

## Effects of Pentoxifylline on Choroidal Blood Flow in Nonproliferative Diabetic Retinopathy

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### ABSTRACT

**Objective:** Diminished blood flow plays an important role in the progression of diabetic retinopathy. Since increased blood viscosity is a contributing factor to hypoperfusion, it was of interest to determine whether therapy intended to decrease blood viscosity and induce vasodilation could increase blood flow in patients with diabetic retinopathy.

**Methodology:** Ten patients, 4 with nonproliferative diabetic retinopathy and 6 age-matched, nondiabetic controls, were studied by a noninvasive system to index choroidal blood flow. Pentoxifylline was administered daily at an oral dose of 400 mg tid in the diabetic patients for nine months.

**Results:** The control group had pulse amplitude =  $2.87 \pm 0.67$  mm Hg with pulsatile choroidal blood flow =  $714 \pm 196$   $\mu$ L/minute. Reproducibility studies in the control group (6 patients measured on three separate occasions) demonstrated an intraclass correlation coefficient of reliability,  $r=0.83$ . In the diabetic patients, pulsatile flow =  $276 \pm 68$   $\mu$ L/minute, 61% lower than the age-matched nondiabetic subjects ( $P=0.003$ ). After nine months of pentoxifylline therapy the diabetic patients had an increase in pulsatile choroidal blood flow to  $469 \pm 152$   $\mu$ L/minute ( $P < 0.002$ ).

**Conclusions:** Pentoxifylline therapy brought blood flow levels in the diabetic patients closer to those of the nondiabetic age-matched control population so that following therapy there was no statistically significant difference between the two groups although the former were still lower. The potential efficacy of pentoxifylline in improving ocular blood flow in patients with diabetic retinopathy should be tested in a large controlled clinical trial.

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Supported by a grant from Hoechst-Roussel Pharmaceuticals, Inc.

No author has proprietary interest in the drug or instrument companies whose products were used in this research.

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### Introduction

In diabetes, diminished ocular blood flow is believed to contribute to progressive diabetic retinopathy.<sup>1,2</sup> Abnormalities in the rheology of various blood elements are thought to contribute to poor circulation in diabetes via increased blood viscosity.<sup>3,4</sup> In the eye, the microcirculation is particularly susceptible to such rheologic changes.<sup>5,6</sup> Thus, it is reasonable to postulate that therapy to decrease blood viscosity would increase ocular blood flow and that this could benefit patients with diabetic retinopathy. Something similar to this was attempted with aspirin by the ETDRS Research Study Group, and although blood flow was not specifically evaluated, no effects on clinical retinopathy were noted.<sup>7</sup>

Pentoxifylline is a methylxanthine derivative that alters leukocytes and platelets<sup>8,9</sup> and also has a vasodilator effect. This agent has been found to improve blood flow in peripheral vascular disease.<sup>10</sup> Clinical trials<sup>11,12</sup> have shown that wound healing in diabetic patients is improved by pentoxifylline therapy, and this is believed to result from increased microcirculatory perfusion.

This pilot study was undertaken to determine whether pentoxifylline therapy in patients with diabetic retinopathy is associated with changes in ocular blood flow. The system employed to measure blood flow provides a noninvasive index of choroidal blood flow. This index has previously been shown to be diminished in diabetic retinopathy in proportion to the severity of disease.<sup>13</sup>

### Materials and Methods

Four women ( $35.5 \pm 12.3$  years old) with type I diabetes ( $15 \pm 6.3$  years' duration; glycated hemoglobin =  $11.9 \pm 2.8\%$  at study entry) and nonproliferative diabetic retinopathy (ETDRS grades 20-40, as established by masked evaluation of stereo fundus photographs at the Fundus Photograph Reading Center in Madison, Wisconsin) were treated with pentoxifylline (400 mg orally tid) for nine months. Glycated hemoglobin, hematologic profiles, and stereo fundus photographs of the seven standard fields were obtained every three months.

Noninvasive measurements to index choroidal blood flow were obtained prior to treatment and at three-month intervals with the Langham OBF system.<sup>13</sup> This involved placing the patient in the supine position, anesthetizing the cornea with 0.5% proparacaine, and placing the

Langham pneumatic probe on the cornea. Digitized measurements of the intraocular pressure (IOP) were recorded every thirty msec. Data were continuously recorded for five seconds and analyzed for pulse amplitude (IOP at peak systole - IOP at minimum diastole) and pulsatile blood flow, as previously described.<sup>13</sup>

The results were compared with those from 6 healthy nondiabetic control subjects (1 man, 5 women; mean age = 35.3 years, SD = 9.6 years) who had the same noninvasive blood flow measurements on three separate occasions. Reproducibility of the blood flow measurements in this group was tested by calculating the intraclass correlation coefficient of reliability.<sup>14</sup>

### Results

Table I presents the results of measurements obtained in the group of normal, nondiabetic subjects. Each individual was measured on three separate occasions and the two eyes were averaged into one data point per patient at each time point. The results showed a pulse amplitude =  $2.87 \pm 0.67$  mm Hg and pulsatile blood flow =  $714 \pm 196$   $\mu\text{L}/\text{minute}$ . These results are consistent with previous reports in nondiabetic subjects.<sup>13</sup> The intraclass correlation coefficient of reliability was 0.83 for pulsatile blood flow measurements. This reproducibility is identical to results previously reported by another group using the same technique.<sup>15</sup>

