Introduction

Transcranial Doppler ultrasonography (TCD) is a noninvasive technique in which sudden cerebral blood flow velocity (CBFV) changes in the basal cerebral arteries can be evaluated. The most important feature is the ability to monitor these sudden changes. It is assumed that the velocity changes during breath-holding are caused by varying resistance secondary to diameter changes in small vessels distal to the M2 segment of the middle cerebral artery (MCA). These changes observed in the velocity are considered to be indicative of the cerebro-vascular reserve of cerebral vascular structures formed in response to hypoxia (1).

The vasodilation capacity of cerebral arterioles can be measured indirectly by changes in the BFV in the main cerebral arteries. This capacity, defined as a cerebrovascular reserve or vasomotor reactivity (VMR), can be evaluated by carbon dioxide inhalation, acetazolamide injection, and breath-holding and vasodilator stimulation (2-4).

Vasomotor reactivity in the ophthalmic artery

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ABSTRACT

Aim: The aim of this study was to obtain information about reactivity differences in ophthalmic artery (OA) and middle cerebral artery (MCA) presented as a change in blood flow velocity (BFV) induced by the breath holding in healthy individuals.

Methods: Cerebral vasomotor reactivity (VMR) is interpreted indirectly with the increase in the BFV detected in the basal arteries, secondary to a vasodilatory stimulus as breath holding. Bilateral MCA and OA were evaluated by using transcranial Doppler ultrasonography in 15 volunteers.

Results: The basal velocities obtained from MCAs and from bilateral OA were symmetrical and did not change according to the side (p>0.05). The ratio of MCA to OA flow velocities had no significant difference between the sides (p>0.05). The OA flow velocities were significantly lower than the ipsilateral MCA flow velocities. Breath-holding index (BHI) was used to evaluate the VMR. Although the BHI values were not symmetrical and statistically different between the sides (p>0.05), the difference between the ipsilateral MCA BHI and OA BHI was significant (p<0.05). We determined the ratio of MCA VMR to OA artery VMR as 1.47±0.15.

Conclusion: We found out that the VMR measurement with the BHI method could be used in the OA and VMR in the OA was decreased compared to the MCA on the same side. Future studies on OA VMR in patients with different degrees of carotid stenosis and determination of changes in the OA VMR as a result of angioplasty or stenting will provide valuable information.
Methods

Fifteen healthy volunteers were included in the study (mean age 26.2±7.8 years). The study described was carried out in accordance with the Declaration of Helsinki for researches involving humans. The ethical approval date and number is 30 Jun 2009/135 (GATA). Informed consent was obtained from all volunteers prior to the study. Strict exclusion criteria were applied with the assumption that comorbidities or treatments might change the measurements. Hypertension, diabetes mellitus, obesity, congestive heart failure, chronic obstructive pulmonary disease, stroke (history of any stroke or transient ischemic attack), carotid artery disease (detection of luminal narrowing at a higher rate than the intima-media thickness), hematological disease or cancer were applied as strict exclusion criteria. None of the volunteers were smokers. Magnetic resonance angiography was performed to exclude possible intracranial stenosis, arteriovenous malformation, aneurysm, or Willis polygon variation (6).

Volunteers were accepted to the ultrasonography laboratory after 8 hours of night sleep on a full stomach at 08:00 in the morning. As sleep deprivation may lead to VMR change, at least 8 hours of night sleep was required. The study was performed with a DWL Multi-Dop X4 TCD device while patients were lying in the supine position on an ultrasonography examination table. Pulsed-wave Doppler probes (2 MHz) were fixed on the bilateral temporal window with a probe holder and stabilizer. The optimal signal from the MCA was obtained from a mean depth of 45-55 mm on both sides. For the OA examination, Pulsed-wave Doppler probes (2 MHz) were placed manually to receive signals from the transorbital window. In the transorbital window examination, the power of the device was reduced to 16 mW/cm². The optimal signal from the OA was obtained from a mean depth of 11-24 mm on both sides. The mean BFV of the arteries under sonographic examination during both basal and breath-holding maneuver were continuously recorded by the software of DWL device. The basal BFV was accepted as the mean of the last 3 minutes BFV of a 10-minute period after the probes were fixed. The breath-holding maneuver was performed to evaluate VMR in vascular structures. The breath-holding maneuver was performed in sets of three at a time. For mean BFV, vascular structures were recorded in ipsilateral pairs. The right MCA and right OA were recorded together, while the left MCA and left OA were recorded together. Volunteers were asked to hold the breath for 30 seconds at 3-minute intervals. If the breath-holding for 30 seconds was not successful, the test was interrupted for 3 minutes. Velocity measurements were made offline afterwards. During the breath-holding maneuver, no side effects were observed to stop the study, but the volunteer was informed again before the procedure and instructed during the procedure so that the volunteer could cooperate.

