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The Effects of ACE Inhibition on Central Retinal Artery in Diabetes Mellitus

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Abstract: Angiotensin converting enzyme (ACE) inhibitors have been known to inhibit the effects of angiotensin II which increases the vascular resistance. In this study, we studied the acute effects of a single dose of 2.5 mg oral cilazapril, ACE inhibitor on blood flow velocity and vascular resistance parameters of central retinal artery (CRA) by color Doppler ultrasonography in 17 patients with nonproliferative diabetic retinopathy (NPDR) and compared the effects of the drug with a placebo group including 17 patients with nonproliferative diabetic retinopathy. After cilazapril medication, peak systolic blood flow velocity of central retinal artery didn't change, while peak diastolic and mean blood flow velocity increased ($p<0.05$, $p<0.05$). Significant decrease in pulsatility and resistivity indices of the vessel were observed ($p<0.05$, $p<0.05$). Cilazapril decreases the resistance parameters of CRA which nourishes one of the target tissues of diabetic retinopathy.

Key Words: Central retinal artery, diabetes retinopathy, cilazapril, color Doppler imaging.

Introduction

Impaired autoregulation of the retinal vasculature, alteration in retinal blood flow and breakdown of the blood-retinal barrier are the certain physiologic abnormalities that have been identified during the early course of diabetic retinopathy (1).

The investigation of retinal blood flow and its regulation in diabetic retinopathy is of primary importance as it may lead better understanding of pathophysiology of the disease (2). Furthermore, it may help the assesment of different treatment modalities and in the monitorization of the progression (3). Color Doppler ultrasonograpy is a noninvasive and simple method which has recently become available for detecting the localisation of vessels and obtaining the data about blood flow velocities and vascular resistance indices (4).

According to the classical concept, angiotensin I (A I) and angiotensin II (A II) are generated within the circulation by sequential cleavage of liver derived renin substrate. Renin, synthesized in the kidney, cleaves this substrate to form A I. Angiotensin converting enzyme (ACE) converts A I to A II, a potent vasoconstrictor and a stimulant of the release of aldosterone from the adrenal (5). Recent evidence suggests that besides this circulating renin-angiotensin system (RAS), there also exist tissue or local renin-renin-angiotensin systems (5-7). Local angiotensin production may therfore occur indepently of the reaction of circulating renin with circulating renin substrate (5-7).

Studies in bovine eyes showed that both renin and prorenin were present in all segments of the eye (8). Moreover, using the polymerase chain reaction, Wagner et al. were able to show expression of the renin-, renin substrate-, and ACE-genes in human ocular tissue (9). The presence of ACE in the eye has been shown as well, not only in the retina, choroid and ciliary body, but also in aqueous fluid (5,10,11). Taken together, these findins suggest that the eye has its own RAS and that it is activated in eyes affected by diabetic retinopathy (5).

Chronic administration of ACE inhibitors is shown to regress the vascular deterioration especially in hypertensives and to have the ability of increasing blood flow velocities after non-selectively decreasing the vascular resistance in various tissues (12). Among the ACE inhibitors cilazapril is a prodrug being converted to its active form cilazaprilat. It is rapidly absorbed with

peak plasma levels which is reached within one to two hours and continues down for eight hours (7).

In this report, the acute effects of cilazapril on blood flow and vascular resistance parameters of CRA has been studied in patiens with nonproliferative diabetic retinopathy.

Material and Methods

In this study, thirty four patients with type II diabetes mellitus followed for NPDR were included. The hospital ethic committee approved the study. Informed consent was obtained from each subject. The prestudy ocular examination of either eye of the patients was as follows; Snellen's visual acuity measurement, anterior segment examination by slit lamb biomicroscopy, applanation tonometry and fundoscopy by Goldman three mirror contact lens and fundus florescein angiography. The prestudy systemic examination of each patient performed by an internist included medical history, heart rate and blood pressure measurements, urinalysis, blood chemistry studies and complete blood cell counts. After systemic and ocular examinations, patients having systemic or ocular pathology other than diabetes mellitus and taking any medication other than oral hypoglycemic agents were excluded. Thirty-four diabetic patients whose metabolic control was accomplished with diet and oral hypoglycemic agents were randomly assigned to form group I and group II each including 17 subjects. The eyes of the patients with better visual acuity were selected for the study. The physicians performing the blood pressure and color Doppler ultrasonographic measurements were unaware of the patient's assignment.

