Effect of Angiotensin-Converting Enzyme Inhibition With Perindopril and β-Blockade With Atenolol on Retinal Blood Flow in Hypertensive Diabetic Subjects

V. Patel, S.M.B. Rassam, H.C. Chen, M. Jones, and E.M. Kohner

The effect of angiotensin-converting enzyme (ACE) inhibitors on the diabetic retinal circulation has not been studied previously. The aim of this study was to evaluate the effect of ACE inhibition and beta-blockade on retinal blood flow (RBF) in a group of 45 hypertensive diabetic subjects using a randomized double-blind trial over a period of 12 months. Laser Doppler velocimetry and computed image analysis were used to measure RBF. The changes in blood pressure over 12 months were comparable (perindopril [PE]: systolic [SBP] 152.1 ± 3.3 and diastolic [DBP] 97.2 ± 1.7 mm Hg to SBP 136.8 ± 3.4 and DBP 85.8 ± 2.1; atenolol: SBP 158.9 ± 5.1 and DBP 97.5 ± 1.6 mm Hg to SBP 137.9 ± 3.4 and DBP 85.1 ± 1.6; $P = .607$, mean ± SEM). RBF decreased from 17.19 ± 2.21 μL · min^{-1} to 14.18 ± 1.50 μL · min^{-1} in the PE group (n = 15, $P = .208$) while it increased with atenolol from 15.80 ± 1.24 μL · min^{-1} to 16.99 ± 1.18 μL · min^{-1} (n = 17, $P = .399$). The comparison of percentage changes in RBF (PE −7.16% ± 11.49%; atenolol, +15.31% ± 9.51%) reached statistical significance ($P < .05$). There was an increase in RBF in 33.3% of subjects receiving PE and in 70.6% of those receiving atenolol. Similar trends were found for retinal conductance. There were no significant changes in the parameters of retinal vascular permeability. Albuminuria decreased to a greater degree with PE, but did not reach significance (PE, 112.1 ± 39.5 mg/24 h to 88.6 ± 30.5 mg/24 h; atenolol, 87.3 ± 51.7 mg/24 h to 82.1 ± 47.7 mg/24 h). This suggests that ACE inhibition therapy may promote a hemodynamic milieu in the hypertensive diabetic retinal circulation that serves to protect against the progression of diabetic retinopathy, whereas beta-blockade has the opposite effect.

DIABETES MELLITUS is accompanied by both microvascular and macrovascular complications. The former include diabetic retinopathy, nephropathy (DN), and neuropathy, all of which have been shown in type I diabetic patients to be retarded by excellent glycemic control.[1] Early studies showed that effective treatment of hypertension reduces the rate of progression to more serious forms of DN, with later studies strongly suggesting a specific effect of angiotensin-converting enzyme (ACE) inhibitors over other agents such as β-blockers and calcium-channel antagonists.[2-4] The specific effect of ACE inhibition was a reduction in microalbuminuria and delayed progression to end-stage renal failure. A local renin-angiotensin system (RAS) has been demonstrated at the level of the retinal vasculature.[5] Increased retinal blood flow (RBF) has been associated with deteriorating diabetic retinopathy and is thought to play a significant role in the progression of relatively mild diabetic retinopathy to sight-threatening forms.[6,7] The ACE inhibitor perindopril (PE), studied extensively, has been found to have vascular remodeling properties.[8,9] The aim of the present study was to evaluate the effect of ACE inhibition with PE and beta-blockade with atenolol on RBF and retinal vascular permeability in diabetic patients with moderate hypertension. The study was a randomized double-blind trial over 12 months.

