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Pupil Motility in Long-Term Diabetes

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Summary. Employing infrared TV-videopupillography and the "open loop" stimulatory technique the ability of the pupil of the eye to react to rhythmic light stimuli of increasing frequencies was studied in 15 control subjects and 14 long-term juvenile diabetics. The degree of retinopathy varied from nil to proliferative changes. The visual acuity of all subjects studied was at least 6/9 and there were no ophthalmoscopic signs of retinopathy in the area stimulated by the light, thereby ensuring roughly uniform retinal sensitivity. The degree of neuropathy ranged from nil to moderate or severe as judged by vibratory perception threshold and pupil size. The pupil response (gain: fractional response to a unit light stimulus, and phase lag: latency period in number of stimulatory cycles) was the same in the group of diabetics as in the control group. The results show that the pupillary abnormalities of long-term diabetic patients (small size and a loss of spontaneous fluctuations) are probably not due to stiffness of the iris tissues. It is suggested that diabetic autonomic neuropathy predominantly affects the sympathetic innervation to the dilator muscle, the parasympathetic innervation to the sphincter muscle being relatively spared.

Key words: Pupil, pupil motility, iris, light reflex, pupillography, long-term diabetes, autonomic nervous system, diabetic neuropathy, diabetic retinopathy.

The pupil of the eye has been recognized for many years as a unique object for the study of the autonomic nervous system. Several quantitative and reproducible stimuli are easily applied to the pupil and with the technology of to-day its responses can be measured in a reliable and precise way.

The pupil is often abnormal in patients who have had diabetes for many years. The poor reaction to some mydriatics is well known from clinical experience [12]. Recent studies with exact techniques have demonstrated the fact that long-term diabetics have a small pupil [6, 13], with reduced spontaneous variations (pupillary unrest, hippus) [6, 11, 13].

In older literature abnormalities of the light reflex, including Argyll Robertson's phenomenon, are often said to occur in diabetes, and pupillographic studies have been reported suggesting a diminished light reflex [2, 5]. Recent studies have indicated, however, that the light reflex is normal when due regard is taken to the reduced pupil size [7, 13].

Besides abnormalities of the nervous system the long-term diabetic state is characterized by vascular disease. In the iris diabetic microangiopathy is seen by biomicroscopy as the various manifestations of diabetic iridopathy [1, 4, 9, 12]. Histological studies have revealed characteristic changes in the pigment epithelium and the iris muscles in diabetics [3, 16, 17].

The pupillary response to rhythmic light stimuli has been reported to be abnormal [5, 15]. It is possible, therefore, that the above mentioned abnormalities of the iris motility were caused by local structural changes and not by autonomic neuropathy. In order to elucidate this problem we have reexamined the pupillary response to a rhythmic light stimulus using techniques allowing a precise calculation of gain and phase lag.

Patients and Methods

Patients

The study includes 15 normal controls and 14 juvenile, long-term diabetics who were outpatients in the diabetic clinic. Random non-fasting blood glucose levels at the time of the study varied between 128 and 298 mg/100 ml. All subjects were between 30 and 40 years of age. Table 1 shows come clinical data on the patients. The duration of diabetes was 15 years or more, but only 4 patients had had diabetes for more than 25 years. Diabetic retinopathy was

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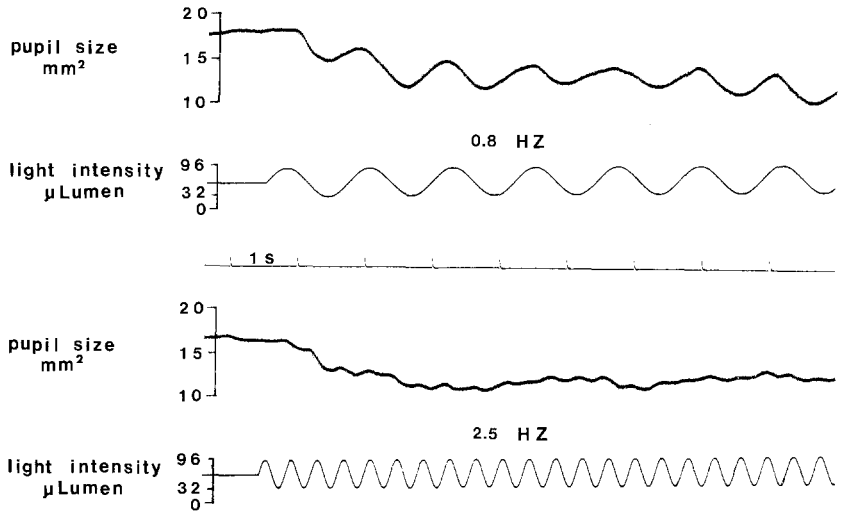


