· Original article ·

Color Doppler ultrasonography evaluation of amblyopia

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弱视的彩色多普勒超声检查评估

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摘要

目的:彩色多普勒超声检查测定远视患者眼眶血管血流动力学改变,与非远视眼进行对比。

方法:18 例患者(36 眼)被纳入该项研究中,其中 20 眼为远视眼,16 眼正常。彩色多普勒超声检查所有眼的眼动脉,视网膜中央动脉,以及睫状后动脉血流情况。

结果:两组间唯一差别为远视眼眼动脉显著降低的最大收缩速度(32.70±11.60 *vs* 55.01±11.68, P=0.001)及舒张末期血流速度(6.83±1.91 *vs* 13.99±4.15, P=0.001)。

结论:该项研究表明弱视眼较正常眼球后血流速度有所减慢。

关键词:弱视;彩色多普勒成像;眼动脉;最大收缩速度;舒张末期血流速度

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Abstract

• AIM: To assess the hemodynamic changes in the extraocular orbital vessels of amblyopic patients in comparison with non-amblyopic fellow eyes, using color Doppler ultrasonography (CDU).

• METHODS: Thirty-six eyes of 18 pediatric patients were included in the study (20 amblyopic, 16 normal). All eyes underwent color Doppler ultrasonography examination of ophthalmic artery, central retinal artery, and posterior ciliary artery.

• RESULTS: The only differences between the two groups with regard to color Doppler ultrasonography parameters was the significantly lower peak systolic velocity (32.70±11.60 *vs* 55.01±11.68, P=0.001) and end-diastolic velocity (6.83±1.91 *vs* 13.99±4.15, P=0.001) for ophthalmic artery in amblyopic eyes.

• CONCLUSION: Our study showed amblyopic eyes may present a decrease in retrobulbar blood flow velocity.

• KEYWORDS: amblyopia; color Doppler imaging; ophthalmic artery; peak systolic velocity; end - diastolic velocity
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INTRODUCTION

Amblyopia is defined as the abnormally low visual acuity in one or both eyes that is not mitigated with optical refractive correction and that occurs in the absence of any retinal or central pathology[1]. It has shown to result from abnormal development of the visual cortex in human and it is associated with the dysfunction of the lateral geniculate nucleus (LGN) in humans[2-3].

Previously a number of different methods have been used to investigate the retinal involvement in amblyopia. For instance, Ikeda and Chino have been able to demonstrate ganglion cell loss and presence of abnormal synapses at the inner plexiform layer[4,5]. Also changes in visual evoked potentials (VEP) and electroretinogram (ERG) have been reported as well as reduced amplitude in pattern electroretinogram (PERG)[6-9]. More recently, an optic disc anomaly in amblyopia has been found using fundus photographs[10,11]. Despite the discrepancy of results across various studies of OCT and amblyopia, subsequent work has not always supported retinal involvement in this condition. Therefore, whether or not amblyopia is associated with any structural or physiological changes of the retina remains to be elucidated.

Color Doppler ultrasonography (CDU) is a widely used non-invasive and reproducible imaging modality that provides quantitative and qualitative information about the blood flow velocity, but not the volume, in retrobulbar vessels[12-13]. Recent uses of this technique include the assessment of a number of ophthalmological conditions such as glaucoma, diabetic retinopathy, uveitis, anterior ischemic optic neuropathy, and optic neuritis[14-16].

This study was undertaken to assess the hemodynamic changes in the extraocular orbital vessels of amblyopic patients using CDU.

SUBJECTS AND METHODS

Subjects Thirty - six eyes of 18 pediatric patients were included in the study. All but two patients had unilateral amblyopia and the intact eyes were used as controls, *i. e.*

Twenty amblyopic eyes were compared to 16 normal eyes. The distribution of the type of amblyopia was as follows: 2 eyes meridional, 10 strabismic, and 8 anisometric. The study protocol was conducted in accordance with Declaration of Helsinki. Prior to inclusion, informed consent was obtained from all parents.