SUBJECTS AND METHODS

Study Subjects

Diabetic patients were recruited from the diabetic retinopathy clinic at the Royal Postgraduate Medical School at Hammersmith Hospital. Inclusion criteria were as follows: age 18 to 65 years; if female, of non–child bearing potential; clinically stable diabetes with duration of diabetes of at least 1 year; type I or type II diabetes; essential arterial hypertension; visual acuity of 6/12 or better in the studied eye; and normal intraocular pressure. Essential arterial hypertension was defined by a supine diastolic blood pressure ([DBP] Korotkoff phase V) in the range of 90 to 110 mm Hg, or in the range of 86 to 110 in patients aged less than 40 years. All subjects were either newly diagnosed as hypertensives or had known hypertension, with their normal antihypertensive treatment stopped for 2 to 4 weeks. Blood pressure readings were taken on two occasions at least 2 weeks apart. All blood pressure readings in the study were taken with a Takeda automated digital sphygmomanometer (A & D, Tokyo, Japan). Exclusion criteria were as follows: diabetic retinopathy requiring laser photocoagulation, contraindication to treatment with beta-blockade, serum creatinine greater than 150 μmol/L, history of myocardial infarction or cerebrovascular accident over the 3 months prior to entry into the study, or evidence of severe hepatic disease. To be included in the study, all patients had to provide written consent after a full and thorough explanation, including a patient information leaflet. The study protocol was approved in writing by the local Hospital Ethics Committee.

Study Protocol

Patients on antihypertensive medication had their treatment discontinued for at least 2 weeks before the first study visit (V_0). At the V_0 visit, the following were recorded and performed: full medical history: details of diabetes, duration of diabetes, complications and details of past medical history, and current drug treatment; clinical examination; standard 12-lead electrocardiogram; hematological and biochemical profile, total cholesterol and triglycerides, ACE activity after at least 3 hours' fasting, and blood glucose and hemoglobin A_1; 24-hour urine collection for albuminuria and the albumin to creatinine ratio; and ophthalmological assessment: best corrected Snellen visual acuity, anterior segment examination, seven-field stereo fundus photography, fluorescein angiography, and vitreous fluorophotometry. RBF was measured using laser Doppler velocimetry in the "study eye" only.

The subject was then issued treatment consisting of either PE 4 mg daily before breakfast or atenolol 50 mg daily before breakfast. The process was prerandomized. Identical capsules of PE and atenolol were used. The subject returned 1 month later (visit V_1) for measurement of blood pressure and a partial biochemical screen consisting of serum creatinine, sodium, potassium, and urea. Side effects, if any, were

From the Diabetes Centre, George Eliot Hospital, Nuneaton, Warwickshire, UK.

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Address reprint requests to V. Patel, MD, Consultant Physician Diabetes & Endocrinology, University of Warwick, Diabetes Centre, George Eliot Hospital, Nuneaton, Warwickshire CV10 7DJ United Kingdom.

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recorded. Compliance was determined from the capsule count. If the blood pressure was controlled to below the inclusion criteria for the study, then the subject was next evaluated 3 months later (V_4). If the blood pressure was not controlled to below the study admission criteria, the treatment was doubled (to PE 8 mg daily or atenolol 100 mg daily) with review 1 month later. At this stage, if the blood pressure was still uncontrolled, then bendrofluazide 2.5 mg daily or nifedipine 10 mg slow-release twice daily was added. Subjects were reviewed monthly until blood pressure control was achieved using nifedipine 20 mg slow-release twice daily if necessary. At the V_4 visit, a protocol similar to the V_0 visit was used. If the blood pressure was controlled, then the subject was reviewed at the V_8 visit, when clinical examination was performed together with an assessment of subject compliance to the medication. The final visit was 12 months after inclusion into the study (V_{12}), when a protocol identical to the V_0 visit was used.

Withdrawal Criteria

Subjects were withdrawn from the study if compliance was less than 75% at the main visits (V_4, V_8, and V_{12}) or if there were serious or troublesome side effects from the antihypertensive treatment. Another withdrawal criterion was the failure to control hypertension to less than 95 mm Hg DBP despite triple therapy.