Fig. 1. Rhythmic stimulation of the pupil. Tracings of the penrecorder. Thick lines represent pupil size and thin lines the light intensity varying from 32 to 96 µLumen around the mean intensity of 64 µLumen. From these curves amplitude, pupil size and phase lag are measured after averaging. Gain is the fractional variation in pupil size, i. e. the average response amplitude divided by the mean pupil size when the stimulatory light varies one relative unit. The phase lag is the distance between maximal light and minimal pupil size. This distance is a certain fraction of one full cycle, i. e. a fraction of 360°. For high frequencies the phase lag may be more than one complete cycle

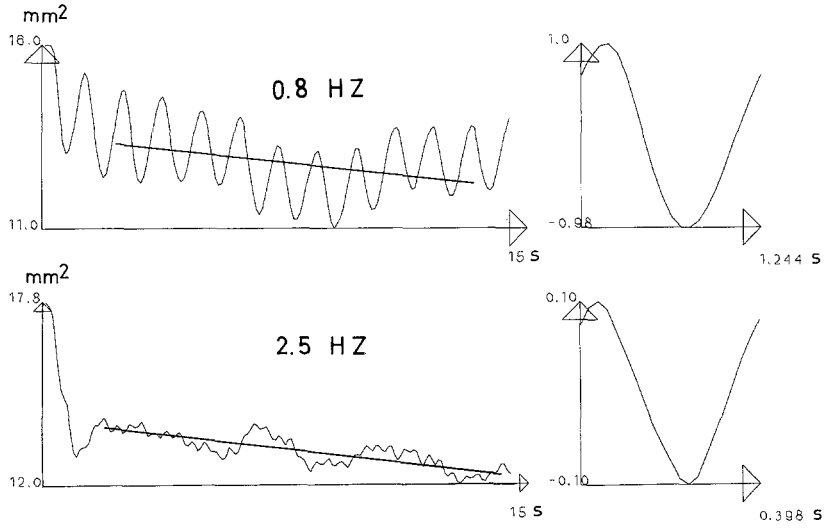


Fig. 2. Computer drawings of the response averaged over 9 and 7 periods, respectively, to a stimulatory frequency of 0.8 Hz (upper left) and 2.5 Hz (lower left) in a normal control person. The regression lines in the period 2 to 15 seconds are shown. The mean responses around the regression lines within one cycle-length are shown to the right. The amplitude is maximal minus minimal value within one cycle length. The two curves seem to correspond in phase. This is due to the fact that in this particular case the lower one is one full cycle behind the upper one (see Fig. 7)

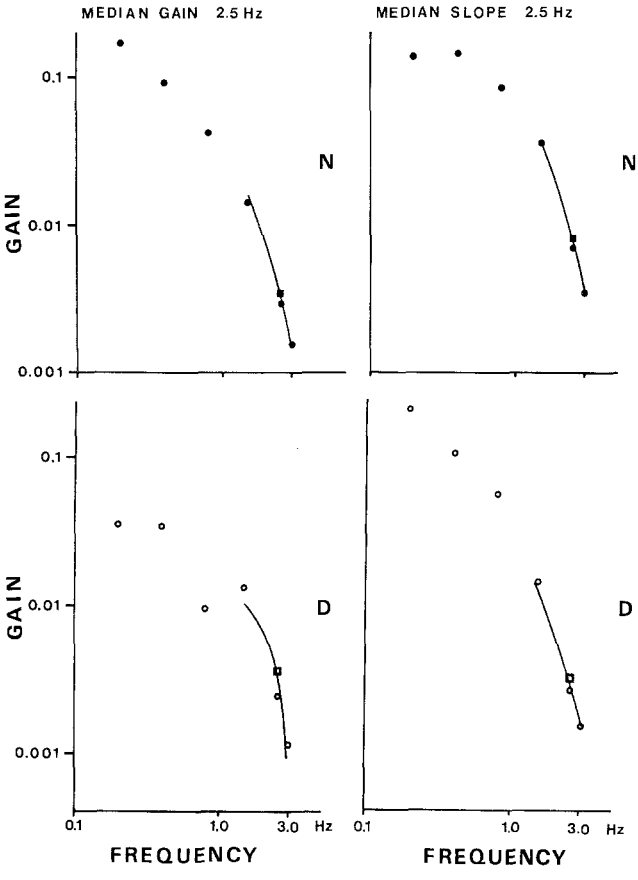
present in 9 patients, but mild vascular proliferation occurred in only one. None of the patients hat rubeosis iridis. In an attempt to ensure retained normal retinal sensitivity it was required that the visual acuity in the eyes stimulated should be at least 6/9 and that there were no signs of retinopathy (except for a few red dots) in the illuminated area. Subjects with myopia or hypermetropia exceeding 1.5 dioptres were excluded. None of the patients were receiving any drugs other than insulin. Informed consent was obtained from all subjects.

