Spontaneous High Frequency Diameter Oscillations of Larger Retinal Arterioles Are Reduced in Type 2 Diabetes Mellitus

Toke Bek,[1] *Peter Jeppesen,*[1] *and Jørgen K. Kanters*[2]

Purpose. Diabetic retinopathy is characterized by morphological changes in the retina secondary to disturbances in retinal blood flow. Vasomotion is a mechanism for regulating blood flow by spontaneous oscillations in the diameter of retinal resistance arterioles, and has been shown to be disturbed outside the eye in diabetic patients. Therefore, the purpose of the present study was to characterize spontaneous oscillations in the diameter of retinal arterioles in normal persons and in persons with different severity of diabetic retinopathy.

Methods. Video recordings of the retina were performed in 19 normal persons and three matched groups of type 2 diabetic patients with no retinopathy, mild retinopathy, and diabetic maculopathy. Continuous recordings of a larger retinal arteriole during rest and during an increase in the arterial blood pressure induced by isometric exercise were subjected to power spectrum analysis of spontaneous oscillations in vessel diameter.

Results. During rest the oscillations in the diameter of retinal arterioles with high frequencies were significantly reduced in patients with diabetic retinopathy. Increased arterial blood pressure did not change the oscillations in normal persons, but further reduced the oscillations in diabetic patients.

Conclusions. Spontaneous high frequency oscillations in the diameter of larger retinal arterioles are reduced in type 2 diabetic patients, and are further reduced during an increase in the arterial blood pressure. The finding may reflect changes in the vascular walls of importance for diagnosing and predicting the visual prognosis in patients with diabetic retinopathy. (*Invest Ophthalmol Vis Sci.* 2013;54:636–640) DOI:10.1167/iovs.12-11182

Diabetic retinopathy is characterized by morphological changes in the retina secondary to disturbances in retinal blood flow.[1] However, since the retinal vessels have no autonomic nervous supply, the retinal blood flow is regulated by local mechanisms. Thus, pressure autoregulation adjusts the diameter of retinal arterioles to keep the capillary blood flow constant when the blood pressure changes,[2] and metabolic autoregulation changes the retinal perfusion in order to compensate for changes in retinal metabolism.[3] Additionally, vasomotion is spontaneous rhythmical oscillations in the diameter of retinal resistance arterioles with accompanying oscillations in retinal blood flow, which is important for regulating retinal blood flow, oxygenation, and fluid homeostasis. These spontaneous diameter changes have been shown in all tissues hitherto studied, including the choriocapillaris,[4] and both in vivo and in vitro studies in the retina have shown that the phenomenon depends on NO-induced synthesis of cyclic guanosine monophosphate (GMP).[5–7] The accompanying oscillations in oxygenation have been recorded both in the retina[7] and in the optic nerve.[9,10] Vasomotion has been found to be disturbed outside the eye in patients with diabetes mellitus,[11] and disturbances in vasomotion has been proposed to be involved in the pathogenesis of diabetic retinopathy.[12] However, the nature of spontaneous rhythmic oscillations in the diameter of retinal arterioles in normal persons and in patients with diabetes mellitus have not been described in vivo.

Therefore, in the present study, video recordings of the ocular fundus during rest and during an increase in the arterial blood pressure induced by isometric exercise were used to study spontaneous oscillations in the diameter of retinal arterioles in normal persons, in patients with diabetes mellitus, and different severity of retinopathy.

