Circadian Fluctuations of Macular Edema in Patients with Morning Vision Blurring: Correlation with Arterial Pressure and Effect of Light Deprivation

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PURPOSE. This study explored the causes of vision fluctuations in patients with chronic macular edema.

METHODS. Fifteen patients (16 eyes) with vision blurring at awakening due to post–central retinal vein occlusion (CRVO) macular edema underwent three examination sessions over 24 hours (at 7 PM, immediately after awakening at 7 AM, and at 7 PM), which comprised assessment of Early Treatment Diabetic Retinopathy Study score and measurement of macular thickness (MT) by optical coherence tomography. Ocular perfusion pressure was calculated from ambulatory arterial pressure measurement. In addition, after the 7 AM measurements, the patients were randomly selected for monocular light deprivation during the day to evaluate the role of retinal illumination in these fluctuations.

RESULTS. Circadian fluctuation of MT was documented in all patients. At 7 AM, mean visual acuity (VA) was worse (mean ± SD of the difference: 6.5 ± 7.2 points; P < 0.002) and mean MT was higher (57.4 ± 34 μm; P < 0.001) than at 7 PM. Fluctuations of MT were correlated to fluctuation of arterial pressure (P = 0.05), but were not influenced by monocular light deprivation.

CONCLUSIONS. In most patients complaining of visual fluctuations due to macular edema secondary to CRVO, MT and VA were found to undergo a circadian cycle. These short-term anatomic and functional variations were associated with arterial pressure variations (that is, macular thickening was inversely correlated to the arterial pressure drop during the night), but were not due to light deprivation. (Invest Ophtalmol Vis Sci. 2005;46:4707-4711) DOI:10.1167/iovs.05-0638

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Supported by a grant from the Délégation à la Recherche Clinique of the Assistance Publique-Hôpitaux de Paris (Crédit d’Investigation et de Recherche Clinique 02.043-P021009). MP and PM were supported by research contracts (Contrats d’Interface) from the Institut National de la Santé et de la Recherche Médicale, the Assistance Publique-Hôpitaux de Paris (PM) and the Fondation Rothschild (MP).

Submitted for publication May 23, 2005; revised July 12, 2005; accepted August 30, 2005.

Disclosure: M. Paques, None; P. Massin, None; J.A. Sabel, None; A. Gaudric, None; J.-F. Bergmann, None; S. Azancot, None; B.I. Lévy, None; E. Vicaut, None

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Patients with chronic macular edema often report fluctuations of vision, with poorer vision at awakening. Few studies have specifically addressed to these fluctuations. Sternberg et al.1 reported the cases of three patients with macular edema in which visual acuity (VA) was worse in the morning than in the evening. During the last decade, the advent of optical coherence tomography (OCT) has allowed objective and reproducible measurement of macular thickness (MT).2,3 thus allowing researchers to objectively assess these variations. Frank et al.4 studied the variations of MT over the day in 10 patients with diabetic macular edema. Repeated OCT measurements demonstrated that MT was at its maximum at awakening, and decreased over a few hours. These findings suggest that mean MT increases during the night.

The factors underlying such variations in macular edema are unknown. Several factors may be involved, such as arterial pressure, neuronal activity, or other metabolic and/or endocrine factors. Since arterial pressure varies during the day,5 it is likely that the ocular perfusion pressure (OPP) is also subject to circadian variations. However, while the short-term effects of positional changes on retinal vessel diameter and OPP have been reported,6–9 the variations of OPP during the day–night cycle have been the subject of few studies.10

Circadian variations in macular edema may also be driven by parallel variations of retinal metabolism. Indeed, the oxygen consumption rate by the retina of experimental animals is higher in the dark-adapted state.11–15 In diabetic patients, electrophysiological parameters such as the oscillatory potential14 and the electrooculogram15 are more severely altered in the dark-adapted retina. The administration of oxygen compensates these abnormalities, suggesting that light deprivation increases the oxygen demand by the pathologic retina. Thus, in a hypoxic retina, ischemia may be more severe during the night.

