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Effect of hypertension and candesartan on the blood flow velocity of the extraocular vessels in hypertensive patients

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Abstract

Objective: To define alterations in the blood flow velocities of the ophthalmic artery (OA), central retinal artery (CRA), posterior ciliary artery (PCA) in essential hypertension and to evaluate the effect of a new antihypertensive drug, candesartan which is an angiotensin II receptor antagonist, on the blood flow velocity in hypertensive patients. *Methods:* Blood flow velocity and resistive index (RI) of the OA, CRA, and PCA were measured in 22 hypertensive patients off medication and 15 controls by color Doppler imaging. After treatment with candesartan, blood flow velocity and RI were again measured in the hypertensive patients. *Results:* In controls ($n = 15$), the OA had a mean peak systolic flow velocity (PSFV) of 48.1 ± 2.6 cm/s, mean end diastolic flow velocity (EDFV) of 16 ± 1.0 cm/s, and RI of 0.65 ± 0.01; the CRA had a PSFV of 20.8 ± 0.4 cm/s, EDFV of 9.4 ± 0.3 cm/s, and RI of 0.54 ± 0.01; the PCA had a PSFV of 23.6 ± 0.7 cm/s, EDFV of 11.2 ± 0.3 cm/s, and RI of 0.52 ± 0.01. There was a significant decrease in the PSFV and EDFV of the vessels in the medication free hypertensive patients when compared with controls ($P < 0.05$). In the hypertensive patients off medication ($n = 22$), the OA had a PSFV of 29.4 ± 1.2 cm/s, EDFV of 10.4 ± 0.5 cm/s, and RI of 0.71 ± 0.01; the CRA had a PSFV of 15.1 ± 0.6 cm/s, EDFV of 5.4 ± 0.3 cm/s, and RI of 0.65 ± 0.02; the PCA had a PSFV of 17.2 ± 0.6 cm/s, EDFV of 6.7 ± 0.3 cm/s, and RI of 0.61 ± 0.01. RI measured in the OA, CRA, PCA were significantly increased in the hypertensive patients when compared with the controls ($P < 0.05$). In hypertensive patients after medication ($n = 22$), OA had a PSFV of 38.3 ± 2.5 cm/s, EDFV of 12.3 ± 0.7 cm/s, and RI of 0.68 ± 0.01; CRA had a PSFV of 19.2 ± 0.5 cm/s, EDFV of 7.8 ± 0.3 cm/s, and RI of 0.59 ± 0.01; PCA had a PSFV of 20.8 ± 0.8 cm/s, EDFV of 9.2 ± 0.4 cm/s, and RI of 0.56 ± 0.01. There was a significant increase in the blood flow velocities of the OA, CRA, PCA ($P < 0.05$) and significant decrease in the RI values in the treated hypertensive patients when compared with the controls ($P < 0.05$). But blood flow velocities and RI values did not reach the control level. *Conclusion:* The increase in the RI values and the decrease in the blood flow velocity of extraocular vessels in the hypertensive patients are thought to be caused by increased peripheral resistance in the vessels of the eye and orbit. Although, it increases blood flow velocity and decreases RI significantly, candesartan treatment in the hypertensive patients cannot increase blood flow velocity and decrease RI to the control level.

Keywords: Essential hypertension; Blood flow velocity; Doppler; Extraocular vessels; Candesartan

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1. Introduction

High blood pressure is a common problem especially in industrialized countries. One-half of the populations above 60 years of age in most industrialized country are hypertensive (Territo, 1999). For years it was believed that progressive higher blood pressure was a physiological consequence but it is clear that elevated blood pressure leads to mortality and morbidity, and requires treatment. Color Doppler imaging (CDI) permits the noninvasive assessment of blood flow velocities in the extraocular blood vessels. Essential hypertension is frequently encountered in medicine and many patients with ocular problems also have essential hypertension. Understanding the general effect of essential hypertension is needed to appreciate its possible effect on the diseased eye. The aim of this study was to define alterations in the blood flow velocities of extraocular vessels in essential hypertension comparing with a normal control group. Patients with essential hypertension were treated with oral medication to reduce systemic blood pressure. We wanted to evaluate effect of a new antihypertensive drug, candesartan that is an angiotensin II type 1 receptor blocker, on the orbital blood flow velocities in hypertensive patients. To define effect of candesartan on the blood flow velocity of the orbital vessels is important because it could reduce the effect of essential hypertension on the retina and optic nerve head.