Materials and Methods

Patients

The details of the patient selection have been described previously.[13] In short, 76 persons divided into four groups each consisting of 19 persons were studied. Group A consisted of normal persons without any known systemic or ocular disease, whereas the other three groups consisted of type 2 diabetic patients. Group B had no retinopathy in either eye, group C had mild retinopathy (1–4 dot and/or blot hemorrhages) in at least one eye, and group D had diabetic maculopathy in at least one eye. All groups were pair-wise matched with respect to age (56.2 ± 1.2 years, overall mean ± SEM) and sex, and additionally the diabetic patients were matched with respect to known duration of diabetes mellitus (9.5 ± 1.2 years, overall mean ± SEM). There was no significant difference between the groups (overall mean ± SEM, P value for groups comparisons) for plasma glucose (10.5 ± 1.0 mM/L, $P = 0.69$), HbA1c (7.9 ± 0.3%, $P = 0.41$), total cholesterol (5.1 ± 0.2 mMl/L, $P = 0.54$), body mass index (29.0 ± 0.9 kg/m^2, $P = 0.17$), systolic (135 ± 3.8 mm Hg, $P = 0.19$), or diastolic (85 ± 2.4 mm Hg, $P = 0.70$) blood pressure.[13] There was no correlation between any of these clinical and biochemical parameters and the diameter measurements and measures of fluctuation derived from these. In preliminary experiments the variation in diameter measurements of retinal arterioles had been found to be 0.06% (confidence

From the [1]Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark; and the [2]Laboratory for Experimental Cardiology, Department of Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

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Corresponding author: Toke Bek, Department of Ophthalmology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark; toke.bek@mail.tele.dk.

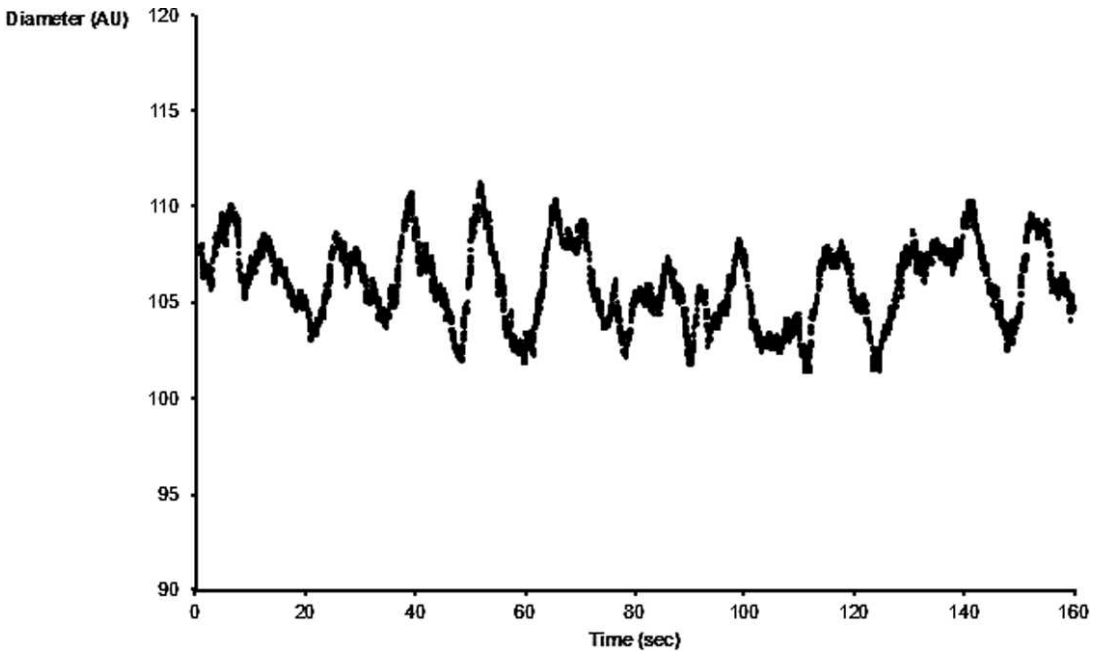

Figure 1. Trace of spontaneous diameter changes in a larger retinal arteriole from a normal person during rest. It appears that the diameter oscillates with several superimposed frequencies.

interval [CI] 95%: –0.92; 1.04) with a Pearson correlation of 0.99 [CI 95%: 0.98; 0.99]. Consequently, in a double-sided *t*-test and with a power of 70%, it would be necessary to include 17 persons in each group in order to detect a 2% change in the vessel diameter.