Therefore, this study was conducted to quantify the circadian fluctuations of MT and VA in patients with chronic macular edema, and to test the effects of OPP variation and monocular light deprivation on these fluctuations. VA and MT were thus measured at awakening and in the evening, in parallel with arterial pressure monitoring. In addition, patients were randomly selected for monocular light deprivation during daytime. Our results show that there is a circadian variation of MT, which is associated with circadian variations in blood pressure but is not influenced by monocular light deprivation.

METHODS

The study protocol was approved by the local Internal Review Board and was conducted in agreement with the Declaration of Helsinki. Among a series of 58 patients with macular edema seen in our department, 23 complaining of worse vision at awakening were screened for the present study. The main inclusion criteria were Early Treatment Diabetic Retinopathy Study (ETDRS) score > 35 and MT > 350 μm. Main exclusion criteria were diabetes, uncontrolled arterial hypertension.
Intraocular pressure (mm Hg) 14.7 (11–19)

Duration of macular edema (months) 9.4 (1–44)

Mean arterial pressure (mm Hg) 93.5 (79–105)

Intraocular pressure (mm Hg) 14.7 (11–19)

Ambulatory arterial pressure over 24 hours was measured using a noninvasive recording system (Diasys Integra; Novacor, Rueil-Malmaison, France). As a rule, arterial pressure was measured every 15 minutes between 7 AM and 11 PM (64 measures), and every 30 minutes between 11 PM and 7 AM (16 measures). Mean arterial pressure (MAP) was calculated with the following formula:

\[ \text{MAP} = \frac{(\text{systolic pressure} + 2 \times \text{diastolic pressure})}{3} \]

As previously reported, we considered that IOP during sleep was on average 6 mm Hg higher than during the day.\textsuperscript{10,19–21} OPP was thus calculated using the formula proposed by Bill\textsuperscript{10,22}:

Daytime OPP = (95/140 MAP) – sitting IOP

Night OPP = (115/130 MAP) – sitting IOP + 6

Daytime MAP corresponded to the mean of MAP measurements during the 7 AM to 11 PM interval, and night MAP to the 11 PM to 7 AM interval. To test the hypothesis that light deprivation influences MT, patients were randomly selected after the 7 AM session for light deprivation of the study eye. The occlusion was performed by applying an eye patch covered with black adhesive tape. It was ensured that the occluded eye had no light perception and could blink under the patch. During VA and MT measurement, the technician was unaware of the group of the patient.

Wilcoxon’s paired test and Spearman’s correlation test were performed using statistical analysis software (GB-stat; Dynamic Microsystems, Silver Spring, MD).

**RESULTS**

Sixteen eyes of 15 patients were studied. The subjects included 9 men and 6 women. All had perfused central retinal vein occlusion (CRVO). The clinical characteristics of the patients are summarized in Table 1. All patients complained of blurred vision at awakening that persisted for 5 to 180 minutes (median, 45 minutes). Visual symptoms at awakening were reported as “overall blurring” or “central dark spot.” Some also reported dyschromatopsia.

**Variations in VA and MT over 24 Hours**

The evolutions of VA and MT over the study period for each patient are shown in Figure 1. The mean ± SD values at 7 PM,
A strong correlation was found between MT and VA at all time points (Fig. 2).

**Correlation of VA and MT with Hemodynamic Parameters**

Individual changes in MAP and OPP are shown in Figure 3. During the night, the MAP decreased significantly (93.5 vs. 77.8 mm Hg; \( P < 0.001 \)). All subjects but one had a significant (>10 mm Hg) decrease in MAP during the night. There was a slight nonsignificant decrease in mean OPP during the night (48.6 vs. 47.1 mm Hg).

Fluctuations in OPP were not correlated to MT fluctuations or to VA variations (Fig. 4). Conversely, there was also a correlation between variations in systolic (\( P = 0.05 \)) and diastolic (\( P = 0.06 \)) pressure and MT variations (Fig. 5); that is, pressure dip during the night was inversely correlated to the increase in MT at awakening.

