan time limitations previous studies achieved only low temporal resolution, >150 ms, or necessitated compromise where higher

temporal resolution was traded for a high temporal footprint. For the same reason, some of the previous studies were limited to two-dimensional (2D) projection imaging or used restricted coverage/small field of views. Some PCASL-based MRA studies also relied on time-consuming gating to avoid flow-related pulsation artifacts or complete signal voids that might arise if a balanced-steady-state free precession (SSFP) readout is used, which could emanate from fast changing, retrograde, or turbulent flow (23).

Here, we present a novel variant of PCASL-based time-resolved MRA, Time-Resolved Angiography using InFlow Subtraction (TRAILS), which enables whole head coverage and the acquisition of both static (akin to TOF-MRA) and dynamic MR angiograms with a high spatial and temporal resolution in a single scan. It uses a fast 3D cones readout (24). Due to its high readout duty cycle and short echo times, the 3D cones readout is signal-to-noise ratio (SNR) and scan time efficient; has good flow compensation properties and has support for asymmetric field of views (FOVs). Whole-brain TRAILS can be achieved within clinically feasible scan times of less than 5 min without using gating or parallel imaging. First proof-of-principle studies of intravascular arteries have been conducted in healthy volunteers to demonstrate the feasibility of this novel method.

METHODS

Study Subjects

This study was approved by our institutional review board and written informed consent was obtained from all subjects who participated in this study. Specifically, TRAILS was performed on five healthy subjects (3m/2f, mean age 30 ± 2 years) using a high-performance 3T MRI unit with a gradient strength of 50 mT/m and a maximum slew rate of 200 mT/m/ms (Discovery HD750, GE Healthcare, Waukesha, WI) with a 32-channel receive only head coil (Nova Medical, Wilmington, MA).

TRAILS Pulse Sequence

As illustrated in Figure 1, TRAILS uses a PCASL approach, which consists of a tagging module with two states, “label” and “control.” Each state is followed by a multiphase, Look-Locker like 3D cones spoiled gradient echo (SPGR) readout that uses a low flip angle slice-selective minimum-phase Shinnar-Le Roux (SLR) pulse (20,24,25). Sequence parameters were: resolution (x, y, z) where x is left-right, y is anterior-posterior and z is superior-inferior: $1.00 \times 1.00 \times 2.00$ mm, flip angle $\alpha = 6^\circ$, readout bandwidth: ± 125 kHz, FOV: $200 \times 200 \times 150$ mm, $TR/TE = 7.2/0.13$ ms. The repetition time of the two tagging states, TR_{Tag} , was 5.6 s (3 s labeling and 2.6 s multiphase readout). A total of 18,456 cone interleaves were acquired in a scan time of 04:52 min. The dynamic inflow of fresh blood is measured using a segmented multiphase readout as shown in Figure 2. Each of the two tagging states (“label” and “control”) uses P tagging repetitions; each consists of M readout sub-blocks, with N different cone interleaves in each sub-blocks. In detail, $P=26$, tagging repetitions of “label” and “control” were used to acquire $M=6$ sub-blocks with each $N=60$ interleaves per readout block. Therefore, for each tagging state, a total of 9228 cones interleaves were acquired, which includes 22 dummy acquisitions for each sub-block in the last tagging cycle to achieve a consistent sub-block size.

The pseudo-continuous tagging module in TRAILS uses a fixed tagging duration of 3 s, to ensure equal and sufficient labeling of all major feeding arteries of the imaging region of interest (ROI).

The label state incorporates a pseudo-continuous flow-driven adiabatic inversion, which uses a thin axial labeling plane, proximal to the imaging slab. Spins that flow through the labeling slice experience a train of Hanning window-shaped radio-frequency (RF) pulses. The RF amplitude and phase is modulated to invert the magnetization of the blood ($B_{1AVE} = 0$, $G_{AVE} = 0$) that flows through this slice. The duration of each pulse was 512 μ s, followed by 700 μ s spacing, and was linked with corresponding gradients on the z -axis.