All individuals were less than 65 years of age and had no previous history of ocular disease other than diabetic retinopathy. The persons had given their oral and written consent to participate; the study adhered to the tenets of the declaration of Helsinki, and was approved by the local committee for scientific ethics.

Examination Procedure

The persons underwent a routine ophthalmological examination including the measurement of visual acuity on early treatment diabetic retinopathy study (ETDRS) charts, slit lamp examination, pneumotonometry, and after dilatation of the pupil with phenylephrine 10% (SAD, Copenhagen, Denmark) and tropicamide 1% (Alcon, Houston, TX), 60° fundus photography (CF 60Z; Canon, Tokyo, Japan) centered on the macula of each eye was performed. Central retinal thickness was measured by optical coherence tomography (OCT) scanning (Humphrey Instruments, San Leandro, CA) using the fast macular scanning program, followed by a recording of the diameter response using the Dynamic Vessel Analyzer (DVA; Imedos, Jena, Germany).[14] All baseline characteristics of the patients are shown in[13]

Diameter Response

The DVA consisted of a fundus camera (Zeiss FF450; Zeiss, Oberkochen, Germany) and a video recording unit (Zeiss) connected to a computer (Zeiss). During an examination or during a later reanalysis of a recorded examination, a video sequence of the ocular fundus was grabbed by the computer and was analyzed in real time. The examiner defined a region of interest (ROI) overlying an arteriole, which was clearly separated from the adjoining venule and was located within 1-disk diameter of the optic disk. Subsequently, the software (25 times per second) found the edges of contrast defining the vessel borders for each 10 μm along the arteriole within the ROI. On the basis of these measurements the vessel diameter was calculated in arbitrary units (AU) that approximately corresponded to micrometers at the retinal plane. The software was able to follow and align the selected ROI on the video recording to compensate for fixation saccades. A representative trace from a normal person is shown in Figure 1.

Examination

The examinations were carried out on the left eye, except for 11 of the diabetic patients with mild retinopathy where the retinopathy changes defining the inclusion criteria were only present in the right eye. Each test person was placed in front of the fundus camera and was asked to look at a fixation bar positioned inside its viewing system. The ROI was placed over one of the temporal retinal arterioles so that it was within 3-disk diameters from the optic disk and was clearly separated from the accompanying venule.[15,16] The systemic blood pressure was measured using a cuff placed on the upper left arm.

The examination consisted of three periods, of which the present results are based on data from the two first periods, performed as follows: the first (baseline) period was a resting period lasting 180 seconds. The second (exercise) period also lasted 180 seconds, during which the blood pressure was increased by lifting a 2-kg hand weight with the right arm, which resulted in an increase in the arterial blood pressure of 21.2 ± 1.0 mm Hg. The diameter of retinal arterioles were sampled during the first 150 seconds of the baseline period and during the last 150 seconds of the lifting period, with a sampling rate of 25 images per second corresponding to 3750 diameter measurements for each analysis. The program automatically excluded missing values due to blinking and saccadic eye movements, resulting in the sampling of on average 2945 ± 75 and 2830 ± 97 measurement points (mean ± SEM) at baseline and during the lifting period, respectively. The blood pressure and the pulse rate were measured on the upper left arm using oscillometric technique (Omron M4; Omron, Tokyo, Japan) at the beginning of the baseline period, and 120 seconds after the beginning of the exercise period.

Data Analysis

Data from one of the normal persons had been lost, reducing this group to 18 individuals. In each patient spectral analysis of diameter values over time was performed by Fourier transformation (PROC SPECTRA, SAS 9.2; SAS Institute, Cary, NC) with a triangular window of a width equaling 5. The power was calculated as the squared