2. Material and methods

Twenty-three patients (13 men, 10 women), age ranged from 52 to 65 years (mean age of 58) diagnosed as essential hypertension in a cardiology outpatient unit were selected for the study. All the patients were evaluated in an ophthalmology outpatient unit if there was any visual problems. Twenty-two patients had visual acuity of 20/20 or better, normal intraocular pressure, and normal fundus examination. Because of high intraocular pressure, one patient was discharged from the study. Fifteen age matched control group, age ranged from 50 to 62 year (mean age of 56) were examined. The controls had no hypertension, heart disease, diabetes or any other systemic disease and were non-smokers and not using any medication. The control group was also evaluated by the same ophthalmologist and had normal visual acuity, intraocular pressure, and fundus examination. The study was explained to the patients and controls, and all the participants gave written informed consent for all the procedures. The patients with hypertension were asked to suspend their medication for a 10-day washout period. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in both groups. After 10 days washout period, the hypertensive patients were treated with candesartan (AstraZeneca AB, Södertalje, Sweden), orally 16 mg per day for 4 weeks. Systemic blood pressure was measured again in the hypertensive patients after treatment. Transorbital Doppler examinations were performed in the hypertensive patients before the start of medication and at the end of 4 weeks treatment period. Before transorbital Doppler examination, using the same Doppler machine, all the hypertensive patients and controls were evaluated to see if there was any carotid disease that could cause hemodynamic changes in the blood flow velocities. Two of the hypertensive patients had carotid plaques at the carotid bifurcation that involved less than 30% of the lumen of the carotids, which would not cause any hemodynamic changes on the blood flow velocity of the internal carotid artery. Controls had no carotid plaques.

A Hithachi EUB 515 scanner (Tokyo, Japan) was used to determine blood flow measurements. A 7.5 MHz linear transducer was used to measure the peak systolic flow velocities (PSFV), end diastolic flow velocities (EDFV) and resistive index (RI) in the ophthalmic artery (OA), central retinal artery (CRA), and posterior ciliary artery (PCA). Eyes for CDI were selected arbitrarily. The same radiologist examined all the patients and controls to avoid interobserver variability. The patients and control group were examined in the supine position with head tilted at an angle about 30° after 10 min of rest. They were asked to close eyes gently, maintain forward gaze and coupling gel was applied externally on the skin of the closed

eyelid. The transducer was applied to the closed eye without applying any pressure to the eye. Blood flow velocities in the OA were measured at the proximal part of the artery before it crosses the optic nerve. Blood flow velocities in the CRA were measured within the optic nerve 2–3 mm behind the posterior margin of the globe (Fig. 1A and B). Blood flow velocity of the PCA were measured lateral to the optic nerve, between the optic nerve and posterior surface of the eye. When more than one PCA was visualized, blood flow velocity was measured in the largest one. Once the location of arterial blood flow within the OA, CRA, and PCA was determined, fine movements of the probe provided sufficient length of the vessels to give the strongest and most uniform readings of arterial flow. After a velocity waveform was obtained, the PSFV, EDFV, and RI values were calculated by using the automated algorithm of the machine. All measurements in the controls and hypertensive patients before and after treatment were performed at least three times and the average values were used in the analysis. Wall filter setting of 200 Hz and 0.2 mm sampling volume were used.

