Four dimensional time-of-flight magnetic resonance angiography using saturation pulse by temporal tilted optimized non saturating excitation and temporal magnetization transfer contrast pulse

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Running title: 4D-TOF for observing intracranial hemodynamics

Abstract

Purpose: We introduce a novel method called four dimensional time-of-flight (4D-TOF) magnetic resonance angiography (MRA) using saturation pulse. 4D-TOF was time resolved non-contrast-enhanced MRA without arterial spin labeling technique. Because this approach uses non-subtraction method, it is important to keep the inflow effect of the arterial blood and to suppress the background signal. We optimized 4D-TOF by temporal magnetization transfer contrast pulse (t-MTC) and temporal tilted optimized non saturating excitation (t-TONE).

Materials and Methods: Three techniques were compared to optimize the visibility of the arteries above the circle of Willis; (a) simple 4D-TOF, (b) 4D-TOF with t-MTC, and (c) 4D-TOF with both t-MTC and t-TONE. Eight healthy volunteers were scanned with these three sequences. The contrast changes between the background tissue and the arteries in temporal phases were assessed, and compared quantitatively and qualitatively.

Results: 4D-TOF offered dynamic information of hemodynamics. The background signal was better suppressed on 4D-TOF with t-MTC than that on simple 4D-TOF. The blood signal was significantly higher on 4T-TOF with both t-MTC and t-TONE than that on the other two methods in delayed phase. Among these 4D-TOF methods, the

techniques combined with both t-MTC and t-TONE provided well visualization of the intracranial hemodynamics.

Conclusion: 4D-TOF with both t-TONE and t-MTC enabled observation of the intracranial hemodynamics. Optimized 4D-TOF provides fast scan without image subtraction, and well visibility of the intracranial arteries even in the prolonged observation time.

Key Words: non-contrast-enhanced MRA; time-of-flight (TOF); time-resolved; hemodynamics; intracranial arteries

Introduction

Assessment of the intracranial arteries has an important role in clinical practice. Conventionally, the arterial lesions are well evaluated by digital subtraction angiography (DSA), which has been used as a gold standard, providing high spatial and temporal resolution image for the cerebral vasculature (1,2). However, DSA examinations have certain risks including vascular occlusions, radiation exposure, and adverse reactions to iodized contrast agents. Therefore, three-dimensional (3D) time-of-flight (TOF) magnetic resonance angiography (MRA) has been used in most of the cases to evaluate and/or role out of the arterial lesions including arterial stenosis, dissections, aneurysms, and arteriovenous malformations (AVM) (3-5). Although 3D TOF-MRA is well established method in assessing the arterial anatomy and pathological lesions, it does not offer cerebral hemodynamics. The assessment of vascular lesions requires both morphological and hemodynamics information, especially in cases with AVM. In a previous study (6), 3D TOF-MRA was shown to lack the cerebral hemodynamics, compared with DSA.

For these reasons, development of a non-invasive MRA to visualize both arterial anatomy and hemodynamics has been a great concern among clinicians and researchers. Time-resolved contrast-enhanced (CE) 3D MRA is one of such method to obtain

dynamic information for the intracerebral vascular lesions(7-9). Time-resolved CE 3D-MRA has an advantage over DSA in information of 3D anatomical structure. However, it needs gadolinium-based contrast agents, which may induce adverse side effects such as anaphylactic shock and nephrogenic systemic fibrosis in patients with impaired renal function (10,11). Against such a background, four dimensional (4D) non-contrast MRA was developed, using various arterial spin labeling (ASL) techniques(12-14). 4D MRA with ASL techniques has been shown to have high diagnostic performance for assessing the cerebral blood flow, compared to DSA(15), providing cerebral hemodynamics as a noninvasive alternative to DSA. The disadvantage of ASL-based 4D MRA is that it needs two sets of scans to subtract control images from label images. Thus, this technique requires a relative long scan time. Although fast scan techniques regarding ASL-based 4D MRA have been proposed such as 3D cones readout (16), and a highly under-sampled 3D radial acquisition (17), they cannot be obtained within an enough short time or are difficult to perform on clinical scanners. Because ASL-based MRA does not have similar characteristic to 3D-TOF-MRA for assessing the arterial morphology, it is mainly used to observe the hemodynamics. In addition, the differences between labeled and unlabeled blood signal decreases sequentially during the inflow blood on ASL-based MRA, resulting in

difficulties in observing the full passage of hemodynamics on the dynamic phases.

