Vasomotion in Retinal Arterioles Is Modified by Exercise and Flicker Stimulation

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Purpose. Vasomotion is spontaneous oscillations in the diameter of resistance vessels with derived effects on blood flow, and it has been proposed that disturbances in vasomotion may be involved in retinal vascular disease. The purpose of this study was to investigate whether retinal vasomotion shows regional variation and is modified by activated autoregulation.

Methods. Video recordings of the diameter of retinal arterioles previously obtained from 55 normal persons were subjected to Fourier analysis to characterize the frequencies and propagation of spontaneous diameter changes in retinal arterioles. The analyses were performed on peripapillary temporal retinal arterioles, on arteriolar branches toward the macular area and the retinal periphery, and were performed during rest, during an increase in the arterial blood pressure induced by isometric exercise, and during increased retinal metabolism induced by flickering light.

Results. There was no propagation of diameter changes along the studied vascular segments. Isometric exercise constricted the arterioles significantly by (mean ± SD) 1.76% ± 3.56% ($P = 0.02$) and increased the power of diameter oscillations at very low frequencies (0.1–1.4 c/min). Flicker stimulation dilated the arterioles significantly by (mean ± SD) 5.10% ± 2.91% ($P < 0.0001$) and reduced the power of diameter oscillations at all but the very low frequencies ($P < 0.006$ for all comparisons). Flicker-induced dilation and changes in hydraulic conductance were lower in peripheral than in macular arterioles.

Conclusions. Retinal vasomotion in normal persons increases during increased arterial blood pressure and decreases during flicker stimulation. The findings may act as a basis for the study of vasomotion in retinal vascular disease.

Keywords: retinal vasomotion, autoregulation, flicker stimulation, Fourier analysis, retinal blood flow

Vasomotion is spontaneous oscillations in the diameter of resistance vessels with derived effects on blood flow, called flowmotion.[1] Vasomotion has been described in multiple vascular beds across different organs and species,[2] and in the retina, the phenomenon has been observed both in vitro[3,4] and in vivo.[5,6] Theoretical studies suggest that vasomotion is important for flow regulation, for tissue oxygenation around microcirculatory units and for fluid homeostasis,[7,8] and it has been proposed that disturbances in vasomotion may be involved in the development of retinal vascular disease.[9] However, an elucidation of the pathophysiological role of retinal vasomotion requires that the phenomenon be characterized under normal conditions. The present study tested the working hypotheses that retinal vasomotion is dominated by specific oscillatory frequencies, that diameter changes are propagating along the resistance vessels, that the phenomenon shows regional variation and varies at different vascular branching levels, and that vasomotion is affected by other mechanisms for flow regulation such as pressure and metabolic autoregulation.

Therefore video recordings of the diameter of retinal arterioles previously obtained from 55 normal persons[10–12] were subjected to Fourier analysis to characterize the frequency content and propagation of spontaneous diameter changes in retinal arterioles. The analyses were performed on peripapillar temporal retinal arterioles, on arteriolar branches toward the macular area, and toward the retinal periphery and were performed during rest, during an increase in the arterial blood pressure induced by isometric exercise, and during an increase in retinal metabolism induced by flickering light.

Material and Methods

Test Persons

Video recordings of retinal vessels previously obtained in 55 normal persons (18 females, 37 males) aged 20 to 31 years without any known previous or present systemic or ophthalmic diseases[10–12] were used. Informed oral and written consent for the analysis has previously been obtained, and it was approved by the Regional Committee for Scientific Ethics that the data could be re-analyzed for this study.

Table 1. The Background Data (Mean ± SD) for the Studied Persons

Age (yr)	24.92 ± 4.64
BCVA (ETDRS letters)	95.02 ± 3.27
IOP (mm Hg)	14.13 ± 2.78
MAP (mm Hg)	85.90 ± 10.88

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; MAP, mean arterial pressure calculated as 2/3*diastolic blood pressure + 1/3*systolic blood pressure.