Student's t-test and paired t-test were used when comparing normal and hypertensive patients, and hypertensive patients before and after treatment, respectively. All statistics were analyzed using SPSS for Windows (SPSS, Inc., Chicago, IL). The results were given as means $\pm$ S.D.

3. Results

Systemic blood pressures of the hypertensive patients before and after treatment compared with the controls were shown in Table 1. Twenty-two hypertensive patients off their oral medication had mean SBP of 158 mmHg (range: 145–175), DBP of 97 mmHg (range: 90–105). The control group had mean SBP of 120 mmHg (range: 100–125), mean DBP of 78 mmHg (range: 65–85). The mean

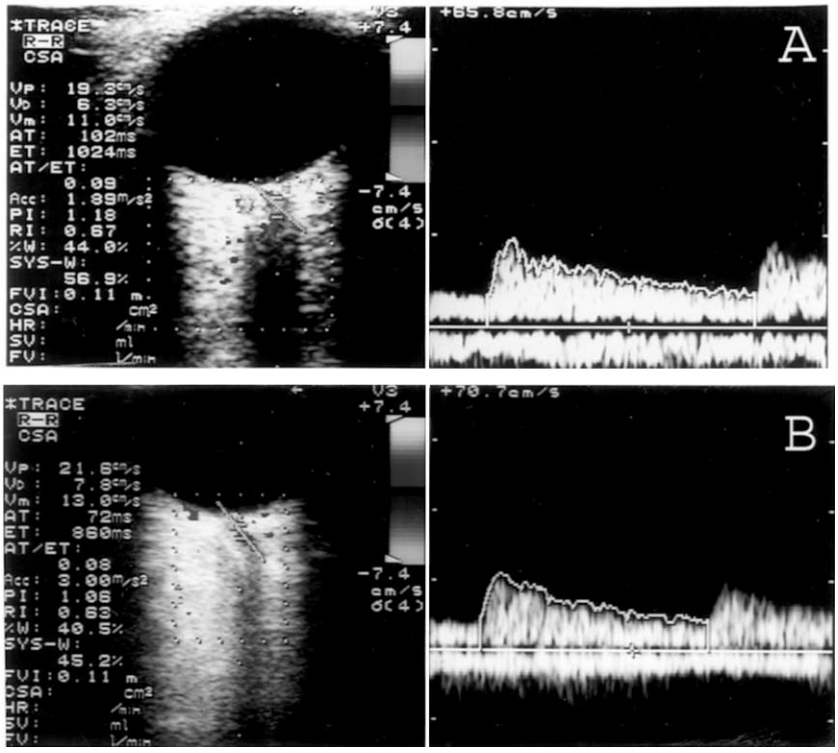

Fig. 1. Blood flow velocity waveform obtained from CRA before (A) and after (B) candesartan treatment in a hypertensive patients.

Table 1
Blood pressure of the hypertensive patients and controls

	Hypertensive patients ($n = 22$)		Controls ($n = 15$)
	Before treatment	After treatment	
Systolic blood pressure (mmHg)	158 (145–175)	128 (110–140)	120 (100–125)
Diastolic blood pressure (mmHg)	97 (90–105)	83 (70–90)	78 (65–85)

SBP and DBP levels in hypertensive patients were significantly higher when compared with those of the controls ($P < 0.05$). Twenty-two hypertensive patients, after 4 weeks of treatment with candesartan had mean SBP of 128 mmHg (range: 110–140) and mean DBP of 83 mmHg (range: 70–90). Decrease in the SBP and DBP in the hypertensive patients before and after treatment was also statistically significant ($P < 0.05$).