In this study, we introduce a novel technique, termed as 4D-TOF for 4D-MRA. 4D-TOF can be acquired with saturation pulse, and it does not require a subtraction. Thus, 4D-TOF were suggested to reduce the scan times. We hypothesized that 4D-TOF not only has similar characteristic to 3D-TOF image in terms of visualizing the arterial morphology, but also has additional information on the cerebral hemodynamics. Because this method uses non subtraction method, it is important to keep the inflow effect of the arterial blood and to suppress the background signal of the brain tissue in each temporal phase. These may be achieved by two techniques; temporal magnetization transfer contrast pulse (t-MTC) and temporal tilted optimized non-saturating excitation pulse (t-TONE). The purpose of this study was to assess the effects of t-MTC and t-TONE in 4D-TOF to observe the intracranial hemodynamics.

Materials and Methods

Study subjects

We examined eight healthy volunteers (five males and three females, age ranged from 22 to 59 years, with a mean age of 35 years) without known cardiovascular disease.

This study was approved by the Institutional Review Board, and written informed consent was obtained by all the participants.

4D-TOF sequences

All examinations were performed on a 3.0T scanner (Achieva R2, Philips Healthcare, Best, the Netherlands). This system can operate at a maximum slew rate of 200 mT/m/ms and a maximum gradient strength of 80 mT/m. A 16-channel receive only head coil was used covering the whole brain area.

The basis of 4D-TOF sequence is illustrated in Fig. 1. The 4D-TOF sequence is based on a combination of saturation pulse and gradient-spoiled segmented 3D turbo field-echo (TFE) readout. First, the imaging section is excited by a selective saturation pulse to suppress the signal of all tissue. This is accomplished using water suppression, enhanced through T_1 effects (WET) pulse (18), to improve T_1 variations, B_1 variations, and off-resonance effects. 4D dynamic imaging was obtained by look-locker sampling (19). The signal variation in saturate recovery look-locker sampling has been reported in a previous study (20); the signal recovery of the background brain tissue depends on the accordance with the spin-lattice relaxation times T_1 of each brain tissue. The signal of background $M(n)$ is given by the following equation (1):

$$M(n) = M^* - \left(M^* - M(0)\right)exp\left(-\frac{n\tau}{T_1^*}\right) \qquad \text{n = 1, 2, 3. . . N,} \quad (1)$$

where M^* is the effective equilibrium longitudinal magnetization, $M(0)$ is the initial longitudinal magnetization at time t = 0 when saturation pulse is applied. T_1^* is the effective longitudinal relaxation time constant and is given by the following equation (2):

$$\frac{1}{T_1^*} = \frac{1}{T_1} - \frac{\ln(\cos\alpha)}{\tau} \qquad (2)$$

where α is flip angle, τ is repetition time (TR). This equation is the solution to the Bloch equations in the absence of the radio frequency field. On the other hand, the signal of arterial blood cannot be described by equation (1); cerebral hemodynamics can be observed by the fresh unsaturated blood, gradually flowing in the imaging section. In this approach, the imaging contrast between the arteries and the background brain tissues reduces according to the following two basic mechanisms: first, the background signal recovery as time progresses, and second, the blood signal loss by repeated irradiation radio frequency pulses. These phenomenons generally become prominent in the delayed phases of dynamic 4D-TOF, resulting in obscured arterial visibility, and can be severe drawback in diagnosing hemodynamics. To suppress this background signal recovery, we suggested using t-MTC technique, which applies off-resonance MTC pulse at the beginning of each temporal phase. Noteworthy, MTC pulse has an effect to

suppress the brain tissue signal, but has no effect for suppressing the blood signal (21,22).

Moreover, we applied t-TONE technique using variable flip angle method (23) to reduce the effects of blood saturation in temporal phases. The flip angle of t-TONE is set to a lower value at the early phases, and then it progressively increases until it reaches to its maximum value at the last phase. This technique can keep the blood signal in delayed phases in higher than the conventional method. Actually, we used variable flip angles from 4° to 20°, increased by 2° in 9 temporal phases.

We used conventional spatial TONE technique in the spatial direction of the imaging in all three 4D-TOF: flip angle were changed from -50% to +50% linearly in a temporal phase depending on each slab.