The normal persons had undergone a standard ophthalmological examination with measurement of best corrected visual acuity using Early Treatment Diabetic Retinopathy Study charts, intraocular pressure (Tonoref II; Nidek, Gamagori Aichi, Japan) and slit lamp examination. The pupils were dilated using phenylephrine 10% (SAD; Amgros I/S, Copenhagen, Denmark) and tropicamide 1% (Alcon, Geneva, Switzerland) eye drops. The background data are shown in Table 1.

The Dynamic Vessel Analyzer

Recordings of the diameter of retinal vessels were obtained with the Dynamic Vessel Analyzer (Imedos, Jena, Germany), which consists of a fundus camera connected to a video unit that allows continuous recordings of the retinal fundus. The participants were positioned with the left eye in front of the camera and were instructed to fixate on the tip of a bar inside the viewing system. This fixation bar was moved so that the vessel of interest was in the center of the image that was visualized on a computer screen.

Vessel Segments

All vessel segments were located within a zone between one-half and three disc diameters from the optic disc and had a minimum length of 200 µm. The selection of vascular segments had two steps. First, in all individuals the most linear segment without any visible branches on either the upper (n = 39) or lower (n = 16) temporal arteriole was selected manually by the examiner and was used to study propagation of diameter changes along the vessel (Fig. 1). Second, in 27 of the cases the frame also contained one or more branches toward, respectively, the macular area and the periphery that were clearly separated from and not crossed by other vessels (Fig. 1). Data collected from these vessels were used to study regional differences in diameter changes.

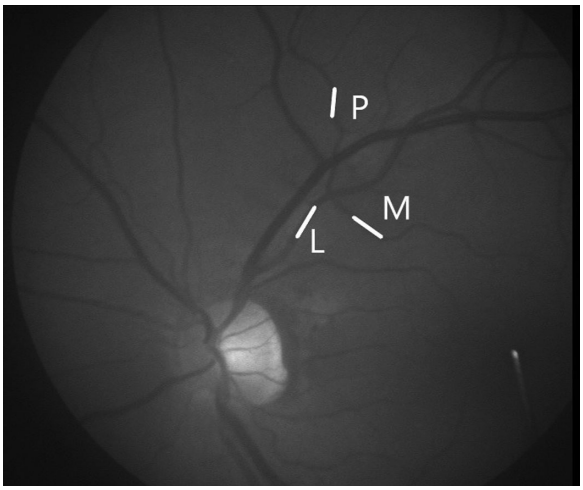

Figure 1. An image from a Dynamic Vessel Analyzer examination. The selected vessel segments are marked with white lines on respectively a peripapillar larger (L), a macular (M) and a peripheral (P) arteriolar branching. The fixation bar is shown to the right.

Based on the contrast between the vessel segment and the surrounding retina, the software measured the diameter 25 times per second for every 10 µm along the vessel segments, which were represented in arbitrary units (aU) approximately corresponding to micrometers at the retinal plane.[13] The Dynamic Vessel Analyzer software automatically adjusted the position of the vessel marker to compensate for saccadic eye movements and interrupted the data capture when the segment could not be identified in the image because of blinking or larger eye movements. With this technique, the diameter of retinal vessels of approximately 60 µm can be assessed with a precision of 1%.[13,14]

Each diameter recording lasted 14 minutes, consisting of seven two-minute phases (Fig. 2): Phase 1 was an initial resting phase, and during phase 2 the test person lifted a hand weight of 2 kg with the right arm (isometric exercise) to increase the arterial blood pressure. Phase 3 was another resting phase, and during phase 4 the retina was stimulated with flickering light at 12.5 Hz generated by a shutter device inside the camera. Phase 5 was a third resting phase, and during phase 6 isometric exercise and flicker stimulation were combined, which was followed by a final resting phase 7. The arterial blood pressure was measured at the end of each period using an oscillometer (705IT; Omron Healthcare, Kyoto, Japan) with the cuff on the left non-lifting arm. The durations of the resting phases were selected to ensure