Method

Pupillography was performed with an infrared sensitive TV-camera (Iriscorder®, Hamamatsu TV Corp., Hamamatsu, Japan). After analogue-to-digital conversion (Schlumberger, Solarthron® A 210 digital voltmeter) the measurements were treated on a large digital computer (CDC CYBER 173®). The stimulus was provided by a photostimulator, which emits a converging beam of yellow-green light reaching the eye with a diameter of one mm in the plane of the pupil, thereby eliminating variation in light input due to variation in the size of the pupil – the so-called "open loop" approach. The light beam impinges on the retina one papillary diameter above the optic disc and covers an area that is about the size of the optic disc. A more detailed description of the equipment has been published elsewhere [8].

The investigation took place in a completely dark room. In order to keep the subject's eye still and prevent accommodation he was made to fix on a red light spot, placed at an optically infinite distance. The retina was stimulated with a sinusoidally modulated light with a variation of 64 µLumen (from 32 to 96 µLumen) around a mean intensity of 64 µLumen, the frequency range being 0.2 to 3.0 Hz. For each frequency several recordings for periods of 15 seconds were made. Fig. 1 shows an example of the actual recording.

The pupil's ability to react to stimuli of varying frequencies is expressed by means of two parameters: gain and phase-lag. Gain is the fractional variation in pupil size divided by the fractional variation in light intensity, the latter being unity in the present study: 64 µLumen/64 µLumen = 1. In the high frequency range gain decreases. If the pupil is abnormally "stiff" this decrease will be more pronounced.



◀ **Fig. 3.** Gain-frequency diagrams from two normal subjects (above) and two long-term diabetics (below). Curves to the left represent the two individuals with a median gain within the respective groups at 2.5 Hz light stimulation and the ones to the right those having median slope at 2.5 Hz. The drawn line is a polynomial fit, which is used in order to avoid the scattering of the data. The gain and the slope is read off on the fitted curve at 2.5 Hz (squares)

Fig. 2 shows the computer drawings of averaged responses to various frequencies. Median gain frequency plots are shown in Fig. 3. Latency or lag of the pupil is measured in terms of cycles of the light stimulus, i. e. in degrees, and it is therefore called phase lag.

The resting pupil size was determined after a period of 15 minutes in darkness.

Estimations of the vibratory perception threshold [14] were performed on the great toe by means of a biothesiometer (Biomedical Instrument Corp., Ohio).

Results

Individual pupil sizes in the diabetics appear in Table 1. The mean value was 27.3 ± 9.4 mm^2 (mean ± SD). The difference of 7.2 mm^2 compared to controls is just on the limit of statistical significance, $2p = 0.50$. Expectedly, the vibratory perception threshold was increased; the elevation was 60 per cent compared to the controls.

Fig. 4 shows the individual values of the slope of

Table 1. Clinical data of long-term diabetic patients and corresponding mean values for control subjects

Patient	Sex	Age (years)	Diabetes duration (years)	Vibratory perception threshold Arbitrary values (volt)	Degree of retinopathy	Pupil size in darkness mm^2
1	F	30	15	7	None	24.3
2	M	31	17	15	Red dots, haemorrh.	30.4
3	F	32	20	12	Red dots, exudates	38.8
4	F	32	20	15	Red dots	34.0
5	F	33	32	16	None	6.5
6	M	35	20	21	Red dots, haemorrh.	20.4
7	F	35	28	9	Red dots	36.2
8	F	35	26	15	Red dots, haemorrh., exudates	17.9
9	M	36	15	18	Red dots, exudates	26.6
10	F	36	26	10	Proliferative	20.8
11	M	36	20	10	Red dots	35.2
12	F	40	15	18	None	35.8
13	M	40	17	27	None	35.5
14	M	40	15	33	None	19.2
Mean	8F/6M	35	20	16		27.3
SD		3	5	7		9.4
Normal controls						
Mean	7F/8M	34		10		34.1
SD		3		2		8.3

