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Intracranial vascular feature changes in time of flight MR angiography in patients undergoing carotid revascularization surgery

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Abstract

Purpose: To characterize the intracranial vascular features extracted from time of flight (TOF) images and their changes from baseline to follow-up in patients undergoing carotid revascularization, using arterial spin labeling (ASL) cerebral blood flow (CBF) measurement as a reference.

Methods: In this retrospective study, brain TOF and ASL images of 99 subjects, acquired before, within 48 h, and/or 6 months after, carotid revascularization surgery were analyzed. TOF images were analyzed using a custom software (iCafe) to quantify intracranial vascular features, including total vessel length, total vessel volume, and number of branches. Mean whole-brain CBF was calculated from ASL images. ASL scans showing low ASL signal in the entire flow territory of an internal carotid artery (ICA), which may be caused by labeling failure, were excluded. Changes and correlations between time points were analyzed separately for TOF intracranial vascular features and ASL CBF.

Results: Similar to ASL CBF, TOF vascular features (i.e. total vessel length, total vessel volume and number of branches) increased dramatically from baseline to post-surgery, then returned to a level slightly higher than the baseline in long-term follow-up (All $P < 0.05$). Correlation between time points was observed for all three TOF vascular features but not for ASL CBF.

Conclusion: Intracranial vascular features, including total vessel length, total vessel volume and number of branches, extracted from TOF images are useful in detecting brain blood flow changes induced by carotid revascularization surgery.

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Declaration of Competing Interest

None.

Keywords

Cerebral blood flow; Time of flight; Magnetic resonance imaging; Carotid revascularization; Intracranial vasculature

1. Introduction

Carotid atherosclerosis is one of the major causes of ischemic stroke [1]. Carotid revascularization surgery, including carotid stenting (CAS) and carotid endarterectomy (CEA), has been demonstrated to be beneficial in selected patients to reduce occurrence of ischemic stroke by restoring the blood supply to the brain [2]. Measuring cerebral perfusion is important for assessing the treatment effects of carotid revascularization surgery.

Different imaging techniques, including transcranial doppler (TCD), positron emission tomography (PET), single-photon emission computed tomography (SPECT), CT perfusion, xenon-enhanced CT, dynamic susceptibility contrast (DSC) MRI and arterial spin labeling (ASL) MRI, have been used to measure cerebral perfusion [3]. Due to its non-invasive nature and capacity for quantifying absolute cerebral blood flow (CBF) values, ASL MRI [4] has recently gained greater application in clinical practice [5,6]. Among the different approaches of ASL, pseudocontinuous ASL (pCASL) is the most widely accepted technique due to its high SNR and easy implementation on clinical MR scanners [4]. Nevertheless, studies have shown that the accuracy of pCASL may be compromised by several factors, such as field inhomogeneity and large blood velocity variations [7–9]. This issue may become particularly significant in the presence of carotid stents that can induce large local field inhomogeneity [10], or severe stenosis and artery tortuosity that may greatly disturb luminal blood flow.

Three-dimensional (3D) brain time of flight (TOF) MR angiography (MRA) is a non-invasive technique routinely used for assessment of stenosis or occlusion of large to medium sized vessels. However, TOF imaging is blood flow-dependent [11], which affects the visibility or intensity of distal smaller-sized vessels on the acquired images. Thus, quantifying the intracranial vasculature on TOF images may provide insight into the status of brain blood flow. Recently, an intracranial artery feature extraction software (iCafe) tool was developed to extract features of the intracranial vasculature, such as vessel length, on TOF images [12]. This has made it possible to explore TOF vascular features as potential imaging indicators of brain blood flow. In fact, previous studies have reported the associations between such TOF vascular features and aging [13,14], which may be explained by age-related blood flow reduction [15].

The goal of this study is to characterize TOF intracranial vascular features and their changes from baseline to follow-up in patients undergoing carotid revascularization, using pCASL CBF measurement as a reference. This may provide evidence regarding the usefulness of TOF intracranial vascular features in monitoring brain blood flow changes induced by carotid revascularization surgery.