All measurements were made offline using the software of the DWL TCD device. At the selected time window and the specified exact time, the mean flow velocities were calculated by the device.

Cerebrovascular reactivity was measured by the breath-holding index (BHI). The percentage of increase in the mean BFV observed after 30 seconds of breath-holding by the volunteers was determined as the BHI: BHI = mean BFV at the end of the breath-holding maneuver - mean BFV at rest / mean BFV at rest x100 / breath-holding time (sec) (1).

Statistical Analysis

Data were entered into SPSS v.15.0 statistics program. The Kolmogorov-Smirnov test was used for continuous variables. All measurements with normal distribution were performed with the t-test. Quantitative data were presented as mean±standard deviation, and the p value <0.05 was accepted to be significant.

Results

Bilateral MCA and OA were evaluated in 15 volunteers (6 females and 9 males, mean age 26.2±7.8 years). The basal velocity obtained from the right MCA was 40.3-83.9 cm/s (mean 59.19±11.65 cm/s), and the basal velocity obtained from the left MCA was 46.8-89.9 cm/s (mean 64.79±12.51 cm/s). The recorded velocities were among the normal values of our laboratory (7). The basal velocity obtained from the OA was 13.0-23.1 cm/s (mean 18.37±2.86 cm/s) on the right and 11.8-24.3 cm/s (mean 17.30±3.91 cm/s) on the left. Table 1 shows the flow velocities obtained. The basal flow speeds were symmetrical and did not change according to the recorded side (p>0.05). When the ratio of MCA flow velocity to OA flow velocity, which can be considered as an indicator of possible distal stenosis, was evaluated, the ratio of MCA to OA flow velocity was 3.30±0.93 on the right and 3.87±0.94 on the left. There was no significant difference in flow velocity between the two sides (p>0.05). As expected anatomically, the OA flow velocities were significantly lower than the ipsilateral MCA flow velocities (Table 2).

When flow velocities were measured from both the MCA and OA after 30 seconds of breath-holding, the BHI was 0.7-3.6 (mean: 1.64±0.53) in the right MCA and 0.8-3.1 (mean 1.57±0.50) in the left MCA. In the OA, the BHI was 0.3-2.7 (mean 1.04±0.59) on the right and 0.2-3.0 (mean: 1.15±0.68) on the left.

Table 1. Comparison of lateralization of middle cerebral artery and ophthalmic artery flow parameters

|          | Right     | Left      | p value |
|----------|-----------|-----------|---------|
| MCA      | 59.19±11.65 | 64.79±12.51 | 0.215   |
| OA       | 18.37±2.86  | 17.30±3.91  | 0.402   |
| MCA/OA   | 3.30±0.93   | 3.87±0.94   | 0.108   |
| MCA BHI  | 1.64±0.53   | 1.57±0.50   | 0.483   |
| OA BHI   | 1.04±0.59   | 1.15±0.68   | 0.427   |
| MCA BHI/OA BHI | 2.15±1.51 | 2.15±2.05 | 0.993   |

MCA: Middle cerebral artery, OA: Ophthalmic artery, BHI: Breath-holding index
Although the BHI values were not symmetrical and statistically different between the sides (p>0.05), the difference between the ipsilateral MCA BHI and OA BHI was significant (p<0.05) (Table 2). The BHI values are shown in Figure 1 and Figure 2. The ipsilateral MCA and OA flow velocities were 3.30±0.93 on the right and 3.87±0.94 on the left. The ratio of MCA BHI to OA BHI was 2.15±1.51 on the right and 2.15±2.05 on the left (p>0.05).