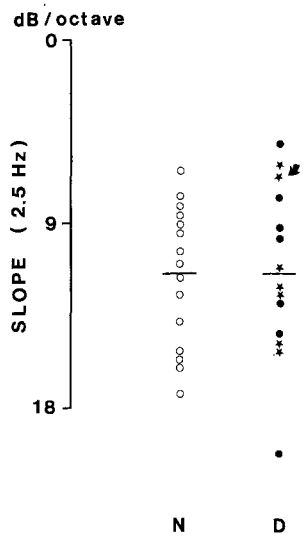


Fig. 4. Individual values of the slope of the gain-frequency plot at a stimulatory frequency of 2.5 Hz in normal subjects (N) and long-term diabetics (D). The conventional unit for the reduction in gain is dB/octave. The stars represent the seven diabetics who had the smallest pupil size and the arrow points to the diabetic (no. 5 in table 1) who had the tiniest pupil, measuring only 6.5 mm^2

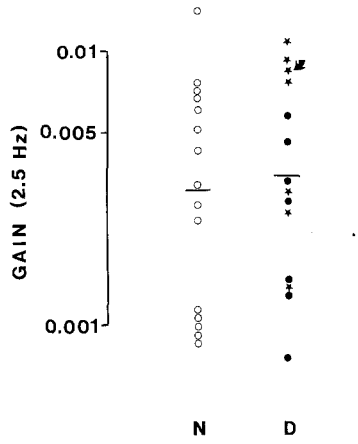


Fig. 5. The individual values of gain at a stimulatory frequency of 2.5 Hz in normal subjects (N) and long-term diabetics (D). The scale is logarithmic. The stars represent the seven diabetics who had the smallest pupil size and the arrow points to the diabetic (no. 5 in table 1) who had the tiniest pupil, measuring only 6.5 mm^2

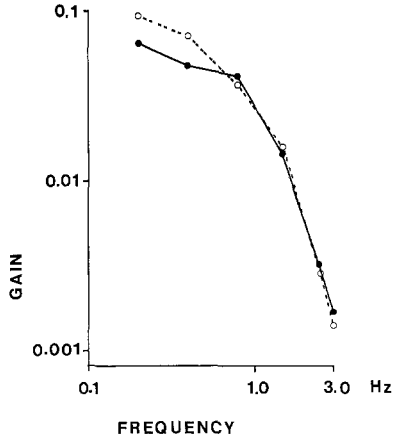


Fig. 6. The mean gain (for one relative unit variation in light stimulus) plotted against frequency. For the comparison of shape and slope the large individual variation in gain (i. e. in position) shown in Fig. 5 is irrelevant, for which reason it is omitted from the figure. ○ = normal, ● = diabetic

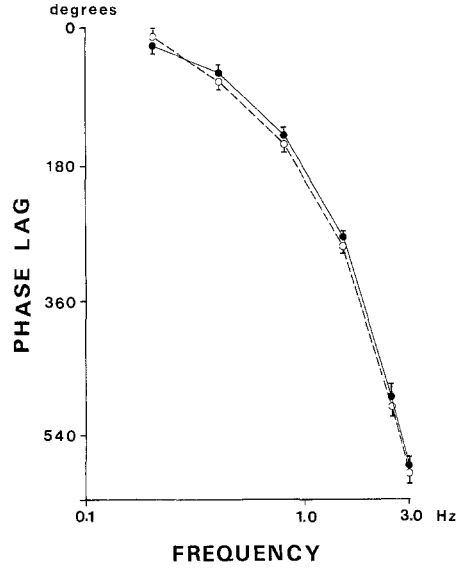


Fig. 7. The mean phase lag plotted against frequency. The vertical lines indicate the SEM. Notice that at approximately 1 Hz there is a phase lag of 180°, meaning that the pupil responds paradoxically by enlarging itself when light intensity is increasing. ○ = normal, ● = diabetic

the gain-frequency relationship at 2.5 Hz in normal and diabetic subjects. It is evident that there are no differences between the two groups.