Data of 4D-TOF was acquired by gradient-spoiled segmented 3D TFE sequence with centric *k*-space ordering. Each temporal phase of 4D-TOF-MRA slab consisted of 100 slices with 0.8 mm thickness to cover the circle of Willis and its main branches, and 4D-TOF consisted of nine temporal phases. The parameters of 4D-TOF images were as follows: field of view = 200 × 200 mm^2, resolution = 1.0 × 1.1 × 0.8 mm^3, TR = 10 ms, echo time (TE) = 1.8 ms, acquisition bandwidth = 1035 Hz/pixel, sensitivity encoding (SENSE) factor = 3, temporal resolution = 180 ms, and a total scan time of

approximately 5 min.

To assess the effects of t-MTC and t-TONE technique, three sequences were conducted in this study: (1) simple 4D-TOF (only spatial TONE pulse with a central flip angle of 10°); (2) 4D-TOF with t-MTC technique (spatial TONE pulse with a central flip angle of 10°); (3) 4D-TOF with both t-MTC and t-TONE techniques.

Image assessment

Visibility of the distal arteries is important in any 4D non-contrast MRA, whether it may achieve the enough imaging contrast between the blood and the brain tissue in the delayed phases. To assess the temporal variation, the signal in the artery and brain tissue on each 4D-TOF were measured in each temporal phase. The receiver gain was kept the same for both each techniques and volunteers. Regions of interests (ROIs) were placed at the horizontal branch (M1) of the right middle cerebral artery (MCA) and white matter (WM) in the vicinity of M1. Then, the signal intensity ratio (SIR) was calculated as an indicator of the imaging contrast in each sequence, according to the following equation (3):

$$SIR = \frac{S_{M1}}{S_{WM}} \quad (3)$$

where S_{M1} and S_{WM} are the signal in the ROI in the M1 and WM, respectively.

Because ROI placement is difficult at the distal blanch such as the cortical branch (M4), a neuroradiologist with 15 years of experience in clinical neuroimaging and a radiologist with 7 years of experience in clinical neuroimaging reviewed the maximum intensity projection (MIP) of last temporal phase of 4D-TOF-MRA in a random order in a blinded manner. Visibility of M4 in the last phases was rated by two radiologists independently using a five-point scale: 1 = poor (non-diagnostic), 2 = fair (observer not confident), 3 = moderate (observer marginally confident), 4 = good (observer confident), 5 = excellent (observer highly confident).

Statistical Analysis

SIR values for each MRA were compared using with Friedman test. The scores for assessing the visibility of M4 on each MRA were compared by Friedman test. Statistical analyses were performed using Medcalc version 12.2.1 (MedCalc Software, Mariakerke, Belgium). *P* values < 0.05 were considered to indicate a statistically significant difference.

Results

The signal intensity curve of the background on each 4D-TOF at the temporal

phases is shown in Figure 2. The signal in the brain tissue was recovered slowly, and was smaller in last phase on 4D-TOF with t-MTC, compared to the other MRA. However, time–signal intensity curve on the brain signal on 4D-TOF with t-MTC was not fit to a general exponential curve.

The signal intensity curve of M1 branch of the MCA in each the temporal phase is shown in Figure 3. The signal clearly demonstrates the increased blood flow arrival time. A similar time–signal intensity curves were obtained on simple 4D-TOF and 4D-TOF with t-MTC at all phases. The signal in the cerebral artery continued to increase on 4D-TOF with both t-MTC and t-TONE, compared to the other two methods.

The SIR between the cerebral arteries and the background is shown in Figure 4. The SIR for each 4D-TOF were significantly difference in 3rd and 4th phases ($P < 0.001$). The SIR for simple 4D-TOF was significantly lower than that for the other techniques in the 5th and 6th phases ($P < 0.001$). At the delayed phases (i.e., 7th, 8th, 9th), the SIR values for 4D-TOF with both t-MTC and t-TONE technique was significantly higher than those for the other two methods ($P<0.001$). The SIR for 4D-TOF with both t-MTC and t-TONE technique at the last temporal phase was 1.6-2.2 times higher than those on the other methods.