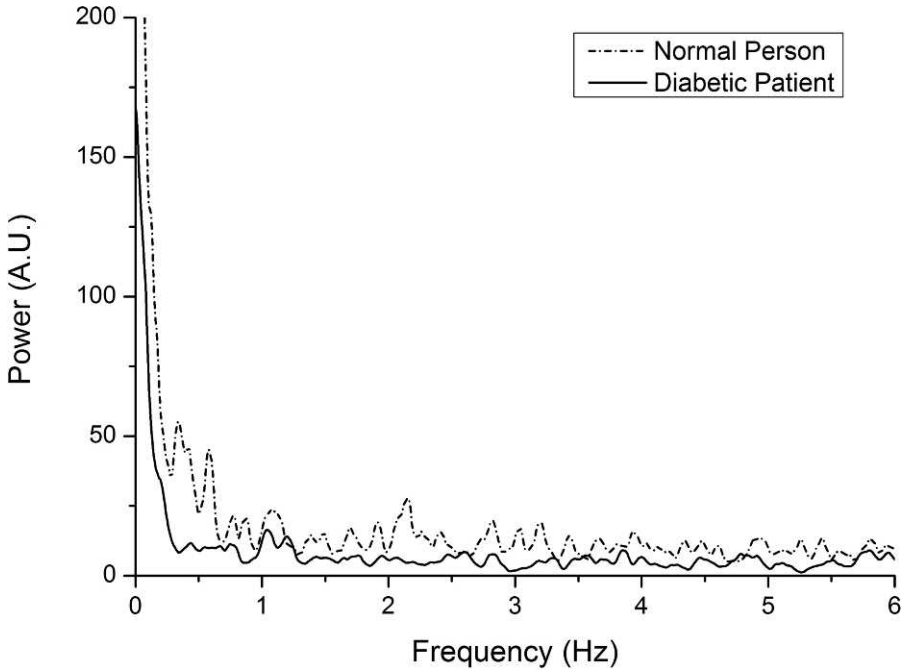

Figure 2. Representative power spectra from a normal person (*broken line*) and a patient with diabetic maculopathy (*solid line*) during rest. The graphic presentation has been enhanced by truncating the axes at high powers and frequencies, and by applying a moving average with a window of width = 30.

amplitudes, and summed within five successive frequency domains defined as: (1) less than 0.04 Hz as the very low frequency (VLF) band, (2) less than or equal to 0.04 and greater than 0.15 Hz as the low frequency (LF) band, (3) greater than or equal to 0.15 Hz and less than 0.4 Hz as high frequency (HF),[17,18] and two novel bands consisting of (4) greater than or equal to 0.4 and less than 2 Hz, which was a very high frequency (VHF) band normally containing the heart rate in most circumstances, and (5) 2 to 12.5 Hz as a ultra high frequency (UHF) band. The upper limit of the latter interval was defined so that frequencies above the Nyquist criterion were excluded from the analysis.

In the examined persons the pulse rate was mean (range): group A: 66.0 (51–89), group B: 75.0 (58–92), group C: 75.6 (55–100), and group D: 76.3 (57–100), corresponding to a range of frequencies of 0.83 to 1.67 Hz for patients in all groups. Therefore, the contribution to the heart beat was included in the VHF band for all the tested persons.

Statistical Analyses

For the comparison of power spectral densities, powers were log-transformed with base 10. A two-way ANOVA was performed with intervention (rest/exercise) and patient group (normal/diabetic patients) as variables, and when significant differences were found, Dunnet's post hoc test was used to identify group(s) that differed significantly from the others. A P value less than 0.05 was considered to be statistically significant.

Results

Figure 2 shows representative examples of the power spectrum during rest in a normal person and a patient with diabetic maculopathy. It appears that the power decreases with increasing frequency f to resemble an 1/f distribution, and that powers are lower in the patient with diabetic maculopathy than in the normal person.

Tables 1 and 2 show that the sum of powers increased significantly with increasing frequency from the VLF to the UHF band due to the increasing band width and the consequent increasing number of frequency peaks included in the calculation.

Table 1 shows that during rest the power values of spontaneous oscillations in the diameter of retinal arterioles were significantly reduced in both the VHF and the UHF band for patients with mild retinopathy, but only in the UHF band for patients with diabetic maculopathy. There was no significant difference between the power spectra from normal persons during rest and during an increase in the arterial blood pressure induced by isometric exercise.