In the control state, the phase of the RF pulse relative to the previous RF pulse cycles by 180°, which has only a minimal effect on the spins and, therefore, does not lead to an inversion ($B_{1AVE} = 0$, $G_{AVE} = 0$). A more detailed description of the PCASL tagging approach can be found elsewhere (26).

After the 3 s labeling period, a 2.6 s multiphase read-out begins in during which the inflowing fresh (not labeled) spins flow into the vascular ROI, displacing the previously labeled spins (Fig. 2). The same readout is performed subsequently to the control state, in which the fresh inflowing blood is displacing the unlabeled spins. TRAILS uses the same thin axial tagging plane placed 30 mm inferior from the imaging volume for both tagging states, label and control. TRAILS uses the same 3.40 mm thick axial tagging plane placed 30 mm inferior from the imaging volume for the tagging of label and control.

The 30 mm gap between the tagging plane and the imaging volume increases the transit time of labeled spins to the imaging volume. This reduces the overall contrast-to-noise ratio (CNR) due to T_1 -decay of the labeled blood, and the increased transit time as the label has to travel 30 mm further downstream to reach the imaging slab. However, without this gap, image contamination might occur in the imaging volume that is caused by imperfect signal suppression of static tissue in the tagging plane which aliases into the imaging slab and the RF side-lobes/out-of-slice profile. This gap also reduces the signal loss that occurs in the proximal region of the angiographic volume, caused by fresh blood that otherwise would immediately displace the labeled spins at the proximal end of the imaging volume after the label module is turned off.

The tagged spins that are already in the vascular ROI experience a number of RF excitations during the read-out, which eventually drives the magnetization from both the label and control state, into the same steady state akin to a Look-Locker approach (20). This effect can be described by an effective $T_{1,eff}$ that is shorter than the original T_1 -relaxation time of blood, which depends on the chosen flip angle, α , and the TR of the multiphase readout:

$$T_{1,eff} = \frac{TR - T_1 \cdot \log(\cos \alpha)}{T_1 - TR}. \quad [1]$$

Bloch-Simulations were performed to analyze signal saturation effects for various blood flow rates in conjunction with the key sequence parameters (e.g., flip angle, TR). For this

study, we kept the flip angle low $\alpha = 6^\circ$ and used a $TR = 7.2$ ms to avoid an early ($<$ readout duration) saturation of the blood signal. Various flow rates were simulated by adapting the number of RF excitations that the blood experiences during the readout time of 2.6 s for a FOV of 15 cm. Blood relaxation times ($T_1=1932$ ms, $T_2=275$ ms) were taken from literature (27).

TRAILS Reconstruction

All reconstructions were implemented and performed in MATLAB (Release 7.1, Natick, MA) and C++ (gcc version 4.2.4) on a multicore machine (8 x Intel Xeon X5570, 2.93 GHz, 192GB RAM, Ubuntu 4.2.4-1ubuntu4). Reconstruction time for the 32-channel head coil data was approximately 12 min/volume for each temporal phase.

After both states (label and control) are acquired, complex sensitive subtraction of label and control on a per interleaf basis are used to form the TRAILS angiographic data set. This subtraction between the label and the control data set is the essential step in TRAILS to cancel the signal from the background tissue and to distinguish the label from the fresh inflowing blood.

Then, from this angiographic data set, N temporal phases, $TP_{n=1\dots N}$, are reconstructed, using a sliding window reconstruction with a sliding window width of 60 interleaves, to collect 1538 interleaves from each the “label” and “control” data set (28). This results in a temporal footprint of $60 \times TR = 432$ ms.