Fig. 5 shows the individual gains at the stimulatory frequency of 2.5 Hz, and again there are no differences between the two groups. Besides, it is evident from these two figures that the diabetics with the smaller pupil size did not differ with respect to slope or gain from the rest of the diabetics or from the normal group.

Fig. 6 shows the mean gain of the two groups plotted against stimulatory frequency. Even at the higher frequencies (1.5, 2.5 and 3.0 Hz) it can be seen that the diabetics responded just as readily as

the normals do. If the pupil were a stiff and poorly reacting organ one would certainly expect this to be revealed at this part of the curves.

Fig. 7 shows the mean phase-lag of the two groups plotted against frequency; both the latency and its variation with frequency were identical in the long-term diabetics and normal subjects.

Discussion

When discussing the light response of the diabetic pupil, certain factors which may explain diverging results have to be taken into account.

The presence of retinopathy in the area stimulated by light is likely to diminish the effective stimulus and thereby the response. This problem can be overcome either by adjusting the stimulus according to the individual visual threshold [13] or by ensuring that the area stimulated by light is not visibly affected by retinopathy.

The small size of the diabetic pupil gives rise to another bias when the eye is stimulated with a light beam that is wider than the pupil i. e. the so-called 'closed loop' approach. In this situation the smaller diabetic pupil will admit less stimulating light resulting in a reduced response. The importance of this bias when applying submaximal stimuli is well illustrated in an earlier report [8].

When the amplitude of the light reflex is expressed in absolute values it is, a priori, not surprising that the diabetics with a small pupil size also show a small amplitude. Obviously, a pupil of e. g. 6.5 mm^2 cannot be reduced by 13 mm^2 in response to a certain light stimulus as it is seen in an average normal subject. From the point of view of the retinal function the correct way to handle this problem is to calculate the *relative* reduction in the area.

The present study, using techniques that ensure equality of the stimulus and a functional expression of the response, has shown that even at high frequency light stimulation the pupil of these long-term diabetics is able to react normally. These findings correspond to the findings of Gundersen [7], who studied the pupil response to short light pulses in diabetics. In his study the dynamic properties of the pupil's movements were evaluated by computer-governed plots of phase-plane trajectories of the velocity against the size of the pupil. Even the five long-term diabetics who had the smallest pupils showed normal-shaped trajectories.

In the previously mentioned study by Gliem [5] the diabetic pupil was found to have a diminished response to rhythmic light stimuli. The most likely explanation is that the absolute values of the amplitude were compared to those of controls, thus not taking into account the reduced pupil size of long-term diabetics. Besides, more than half of the patients had proliferative retinopathy and it is difficult to evaluate to what extent the effect of the stimulating light has been attenuated by a diseased retina.

Smith et al. [13] studied the response to short, single light stimuli in diabetics using the 'open loop' approach and stimuli adjusted for individual retinal sensitivity. They found that the latency time was normal for the reflex size and that there was a significant, positive regression of the amplidute on the resting diameter. Friedman et al. [2] studied the light reflex in maturity onset diabetics finding shallow responses and prolonged latency times in a number of patients. However, since both the response and the latency time were defined by absolute values and the pupil size not given, their results are difficult to interpret.

The presence of advanced iridopathy with extensive neovascularisation (rubeosis iridis) of the iris and accompanying scarring, adhesions and atrophy would inevitably compromise pupil motility [4]. However, none of the patients in the present study had evidence of this very rare diabetic manifestation.

It has been suggested that the functional abnormalities of the long-term diabetic pupil – the small size, reduced spontaneous variation or hippus and incomplete dilatation by mydriatics – could be caused by a rigidity of the iris tissue brought about by more subtle structural changes, such as glycogen accumulation and muscular abnoramlities [3]. The present study, however, provides evidence against the long-term diabetic pupil *generally* being a 'stiff' organ, even if the spontaneous variations are reduced by a factor of 10 or more (Hreidarsson, unpublished observations). On the contrary it seems to preserve its normal ability of dynamic function and this is true even for the tiniest diabetic pupil, at least as long as the retina is sufficiently preserved to be employed as a normal input organ. The abnormality of the pupillary function in long-term diabetic patients must therefore be due to autonomic neuropathy. The diminished pupil size reflects reduced sympathetic acitivity, altering the balance towards parasympathetic dominance. As the light reflex is primarily brought about by the parasympathetically innervated sphincter [10] the results of the present study indicate that the parasympathetic nerves are relatively spared.

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