been demonstrated following adrenalectomy in rats. The present study supports these results. In both cases (rabbit–ciliary process epithelium and rat myocardium), corticosteroids lowered \( k_9 \) for isoproterenol stimulation of the cyclase and were without effect on enzyme activity under basal or maximally stimulating conditions.

Corticosteroid-induced potentiation of ciliary process-\( \beta \)-adrenergic response is a plausible mechanism by which acute pharmacologic doses of glucocorticoids elevate IOP and increase aqueous flow. Further investigation of such a mechanism may clarify the relationship between chronically elevated plasma cortisol levels and elevated IOP as reported by Schwartz and Levene.

**Key words**: adenylate cyclase, cyclic adenosine monophosphate, ciliary process, dexamethasone, corticosterone

**Acknowledgments.** The authors would like to thank James A. Nathanson, MD, PhD, for review of the manuscript and Susan Glick, MS, for editorial assistance.

From the Department of Ophthalmology, New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts. Presented in part at the annual meeting of The Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 2, 1983. Supported by grant EY 05696 from the National Eye Institute of the National Institutes of Health; by training grant EY 07045 from the National Institutes of Health, Bethesda, Maryland; and by Research to Prevent Blindness, Inc., New York, New York. Submitted for publication: July 6, 1984. Reprint requests: Bernard Schwartz, MD, PhD, Department of Ophthalmology, New England Medical Center, 750 Washington Street, Boston, MA 02111.

**References**


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**The Effect of Acute Hyperglycemia on Flow Velocity in the Macular Capillaries**

T. J. Fallon, M. A. Sleighholm, C. Merrick, P. Chahal, and E. M. Kohner

The effect of acute hyperglycemia on retinal blood flow was measured in 12 diabetic patients (mean blood glucose, 276 mg%) on continuous subcutaneous insulin infusion and six nondiabetic controls (mean blood glucose, 198 mg%). Flow velocity measurements in macular capillaries were made using the blue field entoptic method. Retinal artery and vein diameters were measured using red-free fundus photographs. No significant change in flow velocity or retinal vessel diameter was noted in either group. Invest Ophthalmol Vis Sci 28:1027–1030, 1987

Previous work has suggested that retinal blood flow is increased in early diabetes and those with mild retinopathy. However, more recent work using the technique of laser–doppler velocimetry has shown ei-
Three flow velocity measurements at normoglycemia and three measurements at hyperglycemia were made; the mean of each of the three results was then taken. Three flow velocity measurements, in experienced users usually take 2–3 min to complete. Red-free fundus photographs were taken on the fellow eye immediately following the flow velocity measurements. The photographs were used to measure retinal vein and artery diameter in the superior and inferior temporal arcades, between the first and second branches. A computerized, digitizing system was used to measure vessel diameter, the reproducibility of this method being 95%. These results, when taken in conjunction with flow velocity values, indicate whether changes in volume flow have occurred.

Twelve stable diabetic subjects on CSII, with symmetric retinopathy (eight with background retinopathy and four after photocoagulation) were selected for the second part of the study. All subjects were known to be at least 80% reproducible for flow velocity measurements. Each subject was brought for investigation at 0900 hr. Initial mean blood glucose was 108 ± 25.2 mg%. Flow velocity measurements were made in a similar manner to the normal subjects, and red-free photographs were taken of the fellow eye. An oral glucose load of 75 g was then given, and blood glucose was measured every 15 min until it was found to exceed 260 mg% (final mean blood glucose, 276 ± 18.0 mg%). Flow velocity measurements and red-free photographs were repeated. Arterial and venous diameters were measured as before. No measurement of intraocular pressure was made in either group.

### Table 1. Flow velocity values and standard deviation

<table>
<thead>
<tr>
<th>Nondiabetic subject</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.57 ± 0.08</td>
<td>0.80 ± 0.08</td>
</tr>
<tr>
<td>2</td>
<td>1.20 ± 0.19</td>
<td>0.97 ± 0.05</td>
</tr>
<tr>
<td>3</td>
<td>1.09 ± 0.07</td>
<td>0.95 ± 0.02</td>
</tr>
<tr>
<td>4</td>
<td>0.62 ± 0.05</td>
<td>0.81 ± 0.12</td>
</tr>
<tr>
<td>5</td>
<td>0.80 ± 0.12</td>
<td>0.72 ± 0.10</td>
</tr>
<tr>
<td>6</td>
<td>0.68 ± 0.18</td>
<td>0.54 ± 0.05</td>
</tr>
<tr>
<td>Mean flow velocity (±SD)</td>
<td>0.82 ± 0.28</td>
<td>0.80 ± 0.16</td>
</tr>
</tbody>
</table>