Table II presents the results in the patients with diabetic retinopathy. The two eyes of each subject were averaged into one data point for each time point. During the study there were no significant changes in glycated hemoglobin, systemic blood pressure (Table II), platelet count, partial thromboplastin time, and fibrinogen levels. Retinopathy levels (ETDRS classification of masked stereo fundus photographs performed in Madison, Wisconsin) were unchanged at three, six, and nine months from study entry. Table II demonstrates that pulsatile choroidal blood flow at study entry was  $276 \pm 68$   $\mu\text{L}/\text{minute}$ , 61% below that of the age-matched nondiabetic subjects ( $P=0.003$ ). This index of blood flow increased to  $299 \pm 111$   $\mu\text{L}/\text{minute}$  after three months, to  $403 \pm 169$   $\mu\text{L}/\text{minute}$  after six months, and to  $469 \pm 152$   $\mu\text{L}/\text{minute}$  after nine months of daily pentoxifylline therapy. This 70% increase in pulsatile blood flow at nine months was significant at  $P < 0.002$  (Student's *t* test) in comparison with study entry. Furthermore, the

**Table I**  
*Measurements Obtained in the Group of Normal, Nondiabetic Subjects*

Subject	Age (Years)	BP (mm Hg)			PA (mm Hg)			CBF ( $\mu$ L/Minute)		
		1	2	3	1	2	3	1	2	3
1	38	112/80	116/ 78	116/80	2.78	2.77	2.56	708	583	634
2	52	138/78	168/102	140/85	2.48	2.82	3.19	624	662	628
3	36	120/80	120/ 76	120/78	4.11	3.44	3.37	851	925	730
4	28	102/78	102/ 68	100/68	1.54	1.68	1.81	423	456	424
5	21	114/80	116/ 76	120/82	3.64	3.53	2.36	847	670	667
6	37	100/76	128/ 82	120/72	3.87	2.83	2.99	986	1168	877
Mean	35.3					2.87			714	
SD	9.551					0.67			196	

PA=pulse amplitude, CBF=pulsatile choroidal blood flow, BP=brachial artery blood pressure.

\*=mean of all 3 sets of measurements.

**Table II**  
*Measurements Obtained in the Patients with Diabetic Retinopathy*

Pt	Age (Years)	BP (mm Hg)				PA (mm Hg)				CBF ( $\mu$ L/Minute)			
		0	3 (Months)	6	9	0	3 (Months)	6	9	0	3 (Months)	6	9
1	54	140/80	120/70	128/70	130/72	1.6	1.4	2.2	2	302	271	614	445
2	26	100/60	100/60	118/64	106/60	1.4	0.9	0.9	0.8	197	486	150	232
3	23	100/70	110/70	120/70	100/70	2.3	1.2	2.1	1.8	375	191	371	576
4	39	100/60	110/70	104/62	98/76	1.3	1.5	1.6	2	231	248	480	626
Med										267	260	423	511
Avg	35.5					1.6	1.2	1.7	1.6	276	299	403	469
SD	12.3					0.4	0.2	0.5	0.5	68	111	169	152
										*			*

\* P < 0.002.

BP=brachial artery pressure, PA=pulse amplitude, CBF=pulsatile choroidal blood flow.

blood flow levels in the diabetic patients at nine months approached those of the nondiabetic subjects. Indeed, at nine months there was no statistically significant difference between the measurements in the two groups ( $P=0.08$ ), although the former were still lower.

#### Discussion

This study found that in this laboratory the Langham system for indexing ocular blood flow has good reproducibility, with an intraclass correlation coefficient of reliability of 0.83, confirming the findings of another group using the same techniques.<sup>15</sup> The results in the control subjects confirmed previous findings for pulse amplitude and pulsatile choroidal blood flow in normal subjects.<sup>13</sup>

The results in the group of diabetic patients showed a 61% diminution in blood flow as indexed by this measure of choroidal pulsatility during the cardiac cycle, confirming previous reports.<sup>13</sup> During a nine-month course of daily pentoxifylline therapy, pulsatile choroidal blood flow increased at each three-month interval. At nine months there was a 70% increase in pulsatile blood flow, a difference from baseline that was highly significant. Indeed, blood flow levels at this point approached those seen in the control group. There were no differences in systemic blood pressure, level of glycemic control, partial thromboplastin time, platelet count, and fibrinogen levels that could explain these results. Previous studies<sup>16</sup> have shown that high-dose pentoxifylline can increase macular blood flow in

normal subjects. A subsequent study<sup>17</sup> of 5 diabetic patients treated for three months with pentoxifylline showed macular capillary blood flow increased by as much as 37.8%. These results are consistent with those reported herein. Furthermore, that two different circulatory systems are similarly affected is consistent with the concept that an alteration in the blood rheology as well as some generalized vasodilation of the circulatory systems involved in both tissues can explain these findings.

#### Conclusion

These preliminary results, which are limited by the small number of diabetic subjects and lack of a placebo group, suggest that pentoxifylline therapy may help to increase blood flow in patients with diabetic retinopathy. This postulate should be tested in a randomized, controlled trial. If substantiated, the increase in blood flow associated with pentoxifylline therapy may be useful to help avert progression to preproliferative and proliferative diabetic retinopathy.

#### Acknowledgment

The authors are indebted to Larry Hubbard of the Fundus Photograph Reading Center in Madison, Wisconsin.

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