Three 4D-TOF images in a single subject are shown in Figure 5. In this figure,

4D-TOF with t-MTC and with both t-MTC and t-TONE images provided well visualization of M4 in last phases. The mean score for simple 4D-TOF was 2.4 (SD=0.61); for t-MTC was 3.9(SD=0.57); for both t-MTC and t-TONE was 4.1(SD=0.44). The scores for 4D-TOF with t-MTC and with both t-MTC and t-TONE demonstrated a significantly higher than those for simple 4D-TOF on both readers ($P<0.001$). The scores for both t-MTC and t-TONE technique had a higher score slightly compared t-MTC technique, however, there was no significant difference in visualization score between the two ($P>0.05$)

Discussion

We found that 4D-TOF using saturation pulse optimized by t-MTC and t-TONE techniques allowed the visualization of intracranial hemodynamics in this study. Since 4D-TOF is based on the T1-weighted gradient echo sequence by the inflow effect, it may be similar image quality to the 3D-TOF. Moreover, 4D-TOF technique using look-locker sampling provided hemodynamics images, which could be achieved without subtraction. This means that 4D-TOF allows faster acquisition and no misregistration artifacts. Because of these advantages, we assume that 4D-TOF optimized by t-MTC and t-TONE techniques would offer clinical utility.

On conventional 3D TOF, the high contrast between the blood and the background tissues is most important to visualize the intracranial arteries, In this study, the signal of background brain tissues recovered as time progresses because of using look-locker sampling. The background signal was recovered at the most early phase on simple 4D-TOF than the other methods. However, if we optimize the 4D-TOF for background control using MTC pulse, the background signal at the 9th phase on 4D-TOF with t-MTC technique and that at the 3rd phase with simple 4D-TOF were equivalent. These results suggest that the t-MTC technique is very suitable for suppressing the background signal of the brain tissue. However, an increase of the specific absorption ratio (SAR) and to prolong acquisition time per phase occurs with increasing the number of irradiation with the MTC pulse. Therefore, we applied MTC pulse only once in each temporal phase. In addition, the t-TONE technique suppressed the background signal. Despite irradiation with MTC pulse, the background signals on 4D-TOF with both t-MCT and t-TONE technique showed higher signal intensities than those on 4D-TOF with t-MTC technique in from 4th phase to 8th phase. This suggests that the T1* value was shortened at a low flip angle at the early phases as indicated by Equation (2). However, the background signal on 4D-TOF with both t-MCT and t-TONE technique was comparable to that on 4D-TOF with t-MTC technique after the 6th phase. This may

be due to higher flip angle set at the delayed phase on t-TONE technique. The t-TONE technique may suppress the background signal sufficiently by the irradiation high flip angle.

The effect of t-TONE technique is more remarkable focusing on the changes of the blood signal. We found that t-TONE technique effectively of increase the blood signal in delayed phases. While the signal variation in the artery on simple 4D-TOF and 4D-TOF with t-MTC technique was almost the same, a gradual signal increase was shown in the temporal phases using t-TONE technique. The blood signal became approximately 1.5 times on t-TONE technique at the last phase, compared to the other two methods. This phenomenon is similar to a previous report (24), where t-TONE was applied to ASL-based 4D-MRA using b-SSFP sequence combined the variable flip angle sampling.

In this study, we evaluated the SIR values since the signal differences between the background and blood is important in MRA. The SIR values for 4D-TOF with both t-MCT and t-TONE technique was lower than that for 4D-TOF with t-MTC technique in the early phases. This may be due to the fast recovery of background and low signal of the arteries at the low flip angle on t-TONE technique. However, the SIR for 4D-TOF with both t-MTC and t-TONE techniques was the highest at the late phase, compared to

the other methods. This means that 4D-TOF with both t-MTC and t-TONE techniques may improve the limitation of ASL-based 4D MRA. It has been reported that the distal branch of the intracranial arteries was less visualized due to an insufficient labeling to the blood spins as well as T_1 recovery in delayed phases (25). This limitation may be improved using multi-bolus spin labeling in ASL based 4D-MRA (26). In this study, we used inflow effect of the blood instead of labeling technique, which enabled to observe the hemodynamics in a relatively long time. The SIR values on 4D-TOF with both t-MTC and t-TONE techniques might have been higher if larger flip angle was set, instead of linear variation at the early phases.

The visual evaluation of M4 in the last phase showed that the scores on 4D-TOF with both t-MTC and t-TONE techniques were the highest, though there were not significant differences in scores on 4D-TOF with t-MTC technique and with both t-MCT and t-TONE technique. Because we scanned healthy volunteers in twenties of age accounted for 50%, inflow effect in the distal arteries may be well visualized.