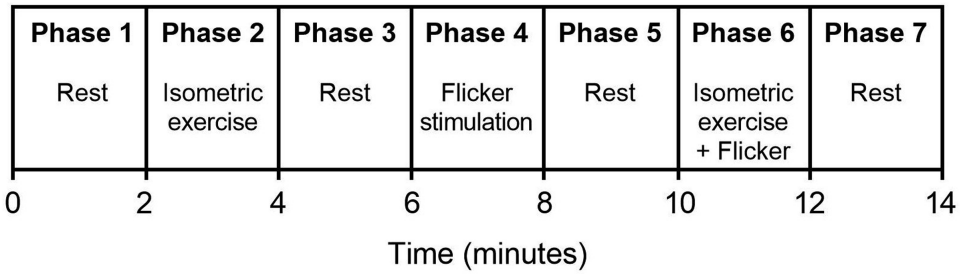

Figure 2. The series of events during a Dynamic Vessel Analyzer examination.

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that the diameters would return to the level before the intervention.[15,16]

Data Analysis

With a video speed of 25 images per second, each two-minute recording consisted of up to 3000 single images, and the diameter measurements from each vessel segment were stored in a comma separated text file. The following analyses of diameter changes were performed in a self-developed software programmed in C++ (Code blocks, open-source, version 20.03).

Frequency Analysis

The number of missing diameter values because of blinking at the different positions in the selected segments in each phase (mean = 664, range 218–882) were substituted with the average of the non-missing diameters over time for that position. There were no significant differences between the number of missing values during the recordings at rest, during isometric exercise and during flicker stimulation ($P > 0.053$) for all comparisons. Subsequently, for each position along the selected vascular segments, the 3000 diameter measurements were subjected to Fourier analysis with a calculation of the amplitude and phase shift for harmonic frequencies in diameter oscillations between 1/min and 300/min. For each position the amplitude was squared and summed to represent the power of oscillations within the following frequency bands (in cycles/minute): 0.1–23.7 (all), 0.1–1.4 (very low frequency [VLF]), 1.4–2.8 (low frequency [LF]), 2.8–4.2 (high frequency [HF]), 4.2–5.6 (very high frequency), and 5.6–23.7 (ultra-high frequency).

Previous studies have shown that vasomotion in vivo may occur at frequencies around 4–6/minutes but that oscillations may not be regularly periodic.[5] To ensure that diameter changes around these frequencies were not evened out in non-periodic patterns of oscillation during the two-minute recordings, the calculation was supplemented with wavelet analysis. For each position on the vessel, time windows consisting of 300 consecutive measurements were subjected to Fourier analysis with the extraction of amplitudes and phase shifts between 5/min and 20/min, and the average amplitudes for each of these frequencies were calculated. Subsequently, the time window was right shifted one position until this procedure had been repeated 1500 times. The average of the amplitudes for each frequency was squared and summed to represent the power of the following frequency bands (in cycles/minute): 2 (Low), 3–9 (Intermediate), and 10-14 (High).

Propagation of Wave Pattern

For each position on the vessel, the diameter in the following position was left shifted 20 times each by one step, and at each shift the difference between the diameters at the shifted and the non-shifted measurements along the segment was squared, summed, and averaged. Subsequently, the minimum of the average sum of squares among the shifts was noted to represent the shift of the total diameter pattern along the vascular segment. This parameter expressed how many steps of 10 µm (position on the vessel) that the pattern of diameter measurements had moved per time step of 1/25 second (image frame).