2. Material and methods

2.1. Subjects

This study retrospectively analyzed MR images of patients who underwent carotid interventions (i.e. CEA or CAS) at a Veterans Medical Center from 2011 to 2017. Indications for the surgical procedures included severe asymptomatic stenosis ($>70\%$) in carotid arteries according to ultrasound examination, or moderate to severe stenosis ($>50\%$) with focal neurological symptoms. The MR images were acquired at three time points: within 3 months prior to surgery (indicated as time point 1, i.e. TP1), within 48 h after surgery (TP2) and 6 months after surgery (TP3). Institutional Review Board (IRB) approval was obtained for this study, and each subject provided the informed consent before participation.

2.2. MR imaging

The MR imaging, including 3D TOF MRA imaging and pCASL perfusion imaging, was performed with a 3 T MR scanner (Discovery MR750, GE Healthcare) and an 8-channel head coil. The sequence parameters of the TOF protocol varied considerably between subjects, as well as over time points for the same patient. In order to mitigate the influence of this protocol variation on the analyses, a commonly used TOF sequence protocol was identified and only TOF scans with small deviations to this protocol were included. Specifically, the TOF sequence imaging parameters in this study were: repetition time (TR) 22–23 ms, echo time (TE) 2.6–2.9 ms, flip angle (FA) 15° , in plane field of view (FOV) 220–260 mm², through plane FOV 75.6–123.2 mm, multi-slab acquisition, slab number 3–5, in plane voxel size 0.74–0.86 mm, slice thickness 1.4 mm, Tilt-Optimized Nonsaturated Excitation (TONE) [16] employed. The imaging volumes of the TOF scans were set to being parallel to the anterior commissure - posterior commissure line and centered at the level of circle of Willis. A default whole-brain 3D pCASL imaging protocol in GE scanner was used with the following imaging parameters: unbalanced pCASL, labeling duration 1450 ms, post labeling delay 2525 ms, using 3D fast-spin echo interleaved stack-of-spirals readout, FOV 240 × 240 mm², image reconstruction matrix 128 × 128, spiral trajectory with 6–8 arms, 36 slices, slice thickness 4–5 mm, number of average 3–4, bandwidth 62.5 kHz, TR 4632–5411 ms, TE 10.14–10.54 ms.

2.3. Image review

Co-registration of the TOF or pCASL images between time points was performed using the SPM toolbox (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). TOF images of the same subject were cropped to achieve the same coverage across all time points, and subsequently semi-automatically processed with iCafe [12] by 5 trained reviewers (C.L., S. M., L.W., O.D. and C.J.), blinded to any clinical information and the ASL perfusion images. In brief, the iCafe software first automatically generated the vessel centerlines and segmented the lumen contours, then the reviewers manually corrected the centerlines and the contours using the tools provided within iCafe. Subsequently, the reviewers manually labeled the different artery segments [12]. The processing order of all subjects' TOF images were randomized. In order to reduce the potential influence of inter-reviewer variation, TOF images belonging to the same subject were processed by the same reviewer. Features that

characterize the intracranial vasculature on TOF images, including total length of the visible vessels distal to ICA or basilar artery, total volume of the visible vessels distal to ICA or basilar artery, and number of branches (i.e. the number of traces which start from a bifurcation and end in another bifurcation or termination in a vascular group) were generated from iCafe. The iCafe tool has been previously demonstrated to have good to excellent intra- and inter-operator reproducibility for extracting the intracranial vascular features on TOF images [17].

ASL perfusion weighted images were assessed by a reviewer (C.Z.) experienced in ASL imaging to identify the ASL scans with severe motion artifact or signal loss in the whole brain. Such ASL scans were excluded from further analysis. CBF quantification from pCASL images was performed using the recommended hemodynamic model [4]. For each subject, a mask of brain was extracted using the brain segmentation tool in SPM on the ASL proton density images (i.e. the M0 images). The mask was then used to calculate mean whole-brain CBF. On the other hand, in order to avoid the influence of ASL labeling failures on our findings, the CBF map of each ASL scan was also reviewed by the reviewer (C.Z.), blinded to the clinical information and TOF images, to determine the presence of low ASL signal in the entire flow territory of an ICA compared to the contralateral side. The ASL scans with such unilateral low ASL signal were excluded from statistical analyses.