This technique has several potential limitations. Since 4D-TOF uses inflow effects instead of labeling technique, the blood wash-out cannot be observed. As mentioned earlier, we used only linear variable flip angle for t-TONE technique. However, there may be more optimum pattern of variable flip angle for t-TONE. Moreover, the

parameters for 4D-TOF were experimented only for healthy volunteers. We will optimize this technique for robust performance in patients with the intracerebral vascular abnormalities.

Conclusion

4D-TOF using saturation pulse without ASL technique was optimized by t-MTC and t-TONE technique. 4D-TOF may provide high quality image for observing the intracranial hemodynamics, and may be useful in clinical practice because of a short scan time.

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Figure Legends

Figure 1.

Overview of the 4D-time-of-flight (TOF) sequence. 4D-TOF is based on 3D-turbo field echo (TFE) sequence combining lock-locker readout to acquire time resolved non-contrast enhanced magnetic resonance angiography (MRA) image. A slice selective saturation pulse is applied at the first part of the sequence to suppress background signal. Subsequently, off-resonance magnetization transfer contrast (MTC) pulse is used for better suppression of the background tissue recovery. As with conventional 3D-TOF, selective saturation pulse for suppression of the intracranial vein signal is applied before the acquisition of each phase data. 4D-TOF acquires only single set data; no necessity for subtraction like ASL-based 4D MRA,

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Figure 2.

The background signal measurements on simple 4D-TOF, 4D-TOF with t-MTC, and

4D-TOF with both t-MTC and t-TONE in the vicinity of M1 branch of the middle cerebral artery. Each column represents average measurements and standard deviation of eight healthy subjects.

Figure 3.

The blood signal measurements on simple 4D-TOF, 4D-TOF with t-MTC, and 4D-TOF with both t-MTC and t-TONE at M1 branch of the middle cerebral artery. Each column represents average measurements and standard deviation of eight healthy subjects.

Figure 4.

Signal intensity ratio (SIR) for simple 4D-TOF, 4D-TOF with t-MTC, and 4D-TOF with both t-MTC and t-TONE. The SIR values for 4D-TOF with both t-MTC and t-TONE technique is significantly higher than those on the other two methods at the late temporal phase. Single asterisks indicate significantly difference among three techiniques($p<0.001$). Double asterisks indicate SIR values for simple 4D-TOF were significantly lower than those for the other two methods($p<0.001$). Daggers indicate SIR values for 4D-TOF with both t-MTC and t-TONE techniques were highest, followed by those for 4D-TOF with t-MTC, and simple 4D-TOF ($p <0.001$).

Figure 5.

Axial MIP images of 4D-TOF MRA using simple 4D-TOF (a), 4D-TOF with t-MTC (b), and 4D-TOF with both t-MCT and t-TONE (c) with temporal resolution time of 180 ms. Intracranial hemodynamics of the circle of Willis are well visualized on 4D-TOF with t-MTC, and both t-MCT and t-TONE techniques.