Table 2 shows that during isometric exercise there was a significant decrease in the power values in the HF band for patients with mild retinopathy, but in both the VHF and the UHF band for all three groups of patients with diabetes mellitus. There was no interaction between the two variables rest/exercise and the presence or not of diabetes mellitus.

Discussion

The present study has shown a significant reduction of spontaneous high frequency oscillations in the diameter of retinal arterioles in patients with diabetes mellitus as compared with normal persons, and these amplitudes were further reduced during an increase in the arterial blood pressure induced by isometric exercise. Spectral analysis was used to compare the responses from the studied groups, since this method has been found to be suitable for analyzing oscillating properties of complex interacting physiologic systems following an 1/f distribution, such as the cardiovascular system.[18,19] Consequently, the frequency bands were defined in accordance with those generally used in cardiovascular research.[17]

Normally, fluctuations in the diameter of retinal arterioles synchronous with fluctuations in the arterial blood pressure during the heart cycle are clearly visible at the optic disk and taper off in the smaller arterioles at a distance from the disk margin.[20,21] It has also been documented that patients with

Table 1. The Power Values (Sum of Squared Amplitudes) for the Four Groups in the Different Frequency Bands Studied during Rest

Frequency Bands	Normal Persons $N = 18$	Diabetic Patients: No Retinopathy $N = 19$	Diabetic Patients: Mild Retinopathy $N = 19$	Diabetic Patients: Diabetic Maculopathy $N = 19$	*P*
VLF	2.78 ± 0.08	2.92 ± 0.13	2.87 ± 0.11	2.80 ± 0.11	0.80
LF	2.83 ± 0.06	2.85 ± 0.09	2.76 ± 0.09	2.74 ± 0.09	0.79
HF	2.99 ± 0.04	2.84 ± 0.08	2.71 ± 0.08	2.75 ± 0.09	0.07
VHF	3.57 ± 0.04	3.40 ± 0.07	**3.32 ± 0.06**	3.36 ± 0.07	0.04*
UHF	4.27 ± 0.05	4.05 ± 0.08	**3.99 ± 0.07**	**3.98 ± 0.08**	0.02*

The *P* values indicate the results of the two-way ANOVA. The bold values are those differing significantly from the others as tested by Dunnet's post hoc test.

* Indicates significant differences among the groups.

diabetic neuropathy may experience changes in the normal fluctuations and frequency of the heart rate,[22] possibly affecting the pulse synchronous fluctuations in the diameter of retinal arterioles. However, this effect is less likely to have influenced the results of the present study. Thus, although the recorded pulse rate differed between normal persons and patients with diabetes mellitus, this rate was within the VHF band in all studied persons from all groups and, therefore, cannot have contributed to the different power values between the different frequency bands.

In normal persons the frequencies of diameter changes in retinal arterioles were consistent with studies of spontaneous oscillations in oxygen supply to the posterior segment of the eye.[8,10] However, increased blood pressure induced by isometric exercise induced no change in the amplitudes of spontaneous diameter changes at any of the studied frequencies. This may indicate that the effects of these diameter changes on retinal hemodynamics are maintained within a range of intraluminal pressures of the retinal arterioles, and, therefore, may affect retinal blood flow independently of pressure autoregulation. However, in diabetic patients the reduction in amplitude of spontaneous diameter changes was observed at much higher frequencies than can be produced by muscle activity in the retinal vascular walls, and, therefore, probably represents a passive phenomenon. These very and ultra high frequency diameter changes might be related to an increased stiffness of the vascular walls in diabetic patients reducing the elasticity and, thereby, the movements of the retinal vascular walls during the cardiac cycle. This is consistent with the observation of a further reduction in amplitudes when the arterial blood pressure was increased by isometric exercise in the diabetic groups. This may be due to an increase in the passive tension of the vascular walls that dilate because of impaired autoregulation,[13] and, consequently, dampen high frequency diameter oscillations further. Both during rest and during isometric exercise, the reduction in the amplitude of diameter oscillations was observed in lower frequency band for patients with mild retinopathy than in diabetic patients without retinopathy, which would also be expected if the stiffness of the vascular wall should correlate with retinopathy grade. However, the fact that patients with diabetic maculopathy had reduced amplitudes over a larger range of frequencies than patients with mild diabetic retinopathy indicates that the relation is more complex. The studied diabetic patients had diabetes a duration of approximately 9 years, and it might be interesting to study at what diabetes duration the reduction in amplitude of high frequency oscillations starts and to what extent this phenomenon correlates with the development of other diabetic retinopathy and diabetic vascular complications elsewhere. Similarly, it might be relevant to study whether the response is similar in type 1 diabetic patients and patients of younger age. Additionally, the vascular disease pattern differs in older persons, including an increased risk of developing retinal vein thrombosis. The preponderance of this disease at arteriovenous crossings is supposed to be due to turbulence in the venous blood flow induced by the arterial pulsations at the point of contact between the two walls.[23,24] It might therefore be interesting to investigate whether retinal vein thromboses in general, and in diabetic patients in particular, might be related to mechanical properties of the vascular wall that could be predicted from spontaneous changes of the vascular diameter.