Hydraulic Conductance

A vessel with an oscillating diameter has a higher hydraulic conductance than what should be expected from the average diameter.[17] Therefore, to study the effect of interventions on changes in the hydraulic conductance, each diameter measurement obtained over time at each position on the vessel was raised to the power of four, the powered values were summed and averaged, and the fourth root of this average of summed values was calculated to represent the diameter that a vessel with a uniform diameter with the same hydraulic conductance would have had.

Statistical Analysis

The average propagation velocity was 0.58 ± 0.92 µm per 1/25 second (video frame interval), which is less than the detection limit (10 µm per 1/25 second). Therefore a sign test with the options 0 (no propagation) or 1 (propagation of one or more steps) was used to test whether the propagation rate differed significantly from zero.

Repeated-measures ANOVA was used to test for differences in propagation velocity for the different locations, interventions and frequency bands. Repeated-measures ANOVA was used to test differences in power of diameter oscillations between larger, macular and peripheral arterioles for each of the five frequency bands. The changes in power values of diameter oscillations from rest to isometric exercise and flicker stimulation were used to test for changes induced by these interventions. Tests for normality were performed using QQ-plots.

Results

Table 2 shows the power of Fourier transformed oscillations at the five frequency bands at rest in the peripapillar retinal arteriole and in the macular and the peripheral arteriolar branches. It appears that the powers of the LF ($P = 0.003$) and HF ($P = 0.005$) bands were significantly higher in the larger arterioles than in the macular and the peripheral arteriolar branches. The increase in the hydraulic conductance induced by the oscillations at rest was (mean ± SD) 1.39% ± 0.24% in the larger arterioles, which was not different from the increase in either the macular (1.52 ± 0.26%) or the peripheral branches (1.50% ± 0.26%), $P > 0.15$ for both comparisons.

Isometric exercise increased the arterial blood pressure by (mean ± SD) 20.33 ± 2.1 mm Hg, which constricted the

Table 2. The Power of Fourier Transformed Oscillations (Mean ± SD) in the Diameter of Peripapillar Temporal Retinal Arterioles and in Macular and the Peripheral Arteriolar Branches at Rest

	Peripapillar (n = 27)	Macular (n = 27)	Peripheral (n = 27)	*P*
VLF	1.28 ± 0.67	1.78 ± 1.65	1.11 ± 0.86	0.06
LF	2.87 ± 1.08	1.48 ± 0.81	1.32 ± 0.65	**<0.0001**
HF	2.43 ± 1.66	1.33 ± 0.72	1.33 ± 0.61	**0.0001**
VHF	5.23 ± 2.33	4.61 ± 2.05	4.53 ± 1.64	0.15
UHF	8.58 ± 3.46	7.86 ± 3.49	7.85 ± 2.47	0.46

VHF, very high frequency; UHF, ultra-high frequency.

P values refer to the testing of differences among the three groups. Statistical significant *P* values are highlighted in bold.

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Table 3. The Change in Power of Fourier Transformed Oscillations (Mean ± SD) From Rest to Exercise

Difference From Rest	Peripapillar (n = 27)	*P*	Macular (n = 27)	*P*	Peripheral (n = 27)	*P*
VLF	2.32 ± 2.89	**0.0003**	0.97 ± 1.84	**0.01**	1.08 ± 1.95	**0.008**
LF	0.50 ± 1.51	0.10	0.13 ± 0.78	0.39	0.28 ± 1.41	0.31
HF	0.04 ± 0.98	0.82	0.21 ± 0.65	0.11	0.02 ± 0.70	0.88
VHF	0.85 ± 2.33	0.07	0.24 ± 1.78	0.50	−0.16 ± 2.33	0.72
UHF	1.06 ± 2.83	0.06	0.01 ± 3.10	0.99	−0.59 ± 3.16	0.34

VHF, very high frequency; UHF, ultra-high frequency.
P values refer to the testing of the null hypothesis of no significant change. Statistical significant *P* values are highlighted in bold.