RBF

The bidirectional Laser Doppler Velocimeter (Oculix, Philadelphia, PA) was used to determine RBF in retinal veins. Full details of these techniques have been published previously.[6,10] This instrument consists of a low-power helium-neon laser (wavelength, 632.8 nm) that can be focused onto the central laminae of the red blood cell column vessel via the illumination path of a retinal camera (TRC-JE; Topcon, Osaka, Japan). The laser light is frequency-shifted by the moving red blood cells and is reflected back through the camera onto two photomultipliers. The velocity of the red blood cells is a function of the Doppler shift (Vmax). The point of measurement of RBF was a superior retinal vein, and the same point in the vessel was used in subsequent determinations in the same patient. This single measure is a reliable measure of RBF, as the arterial retinal circulation drains totally into the venous retinal circulation. The diameter of the retinal vessel was determined from three photographic negatives taken at the time of laser Doppler velocimetry using computed image analysis.[6]

RBF Calculations

Volumetric RBF was calculated from the mean red blood cell velocity (Vmean = Vmax/1.6) and the retinal vessel diameter (D) using the formula, RBF = (π $D^2/4$ × Vmean). Retinal perfusion pressure (PP) was calculated by subtracting the intraocular pressure from two thirds of the mean arterial pressure. The conductance of the circulation is used as a measure of its ability to allow blood flow at a given PP (RBF/PP). Autoregulation is defined as the ability to keep blood flow constant under conditions of varying PP. With a decrease in PP, in an ideally autoregulating system, an increase in conductance in direct proportion to the decrease in PP is expected (expected % increase in conductance). As autoregulation is impaired in hypertensive diabetic patients, if after controlling hypertension[11] the observed increase in conductance (observed % change in conductance) is greater than the expected increase, then autoregulation can be considered to be further impaired. The corollary of this is that an observed increase in conductance less than expected can be considered to show improved autoregulation.

Retinal Photography and Fluorescein Angiography

All patients had ETDRS (Early Treatment of Diabetic Retinopathy Study) seven-field color photography[12] and fluorescein angiography at the V_0, V_4, and V_{12} visits. The color photographic slides were graded by two trained graders independently, with judication from a third senior grader if there was greater than a five-point variation between the two initial graders on the ETDRS scale (10, no diabetic retinopathy; 20 to 55, background diabetic retinopathy; and >61, proliferative diabetic retinopathy). Fluorescein angiographic microaneurysm counts were determined as previously described.[13] All of the measurements, calculations, and gradings were undertaken with the researchers blinded to the treatment modality of the subject.

Statistical Analysis

To compare the two groups at baseline (V_0) for quantitative parameters, Student's *t* test was used unless there was nonhomogeneity of the variances, in which case Yates's correction was also applied. For qualitative parameters, the χ^2 test was used alone or with Fisher's correction if any of the cell values were less than 5. Comparisons within each group over time were analyzed using Student's paired *t* test. Between-group comparisons were made using Student's *t* test when there was normal distribution or the Wilcoxon Mann-Whitney test when the parameter was not normally distributed. The statistical programs used were Oxstat II (Microsoft, United Kingdom; 1985) and SAS version 6.07 (SAS, United Kingdom). Power calculations confirmed that at least 10 subjects would need to be recruited into each limb of the trial to detect a statistically significant difference in RBF of 20% with a power of 95% at the 5% significance level. Results are the mean ± SEM unless stated otherwise. A probability (*P*) value of .05 or less was considered statistically significant.

RESULTS

Clinical Characteristics

Baseline clinical characteristics of the two groups were well matched and are shown in Table 1. There was no significant difference between the two groups with respect to weight, height, absence of ankle jerks, past medical history, and participation in a previous study protocol. Of the total of 45