Previous theoretical and clinical studies indicate that intermittent opening and closure of adjacent microvascular units is important for the microcirculation,[25] and this phenomenon has been shown to be disturbed in patients with diabetes mellitus.[26] It has also been shown that the disturbances in capillary vasomotion in diabetic patients outside the eye predominate within the VLF and the LF bands, which can be explained as a result of changes in muscle activity in the retinal vascular wall.[11] This is different from the observations

Table 2. The Power Values (Sum of Squared Amplitudes) for the Four Groups in the Different Frequency Bands Studied during Exercise

Frequency Bands	Normal Persons $N = 18$	Diabetic Patients: No Retinopathy $N = 19$	Diabetic Patients: Mild Retinopathy $N = 19$	Diabetic Patients: Diabetic Maculopathy $N = 19$	*P*
VLF	2.76 ± 0.09	2.71 ± 0.15	2.74 ± 0.09	2.74 ± 0.13	0.99
LF	2.79 ± 0.08	2.72 ± 0.10	2.60 ± 0.09	2.70 ± 0.10	0.54
HF	2.94 ± 0.06	2.71 ± 0.07	**2.61 ± 0.08**	2.70 ± 0.11	0.04*
VHF	3.57 ± 0.04	**3.30 ± 0.09**	**3.24 ± 0.06**	**3.27 ± 0.08**	0.008*
UHF	4.25 ± 0.05	**3.96 ± 0.11**	**3.90 ± 0.08**	**3.90 ± 0.08**	0.01*

The *P* values indicate the results of the two-way ANOVA. The bold values are those differing significantly from the others as tested by Dunnet's post hoc test.

* Indicates significant differences among the groups.

on larger retinal arterioles in the present study where diameter oscillations with higher frequencies were found to be disturbed. Therefore, it is possible that differences exist between the etiology and pathologic reaction pattern of diameter oscillations in larger arterioles and arterioles supplying the capillary bed.[27] An elucidation of such differences would be important for understanding the consequences of spontaneous diameter changes of retinal arterioles on retinal blood flow. Additionally, spontaneous diameter changes in larger retinal arterioles might occur intermittently, which would imply that the probability of detecting these changes is low when the recording is performed in one delimited vessel segment during af limited time interval. The detection of distributed and intermittent characteristics of spontaneous diameter changes would require simultaneous recordings from a number of retinal arterioles during a longer time period.

In conclusion, the study has shown a decrease in spontaneous high frequency oscillations of larger retinal arterioles in type 2 diabetic patients with retinopathy, probably secondary to structural changes in the retinal arteriolar walls. However, further studies are needed in order to elucidate whether this finding has implications for normal and pathologic retinal blood flow in diabetic patients, and for studying whether disturbances in distributed and intermittent spontaneous diameter oscillations with lower frequencies. These variables may reflect changes in the vascular walls of importance for diagnosing and predicting the visual prognosis in patients with diabetic retinopathy.

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