Fig. 2 shows mean PSFV, EDFV of the OA, CRA, and PCA in the control group and hypertensive patients before and after treatment with candesartan. In the control group, the PSFV and EDFV of the CRA, PCA, OA were significantly greater than those of the hypertensive patients before treatment ($P < 0.05$). Fig. 3 shows mean RI

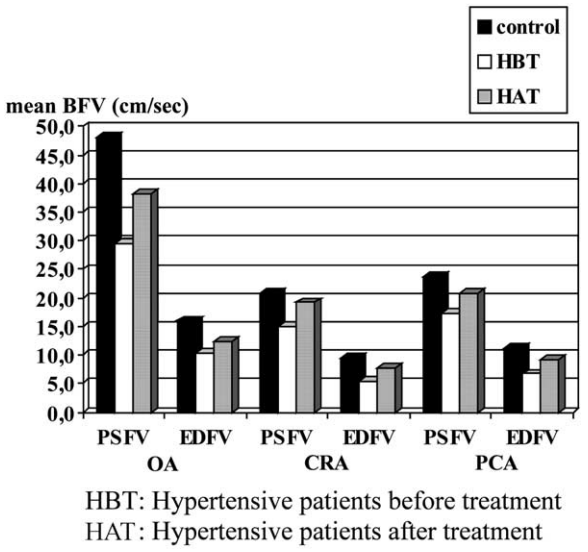

Fig. 2. Graph shows mean PSFV, EDFV of the OA, CRA, and PCA in the control group ($n = 15$), and hypertensive patients before and after treatment ($n = 22$).

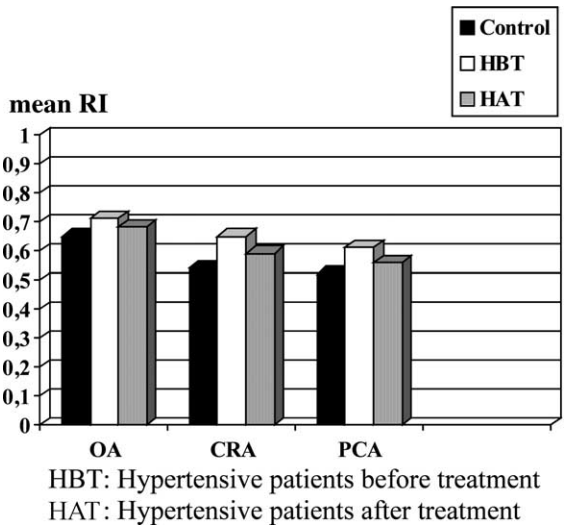

Fig. 3. Graph shows mean RI values of the OA, CRA, and PCA in the control group ($n = 15$), and hypertensive patients before and after treatment ($n = 22$).

values of the OA, CRA, and PCA in the control and hypertensive patients before and after treatment. The RI values of the OA, PCA, and CRA in the hypertensive patients before treatment were significantly greater than the control group ($P < 0.05$). After treatment there was an increase in the PSFV and EDFV of the CRA, PCA, and OA. This increase was statistically significant when compared with pretreatment values ($P < 0.05$). But blood flow velocities were lower than those of control group. After treatment, RI values were significantly decreased when compared with pretreatment RI values ($P < 0.05$). But also RI values remained above the RI values of the control group.

4. Discussion

The CRA supplies the blood flow to the retina and PCA supplies the blood flow to the optic nerve head (Hayreh, 1989). Therefore, measurement of the blood flow velocities of the PCA and CRA with CDI could be a good indicator of the capillary blood flow of the optic nerve head and retina. The measurement of blood flow velocity does not directly correlate with the volume of blood flow. Blood flow volume can be measured if the diameter of the vessel is known and equates to the blood flow velocity multiplied by the cross sectional area of the vessel. As the diameters of the extraocular vessels are too small to measure correctly, we cannot calculate blood flow volume.