Table 1. Clinical Characteristics of Study Subjects

Characteristic	PE	Atenolol	*P*
No. of subjects	22	23	
Sex (male:female)	20:2	20:3	.99
Age (yr)	46.8 ± 9.7	46.3 ± 11.3	.873
Race (White:Asian:Black:Other)	10:9:1:2	17:4:2:0	
Duration of DM (yr)	12.5 ± 9.8	10.5 ± 6.7	.089
Type I:type 2*	9:13	12:11	.449
Family history of DM (%)	50.0	21.3	.048
DM treatment (diet:oral:insulin)	1:10:12	0:10:13	.489
Hb_{A1} (%)	8.93 ± 2.42	8.23 ± 2.10	.308
History of known hypertension (%)	40.9	56.5	
Duration of hypertension (yr)	4.1 ± 3.7	4.7 ± 6.0	.687
Previous antihypertensive treatment (diuretic:β-blocker:Ca antagonist: ACE-inhibitor)	1:3:3:4	4:6:1:7	.295
Nephropathy†	0	0	.99
Diabetic retinopathy (NR:BDR)	1:22	1:22	.99
Duration of diabetic retinopathy (yr)	2.6 ± 2.8	3.3 ± 3.5	.499
Nonsmoker:smoker	21:1	22:1	.99
Cholesterol ≥6.2 mmol/L	7	9	
Ischemic ECG (%)	36.4	39.1	.848
Alcohol consumption (yes:no)	13:9	17:6	.292

NOTE. Data are the mean ± SD.

Abbreviations: DM, diabetes mellitus; NR, no retinopathy; BDR, background diabetic retinopathy.

*Epidemiological criteria.[29]

†Creatinine >200 μmol/L ± proteinuria >300 mg/24 h.

Table 2. Clinical Hemodynamic Parameters (mm Hg)

Parameter	PE		Atenolol		P†
	V_0	V_{12}	V_0	V_{12}	
SBP	152.1 ± 13.6	136.8 ± 14.0*	158.9 ± 23.5	137.9 ± 15.4*	.509
DBP	97.2 ± 7.1	85.8 ± 8.7*	97.5 ± 7.2	85.1 ± 7.4*	.576
MAP	115.5 ± 8.3	102.8 ± 10.0*	118.0 ± 11.9	102.7 ± 9.3*	.607
PP	59.6 ± 5.8	52.4 ± 6.5*	61.4 ± 8.8	51.8 ± 6.3*	.692
HR (bpm)	83.8 ± 14.1	81.2 ± 10.3	78.1 ± 13.6	64.5 ± 11.8*	.007

NOTE. Blood pressure was measured in the supine position. Results are the mean ± SD.

Abbreviations: MAP, mean arterial blood pressure; PP, retinal perfusion pressure; HR, heart rate.

*Evolution within each treatment group based on a Wilcoxon Mann-Whitney test for paired data (all $P < .05$).

†Comparison of the 2 treatment variations based on a Wilcoxon Mann-Whitney test.

subjects included at V_0, seven subjects were subsequently withdrawn. Data are presented on the remaining 38 subjects unless indicated otherwise. In the PE group, three subjects withdrew because of a troublesome cough, one because of impotence that the patient felt was due to the study treatment, and another because of unwillingness to complete the study protocol. In the atenolol group, two subjects were withdrawn because of noncompliance. The only significant differences between the two groups were an increased number of Indo-Asian (subjects originating from the Indian subcontinent by birth or birthplace of their parents) subjects and a greater proportion of subjects with a family history of diabetes in the PE group. The two factors may be related.

Clinical Hemodynamic Parameters

In both the PE and atenolol groups, there was a significant decrease in SBP, DBP, mean arterial blood pressure, and the calculated retinal perfusion pressure (Table 2). In a single subject, the intraocular pressure reading was missing at the 12-month visit; it was therefore assumed to be the mean of the initial value and the other available follow-up value.

Photographic Grading and Fluorescein Angiography

There was no significant change in visual acuity within each treatment group (PE, $P = .414$; atenolol, $P = .982$) or between treatment groups ($P = .872$). Visual acuity remained within 6/12 or better in 17 of 18 subjects in the PE and 21 of 21 subjects in the atenolol group. One subject's vision deteriorated from 6/9 to 6/36 in the PE group because of cataract formation (in the deteriorating eye, there was no evidence of diabetic retinopathy). Retinopathy deteriorated in only four subjects, of whom three were in the atenolol group. All cases of progression of diabetic retinopathy were within the background diabetic grade only (range, 4 to 11 points). One patient was excluded from the analysis, as it became apparent that the patient had minor new vessels on the disc that were missed by direct ophthalmoscopy at the screening visit. There was no significant change in microaneurysm counts (PE, 12.5 ± 3.7 at V_0 to 13.3 ± 3.5 at V_{12}, $P = .1078$, atenolol, 17.6 ± 3.8 at V_0 to 20.7 ± 4.6, $P = .5946$) between treatments ($P = .344$).

RBF Data

There was an increase in RBF with atenolol and a decrease with PE (PE, $P = .208$; atenolol, $P = .399$). There was a statistically significant difference between the two treatments when comparing the percentage increase in RBF, which is a more important parameter in terms of autoregulation ($P \leq .05$). Only 33.3% of the PE group but 70.6% of the atenolol group had an increase in RBF over the 12 months of the study ($P = .035$). A similar pattern was observed for the conductance data (Table 3).

RBF changes were not confounded by whether the subjects were treated with additional nifedipine or diuretic. ANOVA revealed no differences between subjects treated or not with these agents both between the PE and atenolol groups and within each treatment group. There is evidence that nifedipine has no effect on RBF.

Of all the subjects studied with RBF and grading data, four had a deterioration in the ETDRS score and all had an increase in RBF (16.92% ± 5.12%). In 21 subjects with either an improvement in the ETDRS grading (n = 5) or the same ETDRS grading (n = 16), the change in RBF was smaller (1.45% ± 9.79%, $P = .182$). There was no correlation between baseline RBF or the percent change in RBF and change in ETDRS grading scores ($r = .103$, $P = .623$).

Hematological and Biochemical Parameters

There was a decrease in albuminuria in both treatment groups, but this did not reach significance (PE, 75% of the group, $P = .608$; atenolol, 61.5% of the group, $P = .626$). All data are summarized in Table 4.

Table 3. RBF Data (Mean ± SEM)

Parameter	PE ($n = 15$)	Atenolol ($n = 17$)	P
RBF ($\mu L \cdot min^{-1}$)			
V_0	17.19 ± 2.21	15.80 ± 1.24	.154
V_{12}	14.18 ± 1.50	16.99 ± 1.18	
Change in RBF V_0 to V_{12} ($\mu L \cdot min^{-1}$)	−3.01 ± 2.28	1.19 ± 1.37	NS
Percentage change in RBF (%)	−7.16 ± 11.49	15.31 ± 9.51	<.05
Percentage with increased RBF (%)	33.3	70.6	.035
Conductance ($\mu L \cdot min^{-1} \cdot mm\ Hg^{-1}$)			
V_0	0.29 ± 0.04	0.25 ± 0.02	NS
V_{12}	0.28 ± 0.03	0.34 ± 0.03	NS
Expected % change in conductance	13.54 ± 4.22	22.69 ± 4.54	NS
Observed % change in conductance	7.05 ± 15.43	39.67 ± 10.44	<.05
Percentage with increased conductance	33.3	76.5	.036

Table 4. Evolution of Hematological and Biochemical Parameters

Parameter (mean ± SD)	PE	Atenolol	*P*
Microalbuminuria (mg/24 h)			
V_0	112.1 ± 39.5	87.3 ± 51.7	.695
V_{12}	88.6 ± 30.5	82.1 ± 47.7	
Albumin/creatinine ratio (mg · μmol)			
V_0	8.82 ± 3.19	6.46 ± 2.72	.895
V_{12}	7.48 ± 2.99	5.66 ± 3.30	
HbA_1 (%)			
V_0	8.93 ± 2.42	8.23 ± 2.10	.555
V_{12}	9.05 ± 2.37	8.60 ± 2.58	
Blood glucose (mmol/L)			
V_0	10.8 ± 4.6	11.3 ± 5.5	.434
V_{12}	9.9 ± 5.7	9.0 ± 4.4	
Total cholesterol (mmol/L)			
V_0	5.98 ± 1.23	5.83 ± 1.13	.940
V_{12}	5.68 ± 1.01	5.46 ± 1.32	
Hemoglobin (g/dL)			
V_0	15.44 ± 1.18	15.04 ± 1.29	.970
V_{12}	15.21 ± 1.25	14.78 ± 1.28	
Hematocrit (%)			
V_0	45.9 ± 4.0	45.0 ± 4.1	.705
V_{12}	44.7 ± 3.4	44.1 ± 3.8	
Erythrocytes ($\times 10^{12}$/L)			
V_0	5.23 ± 0.46	5.01 ± 0.44	.906
V_{12}	5.06 ± 0.47	4.89 ± 0.47	
Platelets ($\times 10^9$/L)			
V_0	258.7 ± 73.5	261.5 ± 36.9	.7932
V_{12}	247.1 ± 53.3	269.8 ± 64.4	

DISCUSSION

The present study was a 1-year randomized double-blind trial comparing the effects of ACE inhibition with PE and beta-blockade with atenolol on RBF in diabetic patients with a moderate degree of hypertension. Blood pressure was reduced to an equal extent in both groups but with differing consequences for RBF.

The observation in this report that ACE inhibitors may actually decrease RBF in comparison to treatment with beta-blockade is novel and of possible therapeutic consequence. In keeping with current theories applied to the pathogenesis of microvascular complications,[14-16] hyperperfusion and increased perfusion pressure in the retinal circulation have been proposed to be of central importance in the pathogenesis of diabetic retinopathy.[6,7] The hypothesis has recently been tested prospectively in a study of pregnant diabetic subjects, where an initial and continuing increase in RBF throughout the pregnancy was associated with progression of retinopathy.[17] In the group of pregnant diabetic subjects without progression of retinopathy, there was no significant change in RBF. In the present study, basal RBF was increased in comparison to previous data from our unit on nondiabetic hypertensive subjects (13.42 ± 0.90 μL/min), while it is comparable to the diabetic hypertensive subject data in the same study (16.54 ± 1.29 μL/min).[11] This suggests a failure of the diabetic retinal circulation to autoregulate to an increase in blood pressure. In the PE-treated group, RBF at 12 months was comparable to RBF in the treated nondiabetic hypertensive group in the above-mentioned study (12.89 ± 1.03 *v* 14.18 ± 1.50 μL/min), while there was an increase in RBF in the atenolol-treated group. The present study demonstrates a trend toward an increase in conductance with atenolol above the expected values, while there is a decrease in conductance with PE. This effect of atenolol suggests that it impairs vascular autoregulation, but PE may improve it.

The most important and well-characterized effect of ACE inhibitors is a reduction of blood pressure. This is mediated via inhibition of ACE, thereby reducing the activity of angiotensin II (AII), a potent octapeptide vasoconstrictor. ACE inhibitors inhibit the breakdown of the vasodilator bradykinin and increase the formation of nitric oxide (NO) and prostacyclin.[18] All of these factors potentiate vasodilatation with the additional antiplatelet action of NO and prostacyclin. ACE activity is particularly marked in the endothelium of the pulmonary vasculature, but now all of the components of the RAS have been described in many other vascular beds including the coronary, brain, renal, and testicular.[19,20] In diabetic subjects with retinopathy, plasma renin activity is elevated in comparison to both nondiabetic control subjects and diabetic subjects without retinopathy.[21,22] In a prospective study, Luetscher et al[18] found that elevated plasma prorenin levels predicted progression to microalbuminuria and retinopathy in a group of 196 type I diabetes patients. Specific AII receptors on human retinal vessels have been demonstrated.[5] A possible relationship between the impairment of the RAS and the pathogenesis of diabetic retinopathy was proposed by Kohner.[14] The role of AII in neovascularization remains unsubstantiated, but experimental evidence using the rabbit corneal pocket model have shown this substance to be a potent stimulator of neovascularization.[23] The RAS may be particularly important in the retinal circulation, as adrenergic innervation is lacking and therefore the most important components of blood flow regulation would be the RAS and the intrinsic myotonicity of retinal vessels. The vascular effects of ACE inhibitors, particularly PE, have been studied in detail. PE has also been shown to remodel the abnormal hypertensive vascular media to lumen ratio toward normal, improving vessel compliance and blood flow regulatory ability.[8,9,24] Another effect of ACE inhibitors is to increase capillary density at the tissue level, which may be particularly important, as there is rarefaction of the human retinal circulation in hypertension. The improved capillary-level hemodynamics would serve to reduce the ischemic drive resulting in retinal vascular hyperperfusion.

The use of β-blockers in the treatment of hypertension in diabetes is currently losing favor with the evidence of the benefit of ACE inhibitors cited herein. However, it must be kept in mind that β-blockers have been shown to improve survival after acute myocardial infarction in comparison to placebo.[25] The benefit of β-blockers in the diabetic population after acute myocardial infarction is greater than in the nondiabetic population.

In conclusion, this study provides further evidence for the "vascular protection" potential that ACE inhibitors were predicted to confer.[26] The recently reported TREND Study (Trial on Reversing Endothelial Dysfunction) has demonstrated that another lipid-soluble ACE inhibitor, quinapril, is able to improve endothelial vasomotor dysfunction in patients with coronary artery disease.[27] The EUCLID (Eurodiab controlled trial of lisinopril in insulin-dependent diabetes) study has demonstrated

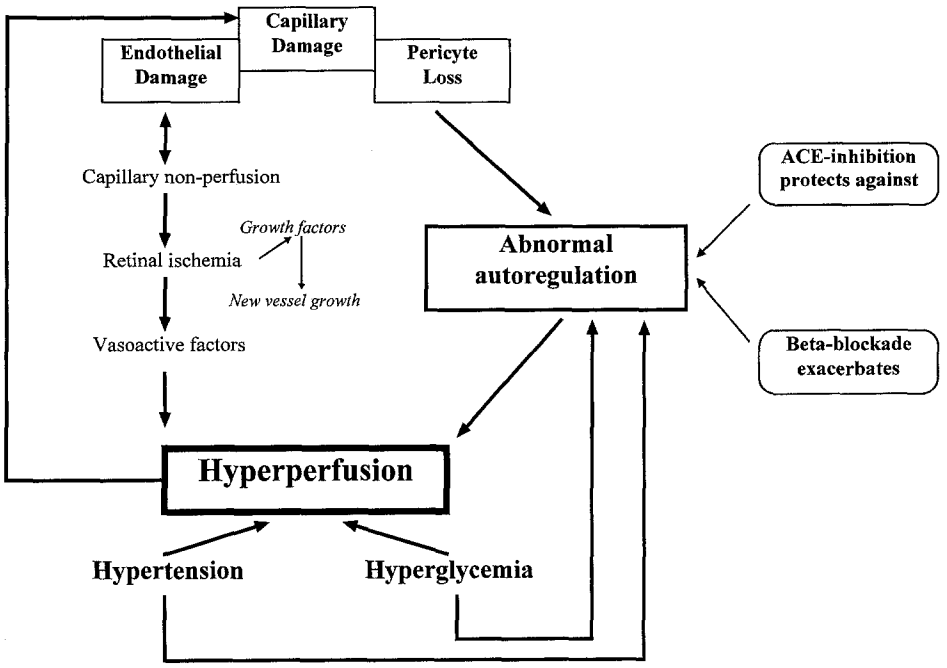

Fig 1. Hemodynamic model of the pathogenesis of diabetic retinopathy: effect of ACE inhibition and β-blockade.

an improvement in diabetic retinopathy in type I subjects with normotension using lisinopril.[28] ACE inhibition with PE improves autoregulation in the retinal circulation in type I and type II hypertensive subjects, whereas beta-blockade with atenolol has the opposite effect. The hemodynamic model for the pathogenesis of diabetic retinopathy can be expanded to accommodate the data presented in this study (Fig 1). Further and larger studies on the effect of ACE inhibitors on microvascular circulation in diabetes are required to substantiate these findings.

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