**Effect of Light Deprivation on Macular Edema**

To determine the role of retinal illumination in MT fluctuations, patients were randomly selected for light deprivation between 7 AM and 7 PM. One patient, assigned to the occlusion group, refused the eye patch and was therefore retrospectively assigned to the control group. The patient with bilateral macular edema was assigned only once, and was in the nonoccluded group. Thus, there were 10 eyes in the control group, and 6 in the light-deprivation group. There were no significant differences in baseline VA and MT between the two groups (data not shown). The decrease in MT during the day was similar in both groups (Fig. 6). Similarly, no effect of light deprivation on VA was noted (data not shown).

**DISCUSSION**

The first objective of our study was to assess the existence of a circadian cycle of macular edema associated with visual fluctuations. All patients in our series had a higher MT at awakening, and most of them had a concomitant decrease in VA. Accordingly, Frank et al.\(^4\) evidenced circadian variations of MT in 4 of 10 diabetic patients with macular edema without visual fluctuations. It can be therefore concluded that, in a high proportion of patients with macular edema, whatever its etiology, MT follows a circadian cycle; that is, MT increases during
the night. MT fluctuations were higher in our patients than in those described by Frank et al.4 This is probably because we selected patients with symptomatic fluctuations in VA, and also because care was taken to perform measurements as soon as possible after awakening.

The second objective of our study was to investigate which factors underlie such fluctuations in MT. It is known that diabetic macular edema may be aggravated by high blood pressure.23 Accordingly, an overall trend toward greater MT variations with increasing arterial pressure during the night was found. Indeed, the degree of nocturnal drop in both systolic and diastolic pressure was strongly correlated to the variations in MT; the lesser the drop, the greater the increase in MT. Some patients had a frank increase in OPP at night, and those were the patients that experienced the greatest increase in MT at awakening. However, due to the small number of patients, no definitive conclusion can be drawn on the risk of increasing macular edema with increasing OPP. Nevertheless, our results strongly suggest that short-term changes in hemodynamic parameters modulate macular edema. Therefore, as for diabetic patients, a tight control of blood pressure might be advised for post-CRVO macular edema. Additional studies specifically addressing hypertensive patients should be of interest in assessing this point.

Other factors may also be involved in these fluctuations. For instance, postural changes induce major variations in venous pressure throughout the body.24 In the retina, acute head-down tilt increases both the OPP and the diameter of veins.6–9 Therefore, we suggest that the positional change from upright to recumbent increases retinal venous pressure, and thus increases transudation through the blood–retinal barrier. Increased venous pressure may also alter the outflow of cell metabolism waste products and of CO₂, further impairing retinal function. Additional studies are needed on this point. If the role of venous pressure in the circadian fluctuation of MT is confirmed, this may have clinical implications. For instance, sleeping with the head in a more upright position may be of interest.

We excluded a direct influence of light on these fluctuations, since monocular light deprivation had no effect. However, other light-induced circadian factors may play a role in these fluctuations. Indeed, a role of the day–night cycle in MT fluctuation cannot be completely excluded, since monocular light deprivation does not affect the circadian modulation of factors such as dopamine and melatonin.25 It has been shown in ex vivo experiments that stimulation of dopamine receptors may contribute to relieve glial cell swelling, by blocking the water channel aquaporins.26 Therefore, light-induced changes in dopamine concentrations may induce parallel variations in MT. The role of other factors, such as retinal and choroidal blood flow or body temperature, remains to be determined.

In conclusion, in most patients with macular edema secondary to CRVO and complaining of visual fluctuations, there is a circadian variation of MT. Light deprivation does not play a significant role in this phenomenon. We hypothesize that variations in arterial perfusion, and possibly in venous pressure, play a role in these fluctuations. Therefore, a tight control of arterial blood pressure at night and head-up positioning may be useful to improve visual function in these patients. Additional studies focused on hypertensive patients are needed to confirm
these results. The implication of other metabolic factors remains to be explored.

References

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