2.4. Statistical analysis

In this retrospective study, not all subjects had three time points of TOF and ASL. In order to maximize the sample size, we included all subjects that have at least 2 time points of TOF or ASL. Thus, each statistical analysis included all useable data from these subjects.

The behavior of TOF intracranial vascular features and ASL CBF across time points were analyzed. For both ASL CBF and TOF vascular features, the correlation and difference between each pair of two time points (i.e. TP1 vs. TP2, TP2 vs. TP3, and TP1 vs. TP3) were calculated with Spearman correlation analysis and Wilcoxon signed-rank test, respectively.

All statistics were performed with MATLAB and Statistics Toolbox Release 2019a (Mathworks, Natick, MA). *P*value <0.05 was considered statistically significant. No adjustment of *P*value due to multiple comparisons was performed.

3. Results

A total of 99 subjects (96 males, 69.2 ± 7.6 years) were included, of which 49 underwent CAS and the other 50 underwent CEA. For these subjects, a total of 147 TOF scans were available, among which 33 used imaging protocols very different from the one defined in Section 2.2 and thus were excluded. Therefore, a total of 114 TOF scans were analyzed with iCafe. A total of 184 ASL scans were available, with 15 showing severe motion artifacts or signal loss in the whole brain. Therefore, 169 ASL scans remained for CBF quantification. Fig. 1 shows the vessel tracing results on TOF and ASL CBF maps of an example subject at three time points. Of the ASL scans, 21.9% (37/169) were observed to have low ASL signal in the entire flow territory of an ICA and excluded from final analyses. Among these 37 scans, the low ASL signal occurred on the surgical side in 73.0% (27/37) scans. Fig. 2 shows

two such examples. The detailed distribution of the TOF and ASL scans on each time point are shown in Table 1, while the sample size for each statistical test is shown below along with the statistical results.

The mean value and standard deviation of ASL CBF or TOF vascular features from each time point are shown in Table 2. The correlations and differences in TOF vascular features or ASL CBF between each pair of two time points are shown in Table 3. For ASL CBF and the TOF vascular features, values increased greatly from TP1 to TP2 and then decreased to a level slightly larger than TP1 at TP3 (all $P < 0.05$). Representative images on 3 subjects are shown in Fig. 3. The ASL CBF showed no correlation between time points, while most of the TOF vascular features did.

4. Discussion

This study retrospectively analyzed TOF and ASL perfusion images acquired at multiple time points in patients undergoing carotid revascularization surgery. Changes in the intracranial vascular features extracted from TOF images using iCafe were analyzed, using ASL CBF as a reference. Generally, TOF intracranial vascular features, such as total vessel length, were found to have similar characteristics as ASL CBF in characterizing surgery-induced flow changes across time points. These findings suggest the potential of TOF intracranial vascular features as surrogate markers of brain blood flow or as a complement to ASL perfusion imaging in patients undergoing carotid revascularization.

The finding that ASL CBF increased dramatically from TP1 to TP2, and then returned to a level similar to TP1 at TP3 (see Table 2–3) is largely in line with previous studies [18–23]. Most of these previous studies acquired perfusion data, either with ASL, DSC or SPECT, before CEA or CAS surgery and early post-operatively (less than 5 days), and showed that the early postoperative perfusion is much larger than preoperative perfusion. Several studies also examined long-term (more than one month after surgery) perfusion measurements and reported findings similar to this study, that long-term perfusion is smaller than that acquired early post-operatively [18,20]. However, unlike findings of the present study that TP3 perfusion is slightly larger than TP1 (see Table 2–3), these previous studies did not observe a significant difference between preoperative and long-term perfusion [18,20] except one study indicating a long-term increase of the ipsilateral ASL CBF in the MCA borderzone region [21]. This inconsistency may be due to multiple factors, such as the small sample size in most of these studies, unattended potential labeling failures in previous studies using ASL imaging [20], different study populations, and different time interval from surgery.

A similar trend of change over time points was observed in ASL CBF and the TOF vascular features (Table 2–3), corroborating our assumption that the TOF sequence is sensitive to blood flow and that intracranial vascular features derived from TOF images are potential imaging markers of brain blood flow. In particular, the observation that the TOF vascular features had slightly larger values at TP3 than TP1 seems to strengthen the same observation on ASL CBF, which was seldomly reported by previous studies. This in turn suggests that the TOF intracranial vascular features may have the potential for detecting small changes in brain blood flow.

On the other hand, unlike ASL CBF, there are correlations between time points for TOF vascular features (Table 3). This is probably because the arterial signal on TOF images is less flow-dependent than ASL CBF. In fact, in routine intracranial TOF MRA imaging, measures such as multislab acquisition (MOTSA) [11] and TONE [16] are employed to reduce dependence on flow while maintaining good visibility of the arteries. Therefore, TOF arterial signals will still have large similarities across time points in spite of flow changes. On the contrary, the ASL imaging sequence is originally designed to be strongly perfusion-weighted [4]. The physiological variation of brain blood flow thus has a large impact on the ASL CBF measurement, decreasing the correlation between time points. The relatively narrow range of ASL CBF values between patients at TP1 and TP3 may also contribute to the lack of correlation between time points.

In this study, a large portion (21.9%) of ASL scans were observed to have lower ASL signal in the entire flow territory of an ICA compared to the contralateral side. This mainly can be explained by the compromised labeling efficiency in pCASL imaging caused by the presence of carotid stent in many of the subjects. In future studies, an additional scan to identify the extent of field inhomogeneity induced by the stent can be performed, and the labeling plane can thus be placed away from the inhomogeneous region [10]. Besides, the labeling efficiency might be also improved by performing f_0 correction and shimming at the labeling plane, which was not done in this study. However, suboptimal labeling may still occur if the inhomogeneous region is too large to avoid, or the vessels are very tortuous at the new labeling plane. On the other hand, it should be noted that not all such unilateral low ASL signals were observed on subjects with carotid stents. For example, the phenomena were observed on 8 ASL scans acquired before carotid revascularization. This may represent either a real low perfusion, signal decrease induced by increased arterial transit time, or a suboptimal labeling efficiency caused by other reasons (e.g. very low carotid flow velocity caused by severe stenosis or occlusion, or very tortuous carotid arteries).

The TOF vascular features are calculated from the distal intracranial arteries, and the measurements are thus not affected by the field inhomogeneity induced by the stent at the external carotid artery. In this sense, the TOF vascular features can serve as a complement to ASL perfusion imaging for disease diagnosis.

This study used a short labeling duration (i.e. 1450 ms) and a long post labeling delay (i.e. 2525 ms), as compared to the recommended values in the ASL consensus paper [4] which was available later than the start date of our data acquisition. A short labeling duration and a long post labeling delay would lead to smaller ASL signal and image SNR [4]. However, this is not expected to affect the finding of this study, since the averaging of ASL CBF over the whole brain should have compensated the SNR loss. Subject's carotid stenosis may increase the arterial transit time, and cause intravascular artifacts and underestimation of parenchymal CBF, if the post labeling delay of the ASL scan is not long enough. In this study, the relatively long post labeling delay is helpful in reducing the sensitivity of the CBF measurement to the increased arterial transit time.

This retrospective study suffers from several limitations. First, the data exclusion, mainly due to differences in imaging protocols, has led to relatively small sample sizes and may

cause bias in our statistics. In particular, we were able to identify only a few cases that had both usable TOF and ASL data at all three time points. Second, as discussed above, the origin of the ASL CBF asymmetry could not be confirmed. Therefore, we are not able to assess the capability of the TOF vascular features to detect inter-hemisphere blood flow asymmetry. Third, the TOF scans included in this study had a large variation of FOV in the feet-head direction. This has made the TOF vascular features incomparable between subjects, thus restricting us from performing direct correlation analyses between the TOF vascular features and ASL CBF. Fourth, due to the retrospective nature of this study, the exact values of some imaging parameters of the TOF scans (e.g. slab thickness) that may have important influence on the TOF blood signal were not available. This is not expected to have considerable impact on the finding of this study, since the TOF imaging protocol did not systematically differ between time points. Fifth, due to the lack of a T1W structural brain MRI, a rough brain segmentation was performed on the ASL proton density images. Therefore, the region with cerebrospinal fluid was included in calculation of the whole-brain ASL CBF. This could slightly affect accuracy of the ASL CBF, but is not expected to impact our current findings about the TOF vascular features.