Methods All patients underwent a complete eye examination including measurement of the refractive error using cycloplegic, best-corrected visual acuity examination, slit lamp examination, evaluations of extraocular movements and intraocular pressure, fundoscopy, and axial length measurement using IOLMaster (Carl Zeis Jena, Germany). A reduced visual acuity in one or both eyes in the absence of any demonstrable abnormality of the visual pathway was considered as amblyopia. In addition, it was defined as a best-corrected visual acuity difference of more than two lines on the Snellen acuity chart at 6m. Anisometropia was defined as a difference in spherical equivalence of 1.0D or more between the two eyes. Patients with a history or evidence of organic eye disease, intraocular surgery, cataract formation, glaucoma, retinal disorders, or laser treatment were not included as well as uncooperative children for Doppler USG examination.

Color Doppler ultrasonography examinations All CDU examinations were performed after a 15-minute rest in a thermally controlled room by the same masked sonographer, avoiding any pressure on the eye of patients in a supine position and with their both eyes closed. Ultrasound gel was applied to the external surface of the eyelids. The head of the patient was tilted forward at an angle approximately 30 degrees since a 30 to 60 degrees of angle is necessary during Doppler US examination for ideal signal acquisition and correct velocity measurements. Examinations were performed using an ultrasound scanner (Aplio XG, Toshiba, Tokyo, Japan) and a 7.5MHz linear-array transducer. All retrobulbar vessels, including ophthalmic artery, posterior ciliary arteries, and central retinal artery, were examined in each subject. Ophthalmic artery measurements were performed approximately 10-15mm posterior to the globe. The nasal and temporal posterior ciliary arteries were examined approximately 5-10mm posterior to the globe and results were averaged. The central retinal artery was examined within 5mm of the retrolaminar portion of the optic nerve. All flow velocity waveforms were obtained after angle correction. Following values were calculated for the ophthalmic, posterior ciliary and central retinal arteries: peak systolic velocity (PSV), and end-diastolic velocity (EDV) and resistivity index (RI=(PSV-EDV)/PSV)[17]. In addition, pulsatility index (PI) was calculated using the formula PI=(PSV-EDV)/Vmean, where Vmean = 1/3(PSV-EDV)+EDV[18].

Statistical Analysis Statistical analyses were performed using NCSS (Number Cruncher Statistical System, 2007) and PASS (Power Analysis and Sample Size Statistical Software, 2008, Utah, USA) statistical software. In addition to descriptive statistics (mean, standard deviation, frequency), independent samples t-test was also used for comparisons. The significance was set at a P value less than 0.05.

Table 1 Comparisons of color Doppler ultrasonography measurements of normal and amblyopic eyes

Artery	Amblyopic eyes (n=20)	Normal eyes (n=16)	P
Ophthalmic artery			
PSV	32.70±11.60	55.01±11.68	0.001
EDV	6.83±1.91	13.99±4.15	0.001
PI	1.78±0.50	1.57±0.47	0.228
RI	0.77±0.08	0.72±0.09	0.120
Central retinal artery			
PSV	16,89±6,63	17,60±8,28	0.778
EDV	4.56±2.29	4.93±2.55	0.654
PI	1.35±0.34	1.31±0.24	0.641
RI	0.72±0.07	0.70±0.07	0.393
Posterior ciliary artery			
PSV	25.53±11.66	25.04±13.96	0.909
EDV	7.38±4.88	7.97±3.81	0.698
PI	1.23±0.29	1,09±0,33	0.192
RI	0.70±0.08	0.63±0.14	0.101

Data are presented as mean±SD. PSV: peak systolic velocity; EDV: end-diastolic velocity; PI: pulsatility index; RI: resistivity index.

RESULTS

Of 18 patients included, 10 were female and 8 were male. The mean age of the patients was 9.47±1.79 years (range, 7-15 years). Sixteen normal eyes had significantly better best-corrected visual acuity when compared to the eyes with amblyopia (0.92±0.25 *vs* 0.24±0.11, P=0.001). However, normal eyes and amblyopic eyes had similar axial length [(22.82±0.76) mm *vs* (22.55±0.73) mm, respectively, P=0.286] and spherical equivalent [(2.84±1.46) D *vs* (3.34±1.34) D, respectively, P=0.299] measurements.