On the study days, between 9: 00 and 10: 00 AM, the resting average brachial arterial blood pressure of the patients in two groups was calculated by using the blood pressure readings from two arms. Then the patients were put in a supine position and ultrasound conductive gel was applied to the external surface of the eye lids. Care was taken to exert as little transducer pressure as possible on the closed eye lids. An ATL Ultramark 9 Duplex Scanner (Advanced Technical Laboratories-Scientific Medical Systems Co, Bothell. Wash) with a 5 MHz probe was used to display the vessel using vascular mode. To examine central retinal artery (CRA), B mode image of the optic nerve was used as a landmark for the identification of the vessel. The angle between the vessel and the sound beam under this circumstance could be easily kept below 20 degrees. The colors can arbitrarily assigned but in this study flow toward the transducer (artery) depicted as red and away from the transducer (vein) as blue. A Doppler gate of 1.5x1.5 mm was directed toward the vessel. The signal coming from CRA can be easily seperated from the signal coming from central retinal vein because of the directional nature of the Doppler signals and the characteristic waveform differences in spectral analysis. To avoid the inclusion of short ciliary arteries into the central retinal artery sample volume, the tracing of the central retinal artery was evaluated only if flow waveforms coming from CRA and central retinal vein could be recorded simultaneously. A reading was taken only when three consecutive pulse waveforms were obtainable from the artery. After spectral analysis was performed to obtain positive waveform for the arterial flow, peak systolic flow velocity (PS; cm/sec), peak diastolic flow velocity (PD; cm/sec) and mean flow velocity (M; cm/sec) for CRA were determined by averaging the readings from three waveforms. Similarly the pulsatility index (PI) and resistive index (RI) which were the vascular resistance parameters for CRA were calculated by using the formula below;

$$PI=PS-PD/M \qquad RI=PS-PD/PD$$

After performing color Doppler utrasonographic examination for two groups, a single dose of 2.5 mg oral cilazapril was administered for the patients in group I and the patients in group II received placebo (vehicle). Three hours after medications, systemic blood pressure measurement and color Doppler ultrasonographic examination were reperformed in both groups.

The results are expressed as the mean value. Differences taking place after medications in systemic blood pressure, blood flow velocity and vascular resistance parameters of CRA are compared with baseline values in both groups by Wilcoxon rank-sum test. Results were considered statistically significant at $p<0.05$.

Results

Group I included 8 males and 9 females while there were 10 males and 7 females in group II. Group I and group II were similar with respect to age, diabetic duration and fasting blood glucose level (Table 1). Group I and II each included 17 eyes with NPDR.

The systolic and diastolic blood pressure values of the two groups before and after cilazapril or placebo administrations are shown in Table 2. After cilazapril medication the mean systolic and diastolic blood pressures of the patients in group I showed significant decrease

Table 1. Features of patients in group I and II.

	Group (mean±SD)	
	Group II (n=17)	Group I (n=17)
Age (year)	53.6±12.4	54.2±13.3
Diabetic duration (year)	9.3±8.2	9.2±8.4
Fasting blood glucose level (mg/dl)	125.7±20.3	129.2±17.4

Group I: cilazapril, Group II: placebo

Table 2. Systolic and diastolic blood pressures and flow velocity and resistance parameters of central retinal artery of the patients

	Group (mean±SD)			
	Group II (n=17)		Group I (n=17)	
Parameters	Baseline	3th hour	Baseline	3th hour
Systolic blood pressure (mmHg)	127.3±14.4	125.1±13.2	126.6±13.8	117.4±12.5*
Diastolic blood pressure (mmHg)	83.4±8.6	82.8±8.4	85.5±7.3	78.6±6.4*
Peak systolic flow velocity (cm/sec)	7.9±1.9	7.9±1.9	7.9±2.0	8.0±1.8
Peak diastolic flow velocity (cm/sec)	2.7±0.5	2.7±0.5	2.7±0.7	3.2±0.7*
Mean flow velocity (cm/sec)	4.5±1.3	4.5±1.1	4.6±1.1	5.0±1.1*
Pulsatility Index	1.1±0.2	1.1±0.2	1.1±0.2	1.0 ±0.2*
Resistive Index	0.7±0.1	0.7±0.1	0.7±0.1	0.6±0.0*

Group I: cilazapril, Group II: placebo, * $p<0.05$, 3th hour vs. baseline

compared with group II ($p<0.05$). We observed no significant change in systemic blood pressure after placebo administration in group II.

Blood flow velocity and vascular resistance parameters of CRA before and after cilazapril or placebo administrations are shown in Table 2. We didn't observe any significant change in blood flow velocity and resistance parameters of CRA after placebo administration in group II. After cilazapril medication PS value of CRA showed insignificant increase while PD and M values were significantly higher compared with placebo ($p<0.05$ and $p<0.05$, respectively). PI and RI values of CRA showed significant decrease after cilazapril administration in group I compared with group II ($p<0.05$ and $p<0.05$, respectively).

Discussion

Diabetic retinopathy is the most frequent cause of blindness among the world. However, the pathophysiology involved in the development of visual damage in this disease is totally unknown.

The function of an ocular RAS is not yet clear. A II may regulate intraocular vascular tone and aqueous fluid hemodynamics (13,14). In addition, A II has trophic and mitogenic actions on vascular smooth muscle and other cells (15,16). Danser et al. found prorenin to be increased in vitreus fluid from patients with proliferative diabetic retinopathy, suggesting that an activated intraocular RAS may be involved in the development of this type of retinopathy (17). Its activation in the eyes of diabetic subjects with proliferative retinopathy may suggest that A II is involved in the development of neovascularization, as has been shown by other (18).

There is no doubt that ACE inhibitors have multiple sites of action on the circulation. The chief and the best understood mechanism is inhibition of the RAS not only of the circulating components but very probably also those found in the various tissues, particularly the vascular bed (7). It has been suggested that ACE inhibitor therapy decrease arterial calcium contents (19). Cilazapril as an ACE inhibitor has also been suggested to reduce the vascular resistance in every organ of hypertensive rats besides its regional blood flow increasing effect in most of the organs (12, 20).

We observed insignificant increase in peak systolic flow velocity while mean and peak diastolic flow velocities of CRA were found significantly higher at the third hour of cilazapril administration compared with the placebo group. Furthermore, there was a significant decrease in the vascular resistance parameters of CRA in cilazapril group compared with the placebo group. These changes have been thought to be consistent with the significant increase in peak diastolic flow velocity.

The decrease in the vascular resistance of CRA after cilazapril administration in group I patients compared with group II made us think that whether the blood flow in the retina might be affected from the decrease taking place in resistance parameters of CRA. However, the possible changes taking place in the circulation of retinal tissue couldn't be measured by color Doppler ultrasonography.

Strocchi et al. reported that enalapril, one of the ACE inhibitors, improved regional hemodynamics in patients with Type II diabetes mellitus (21). We observed similar effects on CRA in diabetic subjects. This improvement in vascular resistance of CRA might be related with the systemic hemodynamic effect of cilazapril as confirmed by the decreasing systemic arterial blood pressure after medication, but indeed it might be related with the inhibition of possibly existing local RAS in or around CRA.

In conclusion; significant decrease caused by an ACE inhibitor in the vascular resistance of the main artery, namely the central retinal artery which nourishes the target tissue of diabetes retinopathy might cause an improvement in the retinal oxygenation as well, therefore further investigation should be warranted to ascertain the possible effect of an ACE inhibitor on retinal tissue circulation (4,5).

