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Caffeine-induced Vascular Reactivity in the Ophthalmic Artery: A Preliminary Study using Phase-contrast MR Angiography

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Present study assesses vascular reactivity of the ophthalmic artery (OA) in the caffeine presence using magnetic resonance (MR) imaging technique, and it was compared with those of intracranial vessels, such as the middle cerebral and internal carotid arteries. All subjects underwent two MR scans in pre- and post-caffeine consumption conditions. Each scan included two imaging data sets, obtained using conventional time-of-flight (TOF) and phase-contrast (PC) MR angiography (MRA) to examine the signal changes of the target cerebral vessels and measure their velocities in 3 Tesla (3T) MRI, respectively. TOF MRA delineates the detail of the OA more clearly in post-caffeine condition, although it was also visualized in pre-caffeine. PC MRA can quantitatively measure changes in the blood flow velocity of OA. In conclusion, this study shows that MR imaging modality, especially PC MRA, can be used to quantify blood flow velocity in the OA, following a caffeine-induced blood flow increase.

Keywords : caffeine, ophthalmic artery, vascular reactivity, phase-contrast, MRA

1. Introduction

Vascular reactivity represents a change of flow status or cerebrovascular information in the target vessels to maintain an adequate blood flow [1]. An understanding of vascular reactivity is important to evaluate auto-regulatory capacity, especially with regard to hemodynamics. Although each cerebral blood vessel is essential for human brain, the ophthalmic artery (OA) is specially considered for two reasons. First, the OA is an extracranial artery, but originated from the intracranial artery, such as the internal carotid artery (ICA) [2]. Second, it supplies the blood to all the structures in the orbit, meaning that OA defects can potentially pose a threat to the proper function of mechanisms related to sight. Furthermore, the ocular circulation does not have any autonomic innervation, so changes in blood flow within the OA completely depend on its auto-regulatory capacity [3-5]. Therefore, it is necessary to assess vascular reactivity in the OA in order to understand its auto-regulation and the hemodynamic features of the ocular circulation.

Transcranial Doppler (TCD) is a representative and noninvasive technique that has previously been used to measure the vascular reactivity of the OA and middle cerebral artery (MCA) [6, 7]. With a well-trained operator and a well-prepared environment, TCD can swiftly produce reliable results [7]. However, TCD uses a transducer, which should be applied in contact with a closed eyelid, using an ultrasound coupling gel. Thus, there is some risk associated with the pressure with which the transducer is placed on the eyelid; it might increase the intraocular pressure (IOP) and alter the normal vascular conditions of the OA [8]. In addition, TCD has an intrinsic limitation; the eyelid must remain closed during the measurement period, making it difficult for flicker or light stimulation to be applied [6].

Phase-contrast magnetic resonance angiography (PC

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MRA) is another reliable and noninvasive technique that has been used to assess the blood flow of the OA and MCA [9, 10]. PC MRA sequences use a bipolar gradient with various amplitudes, to encode the velocity of the blood flow, i.e., velocity encoding (VENC) [11]. Recent technical advancements allowed PC MRA to simultaneously measure the blood flow velocities of all the cerebral vessels, independent of the operator [12]. With further extensive technical advancements in MRI, PC MRA technique has been identified as a candidate technique for the quantification of blood flow in fine vessels such as ocular arteries with a diameter less than 2 mm [9, 10].

Vasodilators, such as acetazolamide (ACZ), have been shown to be useful as clinical stimuli administered to evaluate decreased perfusion vascular reactivity [13]. However, they have some side effects, such as paresthesia, headache, malaise, and reversible pontine ischemia [14, 15]. In contrast, caffeinated beverages, such as coffee, tea, and coke, are relatively safe and can be more comfortably administered to volunteers, compared to clinical vasodilators. Caffeine is more quickly absorbed into body than other vasodilators and has a long biological half-life of about 2.5 to 4.5 hours [16]. It acts as an antagonist of adenosine receptors, causing vasoconstriction [17, 18], but simultaneously increases intracellular calcium, stimulating the increase of nitric oxide (NO), which, in turn, has a vasodilatory effect on vascular smooth muscle [19]. Therefore, caffeine can interestingly be either a vasodilatory or a vasoconstrictive stimulus, depending on several factors, such as the cellular structure of the target, time of exposure, and administered dose.