Comparisons of color Doppler ultrasonography measurements of normal eyes and amblyopic eyes are shown in Table 1. Amblyopic eyes had significantly lower peak systolic velocity (32.70±11.60 *vs* 55.01±11.68, P=0.001) and end-diastolic velocity (6.83±1.91 vs. 13.99±4.15, P=0.001) in ophthalmic artery, but similar pulsatility and resistivity indexes for this artery. On the other hand, normal eyes and amblyopic eyes did not differ with regard to any of the color Doppler parameters of central retinal artery and posterior ciliary artery.

DISCUSSION

Our results showed reduced PSV and EDV for ophthalmic artery (OA) in amblyopic eyes, suggesting a decrease in the arterial perfusion. A single previous study has shown no significant changes in retrobulbar blood flow parameters measured by CDU in amblyopic and fellow eyes. However this study included adult amblyopic patients, but our study included only pediatric amblyopic eyes[19].

While OA is the major blood supply to ocular structures[16], the two most important blood vessels supplying the intraorbital part of the optic nerve are the central retinal artery (CRA)

and posterior ciliary arteries (PCAs). CRA originates from the ophthalmic artery (OA) and enters the optic nerve approximately 7.5mm posterior to the ocular bulb. PCAs are also supplied from the blood flow of OA and divide into multiple branches that supply the pial arteries. These arteries form a pial network adhering to the optic sheath, which also contributes to the blood supply of the optic nerve[20]. PCAs are the only vessels that supply the prelaminar and laminar parts of optic nerve. Thus, anterior part of the optic nerve receives its blood supply from PCAs, while retina is supplied by CRA and PCAs. These suggest that the assessment of PCA and CRA may provide valuable information regarding the blood supply to the optic nerve and retina. OA measurements are reproducible, but PCAs exhibit a greater variability due to difficulties associated with their imaging[13,21]. Presence of decreased blood velocity in only OA-EDV and OA-PSV might be explained based on autoregulation in retinal circulation to compensate for the changes in CRA and PCA since retinal circulation is provided through an autoregulatory mechanism under the influence of local factors. Probably blood flow undergoes a re-regulation under the effect of local mediators, thus securing the adequate blood flow in CRA and PCA despite the reduced OA flow. At this point, it is worth remembering that blood flow velocity does not directly correlate with the volume of blood flow[22].

Amblyopia is a developmental disorder characterized by the uni- or bi-laterally decreased visual acuity without any organic abnormality of the globe or visual pathways[23]. While most of the deficit is thought to arise from the impairment of normal cortical development, changes have been observed in the lateral geniculate nucleus of humans following visual deprivation amblyopia during the neonatal period[2,3]. Furthermore, abnormalities of the afferent visual system have also been observed. While previous studies have shown little evidence of retinal involvement in amblyopia[4,5], changes in retina, optic disc, retinal nerve fiber thickness, and optic disc anatomy have been reported in amblyopic patients, though with no clear consensus on for example the anatomical changes of the optic nerve or nerve fiber thickness of the optic nerve. Also the differences observed between amblyopic and control eyes have failed to reach statistical significance in the majority of these studies[23-25], although some have found decreased retinal nerve fiber layer thickness (RNFLT) in eyes with anisometropic amblyopia[26].

Baddini-Caramelli *et al*[27] used a scanning laser polarimeter in patients with unilateral amblyopia and suggested that the RNFL may be thicker in amblyopic eyes. Similarly, Yen *et al*[26] reported significantly decreased RNFLT in amblyopic eyes that was explained on the basis of an effect of amblyopia on the process of postnatal reduction of ganglion cells.