References

1. Gobel W, Lieb WE, Ho A, Sergott RC, Farhoumand R, Grehn F. Color Doppler imaging: a new technique to assess orbital blood flow in patients with diabetic retinopathy. Invest Ophthalmol Vis Sci 36:864-70,1995.
2. Steigerwalt RD Jr, Belcaro G, Cesarone MR, Laurora G, De Santis M, Incandela L, Christopoulos V. Doppler ultrasonography of the central retinal artery in patients with diabetes and vascular disease treated with topical timolol. Eye 9:495-501,1995.
3. Grunwald JE, Riva CE, Sinclair SH, Brucker AJ, Petrig BL. Laser Doppler velocimetry study of retinal circulation in diabetes mellitus. Arch Ophthalmol 104:991-6,1986.
4. Güven D, Özdemir H, Hasanreisoğlu B. Hemodynamic alterations in diabetic retinopathy. Ophthalmol 103:1245-9,1996.
5. Danser AHJ, Derkx FHM, Admiraal PJ, Deinum J, de Jong PTVM, Schalekamp MADH. Angiotensin levels in the eye. Invest Ophthalmol Vis Sci 35:1008-18,1994.
6. Mac Fadyen RJ, Lees KR, Reid JL. Tissue and plasma angiotensin converting enzyme and the response to ACE inhibitor drugs. Br J Clin Pharmacol 31:1-3,1991.
7. Opie LH: Angiotensin Converting Enzyme Inhibitors: scientific basis for clinical use. Wiley-Liss, New York, 1992.
8. Deinum J, Derkx FHM, Danser AHJ, Schalekamp MADH. Identification and quantification of renin and prorenin in the bovine eye. Endocrinology 126:1673-82,1990.

9. Wagner J, Danser AHJ, Derkx FHM, de Jong PTVM, Paul M, Mullins JJ, Schalekamp MADH, Ganten D. Demonstration of renin-, angitensinogen- and conveting enzyme-mRNA expression in the human eye. Evidence for an intraocular renin-angiotensin system. Br J Ophthalmol 80:159-63,1996.

10. Ferrari-Dileo G, Ryan JW, Rockwood EJ, Davis EB, Anderson DR. Angiotensin-conveting enzyme in bovine, feline and human ocular tissues. Invest Ophthalmol Vis Sci 29:876-81,1988.

11. Weinreb RN, Sandman R, Ryder MI, Friberg TR. Angiotensin-converting enzyme activity in human aqueous humor. Arch Ophthalmol 103:34-6,1985.

12. Clozel JP, Hefti F, Fischli W. Effects of chronic therapy with cilazapril on regional blood flows in conscious spontaneously hypertensive rats. J Hypertens 5:443-5,1987.

13. Giardina WJ, Kleinert HD, Ebert DM, Wismer CT, Chekal MA, Stein HH. Intraocular pressure lowering effects of the renin inhibitor ABBOTT-64662 diacetate in animals. J Ocul Pharmacol 6:75-84,1990.

14. Constad WH, Fiore P, Samson C, Cinotti AA. Use of an angiotensin-converting enzyme inhibitor in ocular hypertension and primary open-angle glaucoma. Am J Ophthalmol 105:674-7,1988.

15. Schelling P, Fischer H, Ganten D. Angiotensin and cell growth: a link to cardiıvascular hypertrophy ? J Hypertens 9:3-15,1991.

16. Paquet JI, Baudoin-Legros M, Meyer P. Angiotensin II-induced proliferation of aortic myocytes in spontaneously hypertensive rats. J Hypertens 8:565-72,1990.

17. Danser AHJ, van den Dorpel MA, Deinum J, Derkx FHM, Franken AA, Peperkamp E, de Jong PTVM, Schalekamp MADH. Renin, prorenin and immunoreactive renin in vitreus fluid from eyes with and without diabetic retinopathy. J Clin Endocrinol Metab 68:160-7,1989.

18. Fernandez LA, Twickler J, Mead A. Neovascularization produced by angiotensin II. J Lab Med 105:141-5,1985.

19. Sada T, Koike H, Ikeda M. Cytosolic-free calcium of aorta in hypertensive rats. Chronic inhibition of angiotensine converting enzyme. Hypertension 16:24-51,1990.

20. Himmelmann A, Hansson L, Hansson BG, Hedstrand H, Skogstrom K, Ohrvik J, Furangen A. ACE inhibition preserves renal function better than beta-blockade in the treatment of essential hypertension. Blood Press 4:85-90,1995.

21. Strocchi E, Malini PL, Ciavarella A, Ricci C, Valtancoli G, Mustacchio A, Vannini P, Ambrosioni E. The effect of ACE inhibition on peripheral hemodynamics in normotensive and hypertensive patients with Type II diabetes. J Clin Pharmacol 31:140-3,1991.