In detail, the temporal phases, TP_n , were computed as follows:

$$TP_n = SoS \left(\mathcal{F}^{-1} (G \cdot (L_i - C_i)) \right), \quad [2]$$

where $SoS()$ denotes sum-of-squares over all 32 coil channels, G is the gridding operator that puts arbitrary sampled (cones) data points onto a Cartesian grid, $\mathcal{F}^{-1}$ the fast inverse Fourier transform, L_i and C_i are the i -acquired group of interleaves (i.e., the difference between label and control) picked using a sliding window to reconstruct the corresponding temporal phase n for the label and control state, respectively.

To reverse the effect of $T_{1,\text{eff}}$ relaxation a scaling factor, s_n , is computed for each temporal phase, n , by determining the signal ratio between the average of the 50 highest pixel intensities of the actual temporal phase and the average of the same pixels in the initial temporal phase. It must be noted that this does not reverse the effect of the decreasing CNR/SNR.

After the scaling factor is applied to each temporal phase individually, the rescaled temporal phases are subtracted from the initial temporal phase, TP_0 (Eq. [3]). In addition, an intuitive visualization of the inflowing tracer that is similar to DSA was achieved by inverting the contrast for each time frame, TF_n :

$$TF_n = | -\text{MIP} \{ TP_0 - s_n \cdot TP_n \} |, \quad [3]$$

where MIP denotes the maximum intensity projection along a certain dimension and $|\cdot|$ denotes the absolute value. Finally, axial, sagittal, and coronal MIPs were computed according to Eq. [3] for each individual time frame TF_n . To better appreciate the dynamic information, a movie can be generated from all time frames that shows the intravascular filling over time.

A multithreaded 3D gridding algorithm developed in-house was used in conjunction with sampling density compensation weightings that were precalculated using a freely available algorithm developed by Johnson and Pipe (29).

Readout Trajectories

The readout trajectory used in TRAILS follows a 3D cones sampling pattern, where the sampling starts from the center of k-space to the outermost part of k-space. The 3D cones design algorithm as described by Gurney et al. (24) was used to generate eight basis waveforms. Each basis waveform can be used for a particular range of polar angles and was scaled and rotated on the scanner to generate 1538 interleaves that sample a complete sphere in k-space without violating gradient amplitude or slew rate constraints. Note that due to grouping of the interleaves and to achieve consistent $T_{1,\text{eff}}$ effects in all temporal phases, we additionally acquired 22 dummy interleaves, in each label and control, during the last readout cycle that were discarded in postprocessing. Additionally, each basis waveform was bridged to crusher gradients at the end of the readout to increase the readout efficiency.

TOF MRA

For a comparative assessment with TRAILS, all volunteers underwent a standard 3D TOF MRA. The magnetization transfer prepared and first-order flow compensated 3D TOF MRA sequence parameters were as follows: four partitions with 24 sections each, $0.68 \times 0.80 \times 1.40$ mm resolution, readout bandwidth ± 31.5 kHz, $200 \times 180 \times 135$ mm FOV, TR/TE 20/2.6 ms, ramped RF flip angle $15\text{--}25^\circ$, 2.8 mm slab overlap, scan time 6:40 min. A 30 mm saturation band that followed the imaging slab to suppress the venous inflow was placed 10 mm distal to the imaging slab. The vendor supplied reconstruction was used and MIPs were manually processed using the free software Osirix (30).

Image and Hemodynamics Analysis

For each volunteer, SNR and CNR were obtained from the axial MIP images of the initial temporal phases, where the label has filled the whole vascular tree of interest. The average signal μ_{Carotid} was computed from of a ROI placed in the left and right carotid arteries. The volume of each ROI was at least 20 voxels. Standard error of noise, σ_{Noise} , was computed from a ROI placed in the background air. The following equations were used:

$$\begin{aligned} \text{SNR} &= \frac{\mu_{\text{Carotid}}}{\sigma_{\text{Noise}}} \\ \text{CNR} &= \frac{\mu_{\text{Carotid}} - \mu_{\text{Tissue}}}{\sigma_{\text{Noise}}}, \end{aligned} \quad [4]$$

where μ_{Tissue} denotes the average signal computed from a ROI in the background tissue.