Table 2. Flow velocity values and standard deviation

<table>
<thead>
<tr>
<th>Diabetic patient</th>
<th>Normoglycemia 1</th>
<th>Hyperglycemia</th>
<th>Normoglycemia 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.56 ± 0.13</td>
<td>0.43 ± 0.07</td>
<td>0.77 ± 0.09</td>
</tr>
<tr>
<td>B</td>
<td>0.37 ± 0.03</td>
<td>0.45 ± 0.07</td>
<td>0.45 ± 0.01</td>
</tr>
<tr>
<td>C</td>
<td>0.57 ± 0.20</td>
<td>0.48 ± 0.04</td>
<td>0.52 ± 0.07</td>
</tr>
<tr>
<td>D</td>
<td>1.06 ± 0.18</td>
<td>0.93 ± 0.007</td>
<td>0.93 ± 0.01</td>
</tr>
<tr>
<td>E</td>
<td>1.02 ± 0.08</td>
<td>0.96 ± 0.02</td>
<td>0.97 ± 0.03</td>
</tr>
<tr>
<td>F</td>
<td>0.87 ± 0.13</td>
<td>0.93 ± 0.002</td>
<td>0.95 ± 0.05</td>
</tr>
<tr>
<td>G</td>
<td>1.58 ± 0.06</td>
<td>0.85 ± 0.20</td>
<td>0.82 ± 0.23</td>
</tr>
<tr>
<td>H</td>
<td>0.92 ± 0.08</td>
<td>1.05 ± 0.12</td>
<td>0.92 ± 0.05</td>
</tr>
<tr>
<td>J</td>
<td>0.72 ± 0.13</td>
<td>0.72 ± 0.18</td>
<td>0.87 ± 0.03</td>
</tr>
<tr>
<td>K</td>
<td>0.79 ± 0.10</td>
<td>0.67 ± 0.11</td>
<td>0.59 ± 0.20</td>
</tr>
<tr>
<td>L</td>
<td>1.43 ± 0.32</td>
<td>1.58 ± 0.22</td>
<td>1.52 ± 0.11</td>
</tr>
<tr>
<td>Mean flow velocity (±SD)</td>
<td>0.87 ± 0.37</td>
<td>0.79 ± 0.34</td>
<td>0.81 ± 0.30</td>
</tr>
</tbody>
</table>

* Photocoagulated patients.  
Two-way analysis of variance not significant (F = 0.872; P = 0.43).
Both parts of the study were approved by the hospital ethical committee. Significance of results was assessed by paired t-test and two-way analysis of variance.

**Results.** Results in the nondiabetic subjects showed a mean flow velocity (±SD) at normoglycemia of 0.82 ± 0.28 mm/sec and at hyperglycemia 0.80 ± 0.16 mm/sec (Table 1). Mean arterial diameter (±SD) was 128 ± 18.9 μm at normoglycemia and 126 ± 16.9 μm during hyperglycemia. Mean venous diameter (±SD) was 162 ± 10.5 μm at normoglycemia and 158 ± 5.0 μm at hyperglycemia. Mean blood pressure (±SD) increased slightly during the experiment from 112 ± 8.4/79 ± 4.2 to 117 ± 4.6/80 ± 0.0 mm Hg. None of these changes was significant.

Results in the diabetic subjects showed a mean flow velocity (±SD) of 0.87 ± 0.37 mm/sec at normoglycemia, 0.79 ± 0.34 mm/sec at hyperglycemia, and 0.81 ± 0.30 mm/sec once normoglycemia was restored (Table 2). Mean arterial diameter (±SD) was 124 ± 14.2 μm at normoglycemia, 125 ± 15.6 μm at hyperglycemia, and 123 ± 15.0 μm once normoglycemia had been restored. Mean venous diameter (±SD) was 158 ± 22.6 μm at normoglycemia, 153 ± 19.9 μm at hyperglycemia, and 155 ± 21.5 μm once normoglycemia had been restored. Mean blood pressure fell slightly during the experiment from 117 ± 10/79 ± 9.2 to the start to 111 ± 13/76 ± 10 at hyperglycemia to 110 ± 13/78 ± 11 when normoglycemia was resumed. None of these changes was significant. If the group with background retinopathy is separated from the group who had undergone photocoagulation, the results are similar (i.e., no significant change occurs at the three glycemic levels).

**Discussion.** Our results did not show any significant change either in flow velocity or retinal artery-vein diameter, implying that there was no change in volume flow during the study.

In view of the fact that animal work has shown an increase in retinal blood flow secondary to hyperglycemia, our failure to find this in our human model is disappointing and requires explanation.

The highest blood glucose reached in our experiments was 200 mg% in normals and 270 mg% in diabetics, well below the level achieved in animal experiments. Therefore, it is possible that repeat experiments at higher blood glucose levels might detect a change. Nevertheless, the levels achieved in our experiments are in the range of blood glucose values seen for much of the diabetics everyday life, and therefore probably represent a more "realistic" level at which to make measurements.