Aberrations in the size of optic disc in patients with amblyopia have also been reported[10,11,28-31]. Duranoglu *et al*[28], in their topographic study of the optic nerve head, found significantly lower rim volume of the cup area in amblyopia patients with strabismus and anisometropia. Lempert showed that the rim areas and disc areas of amblyopic eyes were smaller than those of fellow eyes or normal control eyes[11,29-32]. The same author reported optic nerve abnormality of optic nerve photographs in 45% of 205 amblyopic eyes[10] and suggested that this condition can be referred to as a 'functional amblyopia' due to the reduction in the size of optic nerves in amblyopic subjects. Liberek[33] found differences in arborisation patterns of retinal vessels in amblyopia patients. Therefore, it may be plausible to state that the body of evidence is inconclusive regarding the presence or characteristics of retinal involvement in amblyopia.

On the other hand, there have been several studies suggesting that a number of anatomical and histopathologic changes might occur in amblyopic eyes. As Lempert suggested, in suspicious cases of amblyopia, quantitative assessments can have an important role in the diagnostic work-up. Amblyopia is a curable disease if treated early. However, treatment-refractory amblyopia despite maximum patient compliance is a frequently encountered problem in ophthalmology practices and currently there are no clear-cut indicators enabling clinicians to differentiate between organic, anatomic, or physiological causes of the treatment refractoriness.

CDU is a reliable technique for the evaluation orbital and ocular blood flow[13], which is affected by a number of factors including age, systemic hypertension, systemic or topical drug use, and smoking[34]. Examination of the blood flow parameters in amblyopic eyes may give some clues regarding the pathophysiology of this condition. In some previous studies, the relationship between CDU findings and certain ocular parameters was examined. For example, Dimitrova and Kato [13] found a positive correlation between lens power and the blood velocities in the CRA and PCA, while a negative correlation between the axial length, blood flow velocity and the RI of the CRA was detected. In the present study, amblyopic eyes exhibited decreased ocular artery blood flow with no detectable changes in the other arteries.

Resistivity and pulsatility indexes are calculated from velocity measurements using various formulae; therefore, they do not depend on the angle of Doppler probe. RI provides quantitative measurement of flow patterns for evaluation and comparison of vascular bed resistance. It is an indirect measurement of resistance to blood flow, which can be used to evaluate vascular damage in ophthalmologic diseases[35]. Harris *et al*[36] found a positive correlation between resistivity index and age. Almeida-Freitas *et al*[37] found high resistivity index values among patients with heart failure; and in the

study by Harris-Yitzhak *et al*[38], resistivity index was high in postmenopausal women. High resistivity index has also been reported in association with optic neuritis and primary open angle glaucoma[39].

However, in this study, decreased PSV and EDV of the ophthalmic artery were not accompanied by an increased resistivity index. These findings may be attributed to the low number of patients, but may also indicate that the decrease in PSV and EDV of the OA are not related to an increase in arterial resistivity. The absence of a significant difference in axial lenght and refractive error between amblyopic and fellow eyes rules out a secondary effect in retrobulbar flow due to this characteristics and therefore imply the results as regarding solely amblyopia.

One of the major limitations of our study was the small sample size due to inclusion of only those patients who were able to comply with the study procedures. Another limitation is the absence of a significant difference in axial length measurements and absence of differences in terms of refractive error between the two groups despite presence of anisometropia. In the present study, all participants had moderate amblyopia, which might partly explain the absence of significant difference in CRA and PCA measurements. We believe that inclusion of patients with lower visual acuity could give rise to more substantial differences.

It might be argued that the decreased blood flow in amblyopic eyes is a result rather than a cause. Probably this shares a common pathophysiological background with some other findings such as the thinner peripapillary RNLF, decreased thickness of the neuroretinal rim, and changes in VEP and ERG. Retinal ganglion loss, apoptosis, and anatomic abnormalities may ultimately result in a decreased ocular blood flow due to the anatomic and physiologic changes in amblyopic eyes.

In conclusion, our results show a significant change in ophthalmic artery velocity as measured by CDU in amblyopic eyes. This might be viewed as an evidence for a structural change in anterior visual pathways of amblyopic eyes. Although amblyopia is a functional visual loss, it might also be associated with anatomic, histopathologic and -as suggested by our findings - physiologic changes in the anterior visual pathways.

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