5. Conclusions

In this retrospective study, intracranial vascular features extracted from TOF images with iCafe, including total vessel length, total vessel volume and number of branches, were found to have a similar capability to ASL CBF for detecting changes in brain blood flow over multiple time points in patients undergoing carotid revascularization. Therefore, TOF intracranial vascular features may be useful biomarkers in monitoring brain blood flow changes induced by carotid revascularization surgery and could serve as a complement to ASL perfusion imaging in clinical practice. Further validation of the TOF intracranial vascular features as imaging markers of brain blood flow with a prospective study is warranted.

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Fig. 1. TOF MRA images, vessel tracing results and CBF maps of an example case. TP1, TP2 and TP3 correspond to prior to carotid revascularization surgery, within 48 h after surgery and 6 months after surgery, respectively.

Fig. 2.

Examples of ASL CBF maps (right panels) with low ASL signal in the entire flow territory of an ICA. The vessel tracing results on TOF are shown on the left side for reference. The top row is from TP2 (i.e. within 48 h after surgery) of a patient who underwent carotid stenting (CAS) on the left side, and the bottom row is from TP2 of a patient who underwent carotid endarterectomy (CEA) on the right side. The good inter-hemisphere symmetry of TOF vasculature suggests that the low ASL CBF value in these two subjects is probably an artifact caused by labeling failure.

Fig. 3.

TOF MRA images in axial view (the top row), vessel tracing results in axial view (the second row), and vessel tracing results in coronal view (the third row) and the ASL CBF map (the bottom row) of 3 example subjects (each frame corresponds to a subject). These images show that the visibility of distal arteries on TOF has similar change behaviors as ASL CBF over the three time points, i.e. they both increased greatly from TP1 to TP2, and then decreased to a level slightly larger than TP1 at TP3. Note that the lines in the background of the images in the third row were parts of the bounding boxes, which were displayed in the iCafe software.

Table 1

Sample size of usable TOF and ASL data.

	TP1	TP2	TP3
TOF	38	36	40
ASL	50	70	49
ASL without low ASL signal in the entire flow territory of an ICA	42	53	37
ASL with low ASL signal in the entire flow territory of an ICA	8	17	12

TOF: time of flight; ICA: internal carotid artery; TP1: time point 1, i.e. before surgery; TP2: with 48 h after surgery; TP3: 6 months after surgery

Table 2

ASL CBF or the TOF intracranial vascular features at each time point.

	TP1 (Mean $\pm$ SD)	TP2 (Mean $\pm$ SD)	TP3 (Mean $\pm$ SD)
ASL CBF (ml/100 g/min)	38.8 $\pm$ 6.0	55.1 $\pm$ 16.5	41.9 $\pm$ 10.1
TOF vascular features			
Total length (mm)	2059 $\pm$ 439	2718 $\pm$ 437	2326 $\pm$ 423
Total volume (mm ³)	6138 $\pm$ 1453	8443 $\pm$ 1648	6620 $\pm$ 1361
Number of branches	75.3 $\pm$ 15.9	99.9 $\pm$ 20.1	85.6 $\pm$ 15.8

CBF: cerebral blood flow; TOF: time of flight; iCafe: intracranial artery feature extraction; TP1: time point 1, i.e. before surgery; TP2: with 48 h after surgery; TP3: 6 months after surgery; SD: standard deviation.

Table 3

Correlation and difference* of ASL CBF or the TOF intracranial vascular features between time points.

	TP1 vs. TP2			TP2 vs. TP3			TP1 vs. TP3		
	Correlation		P	Difference		P	Correlation		Difference
	R (N) † *						R (N)*		
ASL CBF	0.25 (33)	0.167	<0.001		0.569	<0.001	0.23 (19)	0.342	0.027
TOF vascular features									
Total length	0.54 (25)	0.006	<0.001	0.42 (26)	0.033	<0.001	0.48 (27)	0.013	<0.001
Total volume	0.18 (25)	0.381	<0.001	0.51 (26)	0.009	<0.001	0.51 (27)	0.007	0.009
Number of branches	0.45 (25)	0.025	<0.001	0.32 (26)	0.106	<0.001	0.53 (27)	0.004	0.004

Significant p-values (<0.05) are highlighted in bold font.