One problem of the blue-field technique is the fact that the measurements made are subjective. In order to reduce the possibilities of error in the subjective measurement of low velocity, all subjects underwent a screening procedure beforehand in order to assess their ability to match velocity standards. Only those who consistently produced an error of less than 20% were included in the study. If the variability in the flow velocity measurements made during the experiments are analyzed, then the nondiabetic patients vary from the mean reading by an average of 12.5%. The diabetic patients vary from the mean reading by an average of 17.6% (the difference between the two groups is not significant). Overall, this result suggests that the sensitivity of the method may not be much better than 20%. Therefore, if changes of flow of less than 20% did occur in either part of the experiment, it may not have been detected by this method. However, previous animal studies found much larger changes than this one.

Failure to find an increase also may be due to the fact that capillary flow is being measured. Previous hyperglycemia experiments in animals measured blood flow in larger vessels. The blue-field entoptic method measures flow velocity of white cells in macular capillaries, which may not respond to hyperglycemia in the same manner as larger retinal vessels. It is also possible that an autoregulatory response protects the macular circulation, with peripheral retinal vascular changes keeping the macular flow at a "normal" level.

**Key words:** blue-light entoptic phenomenon, diabetes mellitus, hyperglycemia, retinal blood flow, continuous subcutaneous insulin infusion

From the Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London. Supported by the Juvenile Diabetes Foundation, the British Diabetic Association, and the Royal National Institute for the Blind (TJF). Submitted for publication: October 3, 1985. Reprint requests: E. M. Kohner, MD, FRCP, Lower Medical Corridor, Hammersmith Hospital, DuCane Road, London W12 0HS, United Kingdom.

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6. Goldstick TK, Ernest JT, and Engerman RL: Infusion of is-
Tubocurarine Chloride Inhibits Rod Outer Segment Shedding in the Frog Retina

William C. Gordon and M. Elizabeth Keith

The cholinergic postsynaptic neuromuscular blocker, tubocurarine chloride (curare), attenuates the rod shedding response of the frog in a dose-dependent manner. Injections of curare into the dorsal lymph sacs or intraocularly into the vitreous of the eye produced similar results. Intraocular injections of Ringer solution or varying quantities of 0.9% NaCl (the carrier solution of the commercially prepared curare), had no adverse effect on the shedding response. Additionally, injections of curare into one eye had no effect on the rod shedding rate of the other eye. Invest Ophthal mol Vis Sci 28:1030-1032, 1987

Tubocurarine chloride (curare), a known postsynaptic blocker of nicotinic cholinergic sites at the neuromuscular junction, has been used routinely in vision research as a paralyzing agent. Earlier studies of the initiation of the rod shedding event used localized retinal stimuli. Frogs were maintained under constant light conditions for 3–5 days to potentiate the shedding response. Following 1–2 hr of dark adaptation, a spot or bar of light 6 deg in width was projected onto the retina. These stimuli produced either no response or pan retinal shedding. Curare was administered routinely throughout these studies by means of dorsal lymph sac injections of 0.15 ml per frog. At no time was the dose corrected for differences in frog weight. A series of test-injection animals were examined for disc shedding before the local stimulus experiments and found to shed in a normal manner. For this reason, it was thought that curare was a reliable means of immobilizing the animals throughout the duration of those experiments. More recently, studies were initiated to study the effect of wavelength on the shedding trigger mechanism. Once again, curare was employed as the immobilizing agent of choice. When attempts were made to replicate experiments, results became ambiguous or, more often, nonexistent. In frustration, a curare dose series was run, and it was found that curare attenuated the shedding response in a dose-dependent manner. This article describes the results of that study, and cautions that curare may act at sites other than those of the neuromuscular junction.

Materials and Methods. Frogs (Rana pipiens, northern variety) were obtained from J. M. Hazen and Co. (Alberg, VT) and acclimated in large bins for 1–4 weeks before use. Animals were maintained on a lighting cycle of 14L:10D under fluorescent bulbs (Westinghouse, 40-W cool-white) that applied 2.4 × 10^3 ergs/cm^2-sec at frog bin floor level. Animals were kept in a constant light incubator under equivalent fluorescent lighting for 24 hr before experiments. On the morning of an experimental series, frogs were injected, and then allowed to stabilize for 20 min. One hr of darkness was followed by 1 hr of light stimulation, after which the eyes were fixed for morphologic examination.

Frogs were injected with varying amounts of commercially prepared curare (tubocurarine chloride injection U.S.P. [3 mg (20 units)/ml], Squibb). Injections were made with 4.315 mM curare into either the dorsal lymph sacs (DLS) or intraocularly (IO) into the vitreous. The weight of a “standard frog” (34.26 g; 0.82 SEM) was determined by randomly selecting and weighing 25 animals. Subsequent experimental animals were weighed, and the amount of curare necessary for a constant concentration per gram body weight calculated. This standardized the amount of curare administered for each experimental point. DLS frogs received increasing amounts (0.00–0.30 ml/standard frog, or 0.00–8.76 /d/g weight) of 4.315 mM curare. Several controls were used. These consisted of normal uninjected frogs, frogs that were treated exactly as the experimental animals except...