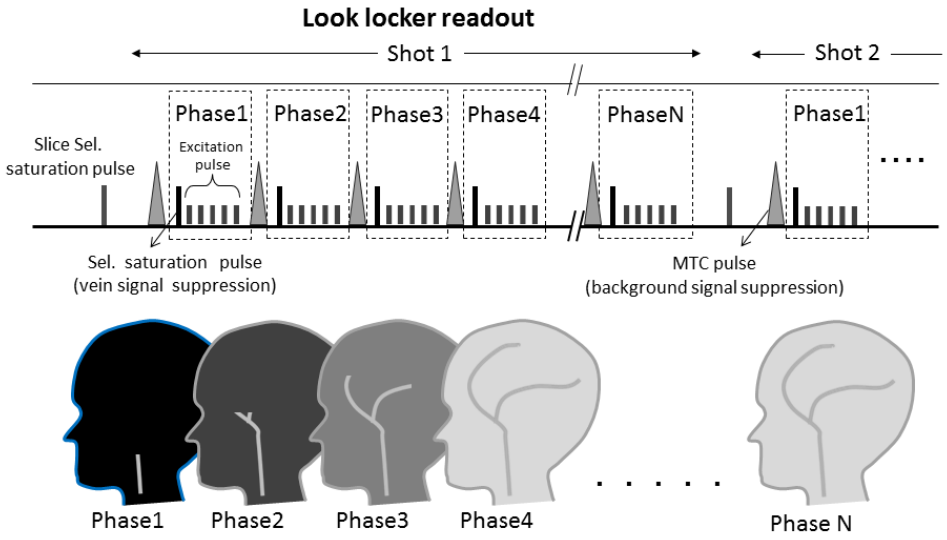

Figure 1

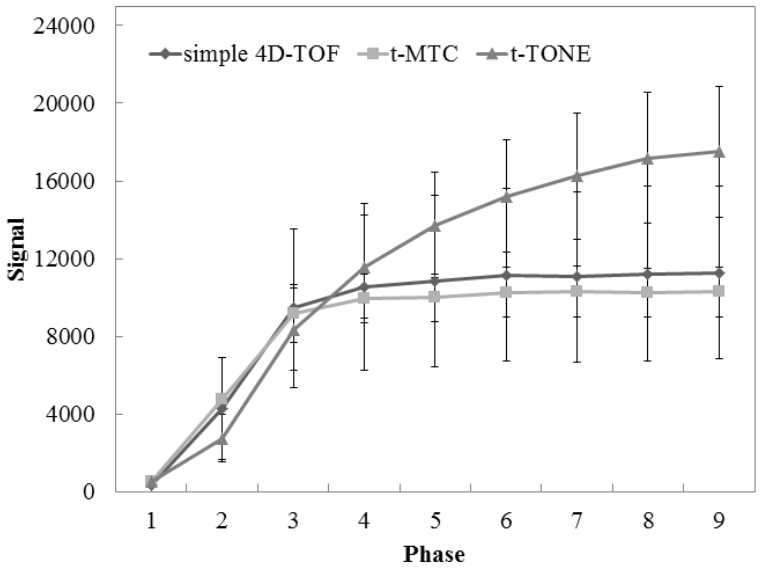

Figure 2

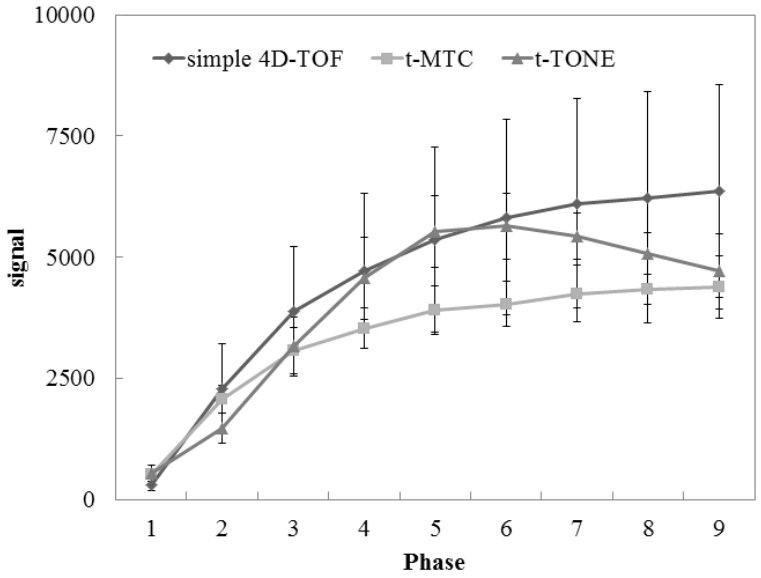

Figure 3

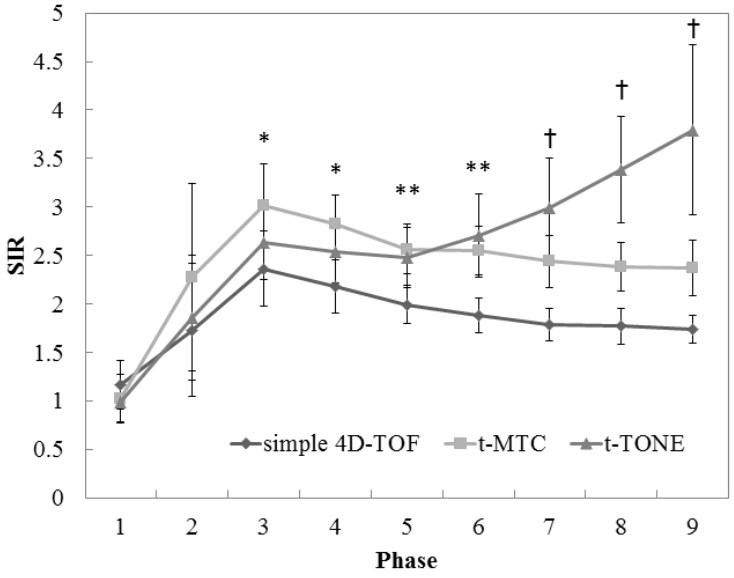

Figure 4

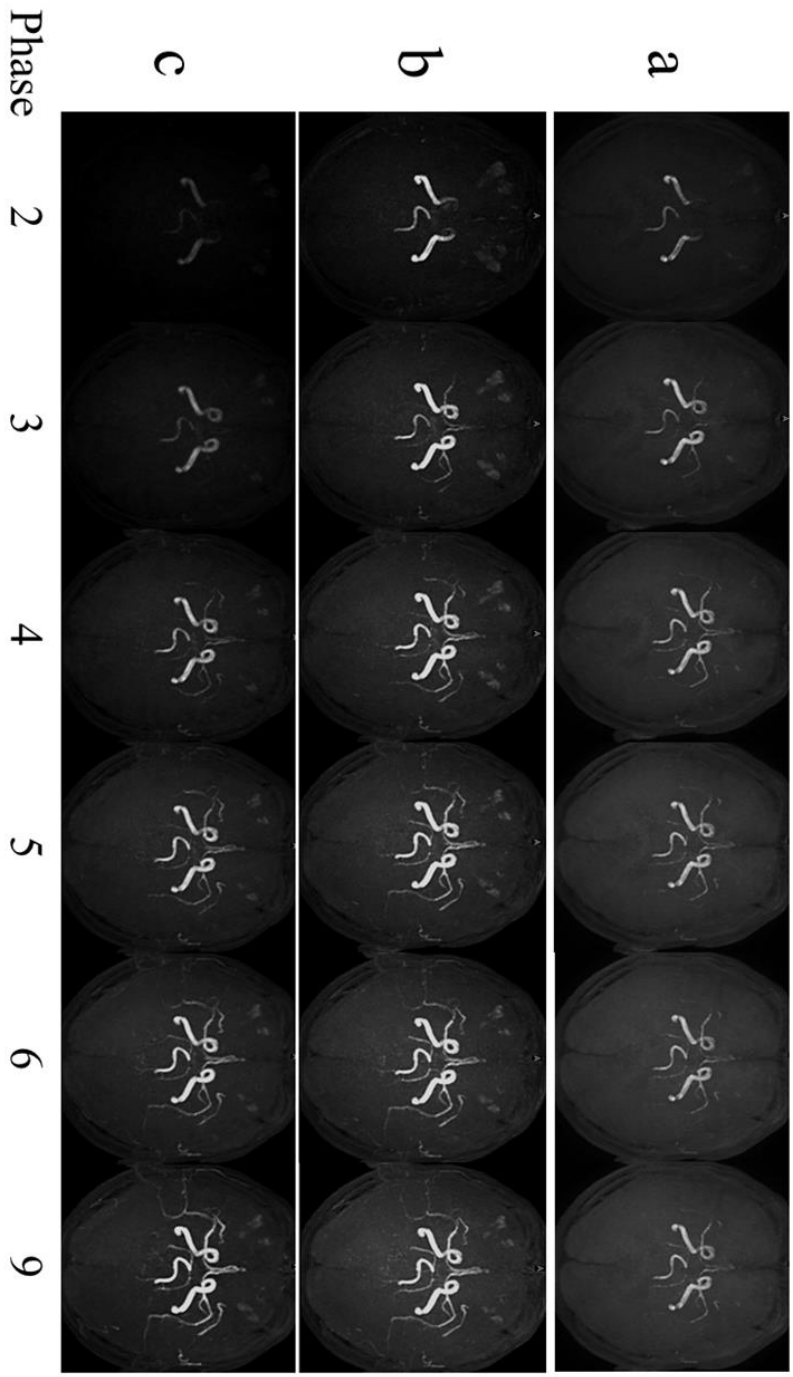

Figure 5