In the hypertensive patients, the PSFV and EDFV of the CRA, PCA, and OA were significantly reduced ($P < 0.05$) and RI values were significantly increased ($P < 0.05$) when compared with those in normal controls. RI is the expression of vascular impedance or resistance. All the other factors remaining constant, resistance is inversely related to flow rate (Taylor et al., 1990). The decrease in the PSFV and EDFV with an increase in the RI values suggests that blood flow is decreased in the OA, CRA, and PCA in hypertensive patients, because of increased peripheral resistance in the small diameter vessels of the retina and optic nerve head. In essential hypertension, it has been shown that skin blood flow is decreased due to increased peripheral resistance or peripheral vasospasm (Cesarone et al., 1992a,b). Studies in hypertensive rats have shown an increase in vasoconstriction and closure of smaller arterioles after a rise in blood pressure (Prewitt et al., 1982). Loss of capillaries in the perifoveal network and decrease in the capillary blood flow has been shown in the hypertensive patients with fluorescein angiography using laser ophthalmoscopy (Wolf et al., 1994). But fluorescein angiography technique is not simple, includes the infusion of a dye and cannot be easily used to evaluate large number of subjects (Cesarone et al., 1992a,b). Steigerwalt et al. (1998) reported in 10 essential hypertensive patients using Duplex scanning imaging that blood flow velocity in the PCA and CRA were decreased. Instead of measuring RI values, they calculated "diastolic component" to show increased peripheral resistance. In hypertension there are intrinsic changes in the structure of the small vessels. It is shown that the media:lumen ratio of both low-resistance arteries and small arteries is increased due to 'remodeling', i.e. redistribution, which leads to increased peripheral resistance (Heagerty et al., 1993). Our findings also suggest that blood flow velocity of the OA, CRA, and PCA are decreased due to increased peripheral vascular resistance in essential hypertensive patients.

Increased blood flow velocity of the CRA in the patients treated with nifedipine or nimodipine (calcium cannel blocker) has been reported (Belcaro et al., 1989). However, nifedipine may induce ankle edema as a side effect during treatment of hypertension and angina pectoris (Terry, 1982). Trandolapril, an ACE inhibitor, was reported in hypertensive patients that it increases blood flow velocity in the CRA and PCA but although that increase was significant, it was reported that flow velocities remained lower than those of controls (Steigerwalt et al., 1998). Angiotensin converting enzyme is a nonspecific enzyme and ACE inhibitors not only prevent angiotensin II formation but also interferes with the breakdown of bradykinin, which can result in side effects such as dry cough and angioneurotic edema (Douglas, 1985). Candesartan is an angiotensin II type 1 (AT1) receptors antagonist, devoid of agonist activity (Tran et al., 2001). It is a relatively new, effective and well tolerated antihypertensive drug in doses ranging from 4 to 16 mg per day and becoming widely accepted for the treatment of hypertension (Sever, 1997; Elmfeldt et al., 1997). In our study, treatment of hypertensive patients with candesartan significantly increased the PSFV and EDFV, and decreased RI values of the CRA, PCA, and OA. Decrease in the RI values concomitant with an increase in the PSFV and EDFV suggest that blood flow in the CRA, PCA, and OA is increased in the treated hypertensive patients. Many hypertensive patients have ocular problem and treatment of hypertension with candesartan could affect the course of their ocular disease. Although blood flow velocities are increased, and RI values decreased in treated hypertensive patients, increase

in the blood flow velocity and decrease in the RI values did not reach to control level. This may be due to structural changes in the extraocular vessels of essential hypertensive patients.

A limitation of our study was that we measured blood flow velocities but measurement of blood flow velocity does not directly correlate with volume of blood flow. Because the diameter of the extraocular vessels is too small to measure correctly, we cannot calculate blood flow volume. The small number of patients is another limitation of our study.

In conclusion, there is significant decrease in the PSFV and EDFV in the OA, CRA, PCA in the hypertensive patients. The RI of the OA, CRA, and PCA in the hypertensive patients were significantly increased. These findings suggest that blood flow in the extraocular vessels decreased due to increased peripheral resistance in hypertensive patients. Treatment with candesartan significantly increases blood flow velocities of the extraocular vessel and decreases the RI values by decreasing peripheral vascular resistance. New studies with large numbers of patients are needed to determine effect of candesartan on the blood flow velocity of the extraocular vessels.

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