Table 4. The Change in Power of Fourier Transformed Oscillations (Mean ± SD) From Rest to Flicker Stimulation

Difference From Rest	Peripapillar (n = 27)	*P*	Macular (n = 27)	*P*	Peripheral (n = 27)	*P*
VLF	−0.25 ± 0.99	0.20	−0.76 ± 3.20	0.23	−1.16 ± 2.14	**0.009**
LF	−1.58 ± 1.23	**<0.0001**	−0.81 ± 0.74	**0.006**	−0.90 ± 1.56	**0.006**
HF	−1.83 ± 1.71	**<0.0001**	−0.82 ± 0.74	**<0.0001**	−0.66 ± 0.90	**0.0007**
VHF	−2.72 ± 2.10	**<0.0001**	−2.34 ± 2.04	**<0.0001**	−1.60 ± 1.75	**<0.0001**
UHF	−4.23 ± 2.93	**<0.0001**	−3.89 ± 3.40	**<0.0001**	−2.44 ± 2.79	**0.0001**

VHF, very high frequency; UHF, ultra-high frequency.
P values refer to the testing of the null hypothesis of no significant change. Statistical significant *P* values are highlighted in bold.

peripapillar arterioles significantly by (mean ± SD) 1.76% ± 3.56% ($P = 0.02$). This constriction was not significantly different ($P = 0.07$) from the constriction in either macular (2.31% ± 2.32%) or peripheral arteriolar branches (5.56% ± 8.20%).

Table 3 shows that in all three vessel types isometric exercise significantly increased the power of diameter oscillations in the VLF band ($P < 0.01$), but not in any of the other frequency bands ($P > 0.06$ for all comparisons). The increase in hydraulic conductance induced by diameter oscillations showed no significant differences among the larger (1.43% ± 0.21%), the macular (1.56% ± 0.21%) or the peripheral (1.57% ± 0.17%) arterioles and no significant changes from rest ($P > 0.07$ for all comparisons).

Flicker stimulation significantly increased the diameter of the peripapillar arterioles of (mean ± SD) 5.10% ± 2.91% ($P < 0.0001$), which was not significantly different ($P = 0.86$) from the dilation of macular branches (4.09% ± 11.19%), but significantly higher (p = 0.01) than the dilation in the peripheral branches (0.39% ± 7.68%).

Table 4 shows that flicker stimulation significantly reduced the power of diameter oscillations at all frequency bands in the studied arterioles, except for the VLF bands in the peripapillar and macular arterioles ($P > 0.20$ for both comparisons). The increase in hydraulic conductance induced by diameter oscillations was significantly lower in both the larger (1.19% ± 0.17%) and the macular (1.23% ± 0.14%) arterioles, than in the peripheral (1.42% ± 0.25%) arterioles and lower than in larger and macular arterioles during rest ($P < 0.0001$ for all comparisons). The significant changes in power of diameter oscillations at the low, intermediate and high frequency bands induced by isometric exercise and flicker stimulation obtained by wavelet analyses were similar to those obtained by Fourier analysis

Figure 3 shows traces with a similar pattern of diameter variation at five different positions along a peripapillar arterial segment with a length of 400 µm. There were no significant right shifts in the pattern of diameter changes along the peripapillar arterioles for any of the studied eyes ($P = 1.00$, n = 55).