Discussion

Transcranial Doppler is a noninvasive, fast and dynamic method that can be applied bedside, can reflect instantaneous changes and provides information about stenosis or occlusion of the main intracranial arteries, BFV and flow directions. At the same time, the VMR test can be performed, providing information about cerebral autoregulation and collateral circulation, and the intracranial hemodynamic status can be evaluated with TCD.

The size of the ischemic region that may develop after cerebral artery occlusion depends on whether cerebral collateral vascularization is sufficient to compensate for decreased blood flow (8-10). The anterior communicating artery and posterior communicating artery, which are intracranial anastomoses of the Willis polygon, are two of the primary collateral circulations (11-14). Anastomoses between the internal maxillary artery, the branch of the external carotid artery, and the OA and leptomeningeal anastomoses are considered as secondary collateral vascularization. The patent secondary collateral pathways may be indicative of inadequate cerebral hemodynamics (14). Many studies have been conducted to evaluate the patent structure and effects of primary and secondary collateral pathways on cerebral hemodynamics in occlusion or severe stenosis of cerebral arteries (8,9,13-15).

Patients with moderate to severe atherosclerotic lesions in the internal carotid artery have more hemodynamic disorders than those without them (9). In order to understand the hemodynamic status, the contribution of the Willis polygon and OA to the collateral circulation should be known (16).

Collateral clinical importance of the OA in patients with carotid artery occlusion has been reported in the literature. VMR studies performed on the OA are both few in number, and the findings obtained are contradictory (17-21). Kerty et al. (17) found that the OA flow velocity decreased after acetazolamide infusion in 15 healthy individuals, while Harer and Thomas found that a decrease occurred in the OA flow velocity and reactivity index after CO₂ inhalation in 15 healthy individuals. Rassam et al. (18) reported that the OA flow velocity increased after acetazolamide infusion as a result of their study on 10 healthy individuals. Harris et al. (20) found out that CO₂ or acetazolamide infusion had no effect on the OA flow velocity in 12 healthy individuals (19). Bornstein et al. (21) found that the VMR value of the OA increased significantly on the side with an internal carotid artery stenosis of 70-99% and that there was no significant increase on the side with normal or hemodynamically insignificant internal carotid artery stenosis, but they could not explain the underlying

| Table 2. Comparison of middle cerebral artery and ophthalmic artery flow parameters bilaterally |
|-----------------------------------------------|------------------|------------------|
| MCA | OA | p value |
| Right | 59.19±11.65 | 18.37±2.86 | <0.001 |
| Left | 64.79±12.51 | 17.30±3.91 | <0.001 |
| MCA BHI | OA BHI | | |
| Right | 1.64±0.53 | 1.04±0.59 | <0.001 |
| Left | 1.57±0.50 | 1.15±0.68 | <0.001 |

MCA: Middle cerebral artery, OA: Ophthalmic artery, CI: Confidence interval

Figure 1. Middle cerebral artery and ophthalmic artery mean flow velocities
MCA: Middle cerebral artery, OA: Ophthalmic artery, CI: Confidence interval

Figure 2. Middle cerebral artery and ophthalmic artery breath-holding index
MCA: Middle cerebral artery, OA: Ophthalmic artery, BHI: Breath-holding index, CI: Confidence interval
cause. In our study, it was aimed to determine the VMR value of the OA and to compare it with the MCA VMR by using the BHI in healthy individuals.

In this study, the ipsilateral OA BHIs of 15 healthy individuals both on the right and left sides were significantly lower (p<0.05) compared to the MCA BHIs. When the ninety BHIs measured from the OA were evaluated, the mean value was 1.10, and SEM was 0.06745. When the 95% confidence interval of the OA BHI of healthy individuals was evaluated, the lower limit was 0.97, and the upper limit was 1.24. The results of our study show that the vascular reserve of the OA is different and lower than the cerebrovascular reserve of the MCA in healthy individuals. In healthy individuals, the OA does not respond to the systemic vasodilator stimulus as much as intracerebral arteries.

The BHI calculated in healthy individuals should be brought to a certain standardization. Although the OA BHI values in healthy individuals were found to be lower than the BHI values of basal cerebral arteries, we think that these values should be accepted within normal limits.