For the dynamic inflow measurements, multiple pixels locations were manually chosen and the mean pixel intensities were extracted from 4 pixels in the 3D volume from each reconstructed temporal frame. Additionally, ROIs were placed at anatomically identical locations across all volunteers and the relative transit time of the blood (rTT) was measured in all volunteers for each vascular segment interrogated. Here, rTT was computed from the maximum value of a 4 pixels ROI selected in each vascular segment.

The rTT was computed from the time when the normalized inflow time curve reached the half of its maximum signal in the vascular segment versus the tagging plane location.

RESULTS

Simulations

Bloch-Simulations using the sequence parameters from this study ($\alpha = 6^\circ$, $TR = 7.2$ ms) showed that 350 TR s can be played out, which corresponds to a readout duration of approximately 2.6 s, before the blood magnetization from both label and control acquisitions enters the same steady state (Fig. 3). After this point, it would be impossible to distinguish between the blood signal from the label or the control acquisition. Figure 3 shows the signal dependence on the number of RF excitations, the initial blood transit time, and the blood velocity in the imaging slab. The simulations assumed that the maximum duration that the blood takes to flow through the imaging volume of interest or before it reaches the capillary tissue bed is 3 s.

Image Appearance

Time-resolved axial, coronal, and sagittal MIPs of the 3D data set from one subject of a subset of individually reconstructed TRAILS time frames are shown in Figure 4. Figure 5 shows time-resolved data from the same volunteer, but reconstructed according to Eq. [3] to visualize the inflow more intuitively and to generate contrast similar to DSA. Clearly, visible is the delayed vascular filling in the distal arteries and left vertebral artery in this volunteer. Also, a video was generated from a data set acquired in volunteer 3 (see Supporting Information), to visualize the arterial filling with a higher temporal resolution. The first row shows axial, sagittal, and coronal MIPs of the initial temporal phase and the bottom row shows the dynamic filling of vessel. Theoretically, a very high temporal resolution (7.2 ms) could be achieved by moving the sliding window one TR at a time during the reconstruction process but to shorten the reconstruction time the sliding window was shifted by five TR for each temporal phase, which corresponds to a temporal resolution of 36 ms per temporal phase. Note that this has no impact on the temporal footprint of 432 ms or the scan time.

Figure 6 provides a comparison of coronal, axial, and sagittal MIPs of the initial temporal phase of the TRAILS acquisition with a 3D TOF MRA between the same volunteer. The main anatomic findings of the first temporal frame of TRAILS were consistent with anatomic findings of 3D TOF MRA and the superior vessel delineation (highlighted with yellow arrows) of TRAILS is clearly visible when compared to 3D TOF MRA. TOF also suffers from slab boundary artifacts, which are highlighted with red arrows.

Qualitative and Quantitative Analysis

Across all volunteers, an average SNR of 100 ± 10 , and an average CNR of 90 ± 3 was achieved in the left and right carotid arteries analyzing the first temporal frame of TRAILS.

In Figure 7a, signal intensities of the dynamic inflow measurements with TRAILS from one subject are shown. The plots clearly demonstrate the increased label/fresh-blood interface arrival time along the vessel. Signal intensities are extracted from the C1, C2, C4, C6 segments of the internal carotid artery and the M1, M2 segments of middle cerebral artery as visualized in Figure 7b. Table 1 shows the computed rTT values for each volunteer including an average over all subjects for the following manually placed ROI locations: tip of the basilar artery and the left and right hemisphere of the A1-segment of the Anterior cerebral artery (ACA-A1), middle cerebral artery-M1, internal carotid artery, vertebral arteries.