Although previous studies have reported partly contradictory results and the precise physiological effects of caffeine have not yet been clearly elucidated, caffeine has an overall vasoconstrictive effect on intracranial arteries, while it has a vasodilatory effect on extracranial arteries [20]. Therefore, the current study aimed to investigate the effects of caffeine on the hemodynamic features of OA compared with its effect on those of the major intracranial arteries such as the MCA, posterior cerebral artery (PCA), and ICA.

2. Materials and Methods

2.1. Subjects and data acquisition

Three normal, healthy volunteers (2 men, 1 woman; mean age, 31 ± 1 years) were recruited for the study. Before the start of the experiments, all participants signed an informed consent form. The experiments were approved by the institutional review board (IRB). All subjects were scanned with 3 Tesla (3T) MR scanner (Siemens Verio, Erlangen, Germany), using a commercially available 12-channel radio-frequency (RF) head matrix coil. Discrepancies between subjects' head positions before and after caffeine ingestion were corrected via alignment with laser beams. Additionally, a soft cushion and head pillow were placed beside each subject's head to minimize physical movement and increase comfort.

Table 1. MR parameters for TOF and PC MRA techniques.

Parameters	TOF	PC
TR (ms)	31	37.7
TE (ms)	3.6	5.45
FA (°)	20	25
FOV (mm^2)	163 × 192	180 × 192
Matrix Size	326 × 384	240 × 256
BW (Hz/Px)	186	399
TA (min:sec)	4:16	5:58
VENC (cm/s)	N/A	100
Resolution (mm)	0.5	0.75
Slice thickness (mm)	0.5	0.75
# of slices	48	80
# of lines (GRAPPA, R = 2)	40	50

All subjects were directed to stay caffeine-free for over 12 hours before the scanning took place. Daily caffeine consumption was estimated through a self-evaluation based on the rate of caffeinated drink (e.g. coffee, tea, and coke) consumption reported by each subject. The mean daily caffeine intake value for the three participants was lower than 200 mg.

Conventional three-dimensional (3D) time-of-flight (TOF) and PC MRA data were acquired for both structural and flow velocity change information from the targeted vessels. The parameters used for these scans are shown in Table 1. After the pre-caffeine scan, the subjects drank a cup of instant coffee (about 200 mg of caffeine) and then rested for approximately 30 min outside of the MRI scanner. A post-caffeine intake scan was conducted after this break. During this scan, all the imaging parameters that had previously been applied (Table 1) remained the same.

2.2. PC MRA Analysis

Blood velocity values can be derived as previously described, in which the velocity was equal to the square root of the sum of the squares of the velocity components of each velocity-encoded direction,

$$v = \sqrt{v_x^2 + v_y^2 + v_z^2} = \frac{\mathrm{VENC}}{\pi}\sqrt{\Delta\varphi_x^2 + \Delta\varphi_y^2 + \Delta\varphi_z^2} \qquad (1)$$

where φ_x, φ_y, and φ_z denote respective phase shifts along the x, y, and z-direction induced by a bipolar gradient [21]. Velocities in the target vessels such as the OA, MCA, PCA, and ICA were calculated within a maximum intensity projection (MIP) image acquired using a 3T MRI scanner. In this study, the VENC used for the PC MRA acquisition was 100 cm/s, but for the clear visualization of the target vessels (e.g., OA) with slow blood flow velocities, the threshold velocity (only for display with a velocity map) was set to 30 cm/s.

3. Results

The changes in the OA between the pre- and post-caffeine consumption conditions were examined using both TOF and PC MRA in 3T MRI as shown in Figs. 1 and 2, respectively. TOF MRA clearly showed an increased signal in the OA after caffeine ingestion, compared to that before caffeine intake. However, caffeine substantially decreased the signals in the other intracranial arteries such as the branches of the MCA, PCA, and ICA. Contrarily to TOF, PC MRA allows blood flow velocity information to be obtained. Nevertheless, it clearly showed, in the TOF MRA images (Fig. 1), that there was a dramatic change in vascular blood flow between the pre- and post-caffeine consumption conditions, even though the velocity could not be measured.

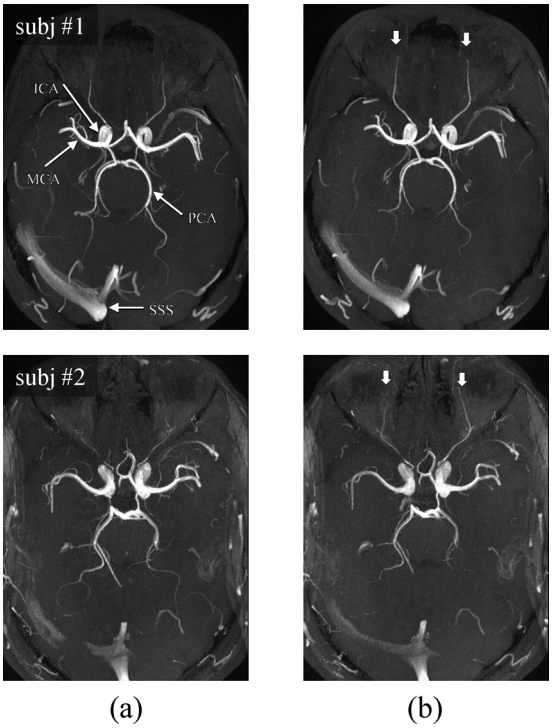

Fig. 1. TOF MRA images obtained in 3T MRI. The signal from the OA increases after caffeine consumption. The images on the left are pre-caffeine consumption (a) and on the right are post-caffeine consumption (b). Both OAs are clearly depicted as indicated by the white arrows in the right side images.

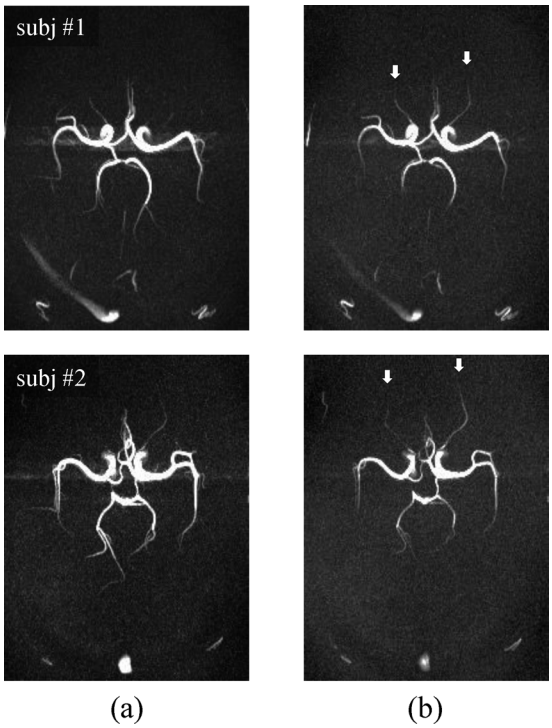

Fig. 2. Images obtained through PC MRA with VENC 100 cm/s in 3T MRI. The OA signal increases after caffeine consumption are shown in the participants. The images on the left are pre-caffeine consumption (a) and on the right are post-caffeine consumption (b). Both OAs are clearly depicted as indicated by the white arrows in the right side images.

In the PC MRA images, each voxel contains velocity information, which is calculated when the pixel signal intensities are converted into velocity values (Fig. 2). The velocity maps for the OA, MCA, PCA, and ICA are shown in Fig. 3, where the threshold velocity was set to 30 cm/s for the clear visualization of OA as shown in the color bar. Therefore, the signals with velocities greater than 30 cm/s, e.g., in large arteries such as the MCA, PCA, ICA, and large veins, such as the superior sagittal sinus (SSS), were saturated as shown in Fig. 3. As a result, most segments of the MCA, PCA, and ICA appear in red in this figure because this color corresponds to the velocity of above 30 cm/s. Only the distal branches of these vessels appear in different colors, since blood flow is slower in these segments. When velocity was quantified, it was shown that caffeine increased the peak flow velocity change in the OA by up to about 25 % and decreased that in the MCA, PCA, and ICA by up to about

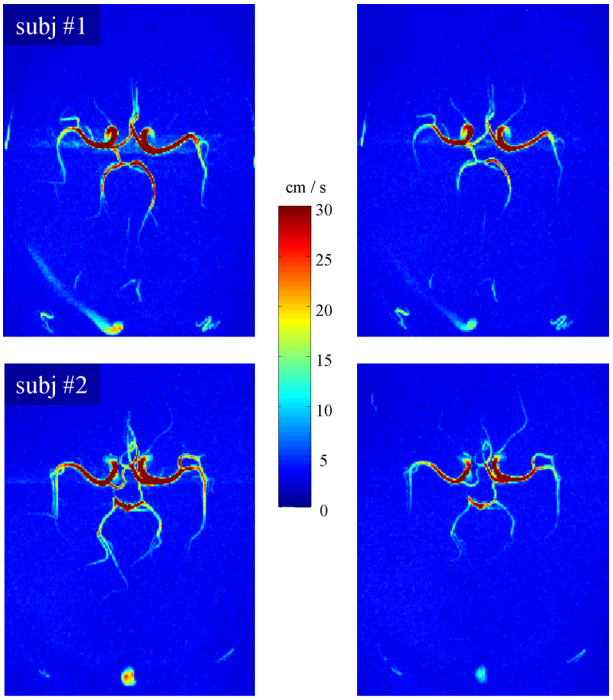

Fig. 3. (Color online) Velocity maps from the PC MRA with VENC 100 cm/s. The maps represent the velocities of the blood flow in the OA, MCA, PCA, and ICA. The images on the left are pre-caffeine consumption (a) and on the right are post-caffeine consumption (b). The color bar indicates the magnitude of the velocity.

Table 2. Peak velocities of the targeted arteries before and after caffeine ingestion.

Velocities	Before (mean ± SD) (cm/s)	After (mean ± SD) (cm/s)	Difference (%)
V_{OA}^{max}	9.52 ± 1.22	11.92 ± 1.59	25.19
V_{MCA}^{max}	65.55 ± 5.07	44.51 ± 5.13	–32.09
V_{PCA}^{max}	56.46 ± 4.08	36.95 ± 4.32	–34.56
V_{ICA}^{max}	87.42 ± 10.21	63.63 ± 4.07	–27.21

–35 %, compared to pre-caffeine condition (Table 2).

4. Discussion

Although TCD is the most common method used in the evaluation of ocular diseases [22], many previous studies have shown that PC MRA has been gaining attention as a method for accurate vascular flow measurement [9, 23-25]. The results of the current study show that PC MRA can be used to display intracranial arteries and the OA and provide simultaneously a direct measurement of the blood flow velocity of each artery. Additionally, this study proves that PC MRA has the potential to become an operator-independent tool for the assessment of the vascular reactivity of ICA branches including the OA (extracranial artery) versus MCA, PCA, and ICA (intracranial arteries). Furthermore, the results show that caffeine can enhance MRA signal using TOF and PC sequences in the OA due to an increased blood flow, but it cannot do so in MCA, PCA, or ICA due to a decreased blood flow (Figs. 1 and 2). Although the intracranial vascular status can be defined as the vascular reactivity of the MCA, which is originated from the ICA [2, 26], PCA is also one of the representative arteries among the intracranial vessels, which comes from the basilar artery. Therefore, a vascular reactivity assessment including PCA was required to evaluate comparatively the hemodynamic features of the OA.

In terms of the qualitative analysis and visualization of the OA, our observations indicate that TOF MRA generates better results than PC MRA, since it takes less time and discriminates fine vascular structures better (see Fig. 3 and Table 2). However, TOF MRA does not provide quantitative information of the flow change in the OA. Therefore, PC MRA is suggested as a solution to examine the blood flow change in the OA after caffeine ingestion, especially for the quantitative analysis of velocity in the target vessels.

Moreover, this study demonstrates that caffeine might be a potential candidate for use as a vascular contrast boost agent in imaging techniques, especially for both TOF and PC MRA sequences. In the present study, vascular reactivity is estimated by measuring the change in blood flow in response to the caffeine stimulus. Caffeine ingestion substantially enhances the blood vessel signal in the OA. Therefore, our results also demonstrated that caffeine could play an important role as a contrast enhancer, specifically for the research of vascular reactivity in the OA. To date, breath-holding, hyperventilation, and inhalation of CO_2 have been used as stimuli in the evaluation of vascular reactivity. These stimuli increase the blood concentration of CO_2, which acts as a vasodilator [6, 27]. However, breath-holding and hyperventilation are highly dependent on patient cooperation and are sometimes accompanied by a risk of provoking some motion, which may result in motion artifacts in the acquired MR data. Furthermore, CO_2 inhalation may cause nervousness, restlessness, fear, and nausea. Alternatively, a systematic metabolic change can be induced by a very short period of exercise. This exercise could be applied as a stimulus. However, this method makes it difficult for the experiment to be controlled [28].

Previous studies demonstrated that ACZ or carbon dioxide inhalation had different effects on MCA and OA [4, 5, 29]. For instance, it has been reported that the flow velocity in the MCA is substantially dependent on the vasodilators, such as CO_2 and ACZ, while the OA is less dependent on them [29]. Presently, there is no physiological explanation for this difference. However, previous studies suggest that there might be a more specific auto-regulatory mechanism for the OA compared to that of the ICA [4, 23, 29, 30]. The existing evidence indicating that the ocular circulation does not have autonomic innervation supports this suggestion [3, 4]. Moreover, the idea that an endothelium-dependent vasoactive modulation mechanism might play a role in the ophthalmic circulation has been suggested as an alternative explanation for this feature [31]. Additionally, a local hemispheric anesthesia of the sympathetic nervous system led to results that are in accordance with the hypotheses stated above [30].

In this study, we measured a blood flow change in the OA immediately after the ingestion of caffeine, meaning that the caffeine played a role as vasodilatory stimulant in the OA. The major effect of caffeine on the vascular wall is vasodilation, though it also has mild and transitory vasoconstrictive effects as it acts as an adenosine receptor antagonist [20]. This may be the cause for the direct effect of caffeine, i.e., vasodilation, which is predominant, in the case of the OA because endothelium-dependent vasoactive modulation is predominant in the ophthalmic circulation and caffeine is a vasodilator with regard to its effect on endothelium and NO concentration [3, 5, 20]. However, the blood flow of the intracranial arteries, which has the tendency to be dependent on various factors, shows a systemic response to the cerebral vessels. Thus, the action of caffeine seems complex, especially considering the case of the OA. Hence, there is no clear indication of what the predominant mechanism mediating the effect of caffeine might be. Previous studies have reported that caffeine reduces blood flow velocity in the MCA, which is in agreement with the results of our study [32]. However, the further studies are required to clarify the cause for the observed increase in blood flow velocity in the OA and its concomitant decrease in the MCA, PCA, and ICA after caffeine administration.

Present study has several limitations, which need to be taken into consideration when it comes to interpreting the current results, although we confirmed to the reproducibility of caffeine effects in PC MRA in one of participants (the data was not been shown). In order to assess vascular reactivity, a volumetric blood flow measure is generally used. However, assessing quantitatively vascular reactivity using PC MRA was difficult because there are technical limitations related to the determination of vessel diameter (especially in the OA) on MR based images. In addition, caution must be taken when making the differences in blood flow velocity among the arteries, even though the present study could provide the obvious results even with a small number of subjects. The effect and safety of caffeine has been the most commonly investigated with about 200 mg of caffeine [33, 34], and the exact amount of caffeine necessary to produce an adverse effect varied from person to person depending on their weight and sensitivity to caffeine [35]. Therefore, we designed the experiment to let participants to drink a cup of coffee containing a 200 mg of caffeine and the normal healthy subjects were examined, but in case further studies regarding to the dose and weight dependence on caffeine should be followed.

5. Conclusions

In conclusion, we showed that PC MRA can be used to quantify the blood flow velocity change in the OA induced by an external stimulus. Furthermore, we showed that caffeine can serve as this external stimulus, and that it could be useful in further studies of this nature, given that caffeinated beverages could provide an efficient and comfortable option for OA vasodilation. Finally, this study suggests that the auto-regulatory mechanism affecting the OA may be different from that which controls blood flow in intracranial vessels, such as the MCA, PCA, and ICA.

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