Cerebral VMR is interpreted indirectly with the increase in the BFV detected in the basal arteries secondary to vasodilatation in cerebral arterioles. While there is no calibration change in the M1 and M2 segments of the MCA against a vasodilator stimulus, the more distal segments are considered reactive (1).

It is not wrong to state that VMR in the OA is decreased compared to the MCA. In this study, the BHI was used to evaluate the OA VMR. In the literature, it is observed that acetazolamide and CO₂ inhalation are used as a vasodilator stimulus in OA studies.

Although the mechanism is not the same as in the MCA, reactivity to a vasodilator stimulus is also observed in the OA, and this response is lower than in the MCA. The reduced reactivity in the OA determined in this study is consistent with other studies in the literature (17-19). Kerty et al. (22) examined healthy individuals and patients with internal carotid artery occlusion or severe internal carotid artery stenosis greater than 75%. They also divided the patient group into 3 subgroups according to the direction of flow in the OA after basal and acetazolamide injections. Group 1 consisted of patients in whom the OA flow was anterograde after basal and acetazolamide injection, it was basal anterograde and retrograde after injection in group 2, and retrograde in both cases in group 3. In this study, it was important that the flow velocity of the OA decreased in healthy volunteers after injection, there was no change in group 1, and it increased after injection in groups 2 and 3. In the same study, the basal anterior cerebral artery and MCA flow velocities were found to be lower on the symptomatic side compared to the contralateral side in groups 2 and 3, but the flow velocity after acetazolamide injection was found to be low only in group 3. These results show that in internal carotid artery occlusion or severe stenosis, VMR is increased as a compensatory mechanism in the OA, but if there is retrograde flow in the OA in the basal state, this increase is insufficient at the central level. These results are consistent with the results we found in healthy volunteers.

When the cerebral blood flow is decreased in the theoretical framework, it can be assumed that the risk of ischemic stroke increases with the decrease in systemic arterial blood pressure. If there is a serious stenosis or occlusion in the internal carotid artery that causes this disorder, it would not be wrong to say that VMR evaluation before applying with recanalization treatment modalities and even VMR results may be effective in the decision of recanalization or even the selection of a recanalization method.

In clinical practice, “blackout” defined by patients without a loss of consciousness in presyncope due to hypotension may be caused by reduced VMR in the OA. Again, in the case of amaurosis fugax, it may be stated that reduced VMR is more effective than the source of an embolism, which is almost always considered.

In this study, we demonstrated that the MCA BFV on both sides were similar at rest and that the OA flow hemodynamics of both sides were similar in terms of BFV at rest. We found that the MCA/OA BFV were similar between the two sides, and the flow rates between the two sides were identical. In the VMR parameters evaluated by the BHI, we demonstrated that the MCA and OA hemodynamic changes of both sides were similar after a dynamic test as at rest. As a result of this hemodynamic test performed in healthy individuals, we determined the ratio of MCA VMR to OA artery VMR as 1.47±0.15.

**Conclusion**

At the end of this study, we found out that the VMR measurement with the BHI method could be used in the OA and VMR in the OA was decreased compared to the MCA on the same side. In future studies, we think that evaluating the OA VMR in patients with different degrees of carotid stenosis and determining changes in the OA VMR as a result of angioplasty or stenting will provide valuable information.

The low OA VMR is actually regarded as an expected result in a healthy individual. In case of the insufficient central flow, VMR may increase in the OA as the collateral circulation becomes active and the OA begins to show central flow characteristics, and the fact that it begins to show central cerebral artery characteristics while it should be accepted as a peripheral artery, together with successful collateralization, can actually be considered as an indirect indicator of significant stenosis in central pathways.

In prospective studies to be planned in carotid artery patients with and without active collateral circulation, the association of VMR observed in the MCA and OA with the risk of recurrent stroke can be demonstrated.
Ethics

Ethics Committee Approval: The ethical approval date and number is 30 Jun 2009/135 (GATA).

Informed Consent: Informed consent was obtained from all volunteers prior to the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T.K., G.K., Concept: M.T.K., G.K., Design: M.T.K., G.K., Data Collection or Processing: M.T.K., G.K., Analysis or Interpretation: M.T.K., G.K., Literature Search: M.T.K., G.K., Writing: M.T.K., G.K.

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