DISCUSSION

TRAILS differs from existing time-resolved, non-CE spin labeling angiographic methods in that it covers the whole brain with a higher spatial and temporal resolution and smaller temporal footprint than the majority of other time-resolved approaches. It also does not require cardiac gating, which reduces patient preparation time, scan time, and patient discomfort (15,18). Specifically, TRAILS differs from previous noninvasive, time-resolved PCASL-based angiographic approaches in that it visualizes the signal cancellation effect from inflowing fresh blood rather than directly follow the magnetization-prepped bolus for the assessment of the intravascular structures. This allows the simultaneous acquisition of a static and dynamic TOF-like angiogram to visualize vascular morphology and hemodynamic information.

Also, TRAILS allows an intuitive visualization of tracer dynamics and the arterial filling. The good SNR and CNR indicates that in TRAILS, the background signal cancellation is very effective and that no additional background suppression techniques, such as RF saturation/inversion pulses, which have been used in other studies (10,14), are necessary. Obviously, the avoidance of such saturation/inversion pulses reduces specific absorption rate (SAR) levels.

The results of this study indicated that with TRAILS, it is possible to acquire hemodynamic information including the estimation of flow-related information such as blood transit times. As indicated in Table 1, TRAILS detected different blood arrival times for each segment and can even depict small rTT differences between subjects and their left and right hemispheres. However, it must be noted that small differences could be introduced from the varying placement of each ROI between left and right hemispheres due to normal variations of the underlying vascular structures. Therefore, such arrival time measurements must be interpreted carefully and further clinical evaluations to analyze the diagnostic relevance for such a high sensitivity to differences in rTT.

Also, due to the absence of cardiac gating in TRAILS, each temporal phase will contain the averaged signal from multiple cardiac cycles. This ultimately lowers the effective temporal

footprint and limits the practical use of super lower temporal footprints because averaging will always occur without ECG-gating. In future clinical studies, if deemed necessary, ECG-gating could be performed with TRAILS.

A general benefit of all 3D sampling trajectories that go through the center of k-space each TR is that every readout is nearly equally important. This makes the sliding window reconstruction straightforward because no weighting or filtering needs to be applied to the temporal domain. Additionally, the 3D cones readout and their inherit short echo time provided very good flow capabilities and low sensitivity to pulsate artifacts; therefore, no other flow compensation techniques were used.

The total scan time of TRAILS is determined by the spatial-, temporal resolution, the temporal footprint, and tagging duration. A scan time of less than 5 min is already clinically acceptable but a number of strategies could be explored to reduce scan time even further. Given the fact that the data in image space are relatively sparse after the subtraction of label and control in k-space, and that the cones trajectories are heavily oversampled at the center of k-space, an undersampling factor of $R > 2$ should be possible using a 32-channel head coil. Even for an 8-channel head coil, which is widely used in clinical settings, undersampling factors of > 2 could be explored due to the sparsity of the angiographic image. In the study presented here, a temporal footprint of 432 ms was achieved. Even a modest undersampling factor of $R = 2$ would reduce the temporal footprint or the scan time by half. Exploring this parallel imaging strategies to further improve the spatio- and temporal resolution and to further reduce the already clinically acceptable scan time will be part of future work.

The tagging duration for this study was chosen to be 3 s. A shorter tagging duration could have been used to further reduce scan time, but might not have achieved a complete filling of the vascular region interest. Contrary to that, a longer tagging duration could have been used as well to ensure that even with slow-flow sufficient filling is achieved. It must be noted that a longer tagging duration does not necessarily improve the SNR or CNR since the label decays with T_1 but it prolongs scan time. Future, work will focus on an optimization of the tagging duration, depending on the required coverage, and the expected blood flow in the vasculature ROI.

Current Limitations

As background suppression and overall CNR is based on the subtraction of label and control, patient motion needs to be considered. However, based on our experience, alternating the two tagging states dramatically reduces background artifacts that otherwise might arise from patient motion and misregistration. Next, efforts to reduce patient-induced motion artifacts, such as optical motion correction or navigator-based tracking approaches will be investigated.

Currently, a reconstruction time of 12 min per temporal phase is probably too long for regular clinical use, especially when multiple or all 360 temporal frames are reconstructed. Therefore, further investigation is necessary to explore possible speedup options, such as coil compression or GPU-supported reconstruction, especially when using a 32-channel coil (31).

PCASL-based techniques are in general limited by T_1 -relaxation effects and can negatively affect the achievable SNR and CNR if the blood transit time is extremely long. It may become challenging when whole head coverage is desired in combination with extremely slow flow due to the longer transit times from the labeling plane. An obvious solution to increase slow-flow sensitivity would be to reduce the transit time of the label to the imaging ROI. This could be achieved by simply reducing the gap between the tagging plane and the vascular ROI, which in extreme cases could mean a reduced coverage. Alternatively, various posttagging delays could be explored to avoid saturation effects that are due to $T_{1,\text{eff}}$ -relaxation. This could potentially be useful for the later temporal phases in slow-flow conditions. Alternatively, vessel-selective labeling which allows one to target a specific feeding artery, similar to DSA, could be used to label specific section of an artery, usually proximal to where slow flow is expected. The combination of a vessel-selective labeling approach as described by Dai et al. (32) with TRAILS is straight forward. If deemed necessary, such slow-flow imaging strategies could be part of future studies.

A clear limitation of this study was that all experiments were performed in healthy volunteers where blood transit time to the distal vessels is expected to be relatively fast. The feasibility of TRAILS to analyze intravascular flow patterns in healthy volunteer looks promising, but the clinical feasibility for patients that suffer from fistulas, occluded, shunted, and extremely slow blood flow needs to be evaluated in future clinical studies.

CONCLUSIONS

In this study, PCASL-based whole-brain TRAILS has been presented and applied to imaging of healthy volunteers. It has been demonstrated in healthy volunteers that the new contrast mechanism of TRAILS combined with a multiphase 3D cones readout can be used to acquire both static and dynamic angiograms of the whole head with a high spatial and temporal resolution in a clinically feasible scan time without using gating or parallel imaging.

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FIG. 1.

Overview of the TRAILS tagging (a) and readout (b) strategy. The tagging module (a) consists of two states, “label” and “control.” During the label period of 3 s, the magnetization of the blood flowing downstream through the thin labeling plane is inverted to $-M_0$. The blood continues to flow downstream into the vascular tree of interest and the magnetization starts to recover from $-M_0$ according to: $M_z = M_0 - 2M_0 * e^{-t/T_1}$, where t_t is the initial blood transit time and T_1 is the relaxation time of fresh blood. This will create an initial signal distribution in the intravascular system (before the readout starts) that follows an inversion recovery signal decay (assuming a perfect inversion). After 3 s, labeling is turned off and the readout starts (b), where each RF excitation drives the magnetization closer to a steady state, akin to a Look-Locker acquisition. It is important to note that the

signal at each location in the vascular tree is now depending on two parameters: initial transit time and the number of RF pulses that the spins are exposed to during the readout train. In the control state, the inflowing blood magnetization is left untouched and after 3 s, the whole vascular tree is filled with fresh blood. Therefore, all blood magnetization in the vascular tree of interest is at $+M_0$ when the readout starts. The following readout drives the spins into steady state while fresh blood is flowing into the imaging slab. Note that this is similar to a TOF MRA acquisition with a very short readout duration.

FIG. 2.

Timing diagram for TRAILS, which consists of a label/control block that is followed by $M=6$ readout sub-blocks. The whole block, which includes the tagging and all readout blocks, is repeated $P = H/N$ times, where $H=1538$ denotes the number of interleaves that are needed (Nyquist criteria) to reconstruct each temporal phase and N is the number of interleaves (denoted $I_i, I_{i+1}, \dots, I_{i+(N-1)}$) that are acquired in each readout sub-block M . Also, N trades off the temporal foot-print against total scan time. With a larger temporal footprint P declines and, thus, scan time and vice versa. Using 60 interleaves for each sub-blocks, $N=60$, would require $P=26$ “label” and “control” cycles. Therefore, we acquired $P \times N = 26 \times 60 = 1560$ cones interleaves even though we only needed 1538 interleaves to fully cover k-space, but to achieve a consistent $T_{1,\text{eff}}$ effect in all temporal phases and readout blocks, 22 dummy interleaves were additionally acquired and discarded in postprocessing. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 3.

Bloch simulations of the TRAILS signal evolution for a flip angle of 6° and a sequence $TR = 7.2\text{ms}$ is shown. Here, we assume that the blood is leaving the vessel of interest after a total blood transit time, t_{BtT} , of 3 s, where $t_{BtT} = \text{initial transit time} + \text{RF Excitation } TR$. After a t_{BtT} of 3 s the blood has, therefore, either left the imaging slab or has reached the capillary tissue bed. As described in Figure 1 during the labeling period, the blood will experience T_1 relaxation effects while it is traveling downstream, which will create an initial distribution in the intravascular system that is depending on the initial transit time of blood. The initial transit time is measured from the tagging plane. It clearly shows the signal saturation effects for extremely slow blood flow $<5\text{ cm/s}$ and the dependence on the number of the initial blood transit time with the number of RF excitations that the blood can experience before the signal vanishes. Note, that for simplicity, the simulations assume a constant flow through the imaging slab and a perfect tagging efficiency. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 4.

A selection of seven out of 360 temporal phases as axial, coronal, and sagittal MIPs from the TRAILS data set of subject #5 and reconstructed according to Eq. [2].

FIG. 5.

Axial, coronal, and sagittal MIPs of six selected TRAILS time frames from subject #5, which were reconstructed as described in Eq. [3]. Clearly, visible is the late arterial filling in the hypoplastic right vertebral artery.

FIG. 6.

Comparison of coronal (**a, d**), axial (**b, e**), and sagittal (**c, f**) MIPs between the 3D TOF MRA acquisition (**a–c**) and the a corresponding MIP from TRAILS of initial temporal phase, TP_0 (**d–f**). Slab boundary artifacts (red arrows) are clearly visible in the sagittal (**a**) and coronal (**c**) MIPs of the TOF data set. The inherent background suppression of TRAILS improved vessel conspicuity quite dramatically (yellow arrows). Even, distal vessels are clearly visible in this volunteer. Due to the larger coverage of TRAILS, the non-Cartesian readout, and B_0 inhomogeneities, off-resonance induced blurring over this much larger z-FOV is visible at the lower image boundaries of the coronal (**d**) MIP (green arrows). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 7.

Normalized signal intensities of a TRAILS acquisition are plotted versus time (**a**). The time curves are extracted from selected regions of interest as indicated the sagittal MIP (**b**).

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

The Relative Transit Time (rTT) with the Tagging Plane as Reference Plane was Measured for all Subjects and the Average over all Subjects Including Standard Error is Shown for Each ROI. The ROIs were Placed as Follow: Tip of the Basilar Artery (BA) and the Left and Right Hemisphere of the A1-Segment of the Anterior Cerebral Artery (ACA-A1), M1 Segment of Middle Cerebral Artery (MCA-M1), Internal Carotid Artery (ICA), Vertebral Arteries (VA)

	Mean rTT (ms)	rTT for each subject (ms)				
		#1	#2	#3	#4	#5
ICA-left	173.7 ± 51	181	122	156	255	146
ICA-right	202.2 ± 61	238	130	190	286	164
VA-left	469.4 ± 129	508	289	448	452	647
VA-right	390.1 ± 86	417	259	489	425	358
BA-tip	597.3 ± 91	671	448	635	656	574
MCA-M1 left	511.0 ± 132	509	308	497	670	569
MCA-M1 right	484.6 ± 99	498	312	511	553	546
ACA-A1 left	518.6 ± 160	461	295	516	727	592
ACA-A1 right	471.8 ± 116	434	281	540	551	546