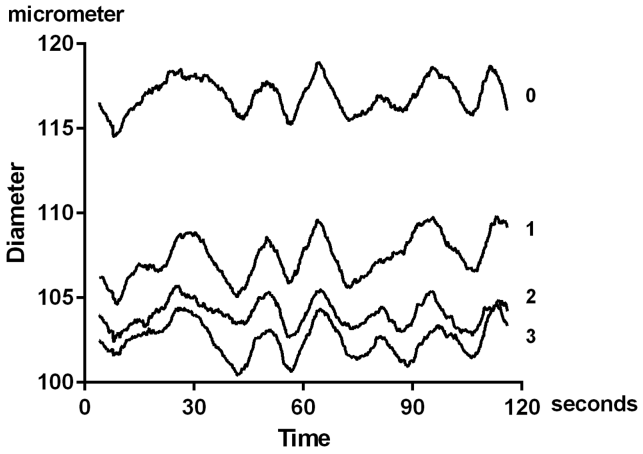

Figure 3. Diameter traces obtained simultaneously at four positions along a peripapillar arteriolar segment with a length of 400 µm. 0 = Most proximal location on the segment, and, respectively, 1 = 100 µm, 2 = 200µm, and 3 = 400 µm along the segment.

Discussion

The pattern of spontaneous diameter oscillations observed in larger retinal vessels from normal persons in the present study support previous data obtained both in the retinal vascular system[5] and outside the eye.[18] In studies using the Dynamic Vessel Analyzer, 17 persons are needed to obtain a statistical power for the measurement of intervention effects on the diameter of retinal vessels.[19] Although the number of observations included in the present study was much higher, it cannot be excluded that some of the negative results of the frequency analyses may have been due to underpowering because the preconditions for a power analysis of oscillations of vessel diameters are different in the frequency than in the time domain. Another potential source of bias is that the diameter recordings were abrupted during blinking and fixation losses. This resulted in missing values that were replaced by the average of all non-missing values in the recording. This would reduce the amplitudes of

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diameter oscillations with increasing effect on higher frequencies and therefore cannot explain the observations where effects were also observed on the amplitudes of the lower frequencies.

The observed patterns of diameter variation over time were unique for each vessel, which may be due to influences from more central parts of the cardiovascular system.[20–22] These patterns showed no significant changes along the studied vascular segments, but it cannot be excluded that the pattern may have changed at either a slower or a faster rate than what could be detected within the duration and the capture rate of the recordings obtained in the present study. The vascular resistance is determined by the diameter at the positions where constriction is most pronounced with the consequent stress on the vascular smooth muscle cells in these areas. The lack of observable short-term propagation of diameter oscillations along the larger vessels argues against a role of vasomotion for mass transport in these vessels and implies that diameter changes at one location are not counteracted by opposite diameter changes at other locations. This highlights the importance of temporal changes in vessel diameters for the regulation of retinal blood flow. The vasomotor activity can be considered important for oxygenation, fluid homeostasis, and flow regulation in the retinal vascular system.[7,8] However, the alternating constriction and dilation of the vessels also has the consequence that periods of activity in the vascular smooth muscle cells interchange with periods of rest, which may prevent fatigue and maintain contractility of the vessels over time. Additionally, vasomotion has derived effects on the hydraulic conductance of the vessels. Changes in vessel diameter translate to changes to the power of four in blood flow. This implies that an increase in diameter above the average in an oscillating vessel induces a higher increase in flow than the decrease in flow induced by the corresponding reduction in diameter below average. This effect on the hydraulic conductance increases with the amplitude of the diameter oscillations. Therefore, for a given hydraulic resistance, oscillations in diameter can reduce the overall workload of the vascular smooth muscle cells. This effect may contribute to a modification of other regulatory mechanisms as found in the present study where the reduced vasomotion amplitude during flicker stimulation tended to reduce the effects of metabolic autoregulation on blood flow in larger and macular arterioles. This feature may help understanding how retinal blood flow is regulated under normal conditions where a coupling to metabolism induced by neuronal activity can be expected to be critical.[18] The findings may also act as a basis for understanding pathological responses in the retinal vasculature. The observed effects of vasomotion on hydraulic conductance are likely too small to play a role for flow regulation but might be of importance in physiological or pathophysiological conditions where the amplitude of diameter oscillations are potentially increased. Future studies should aim at characterizing the role of spontaneous diameter changes for the development of retinal vascular disease and how these changes are affected by treatment interventions.[19] The finding that wavelet analyses of the diameter oscillations resulted in similar conclusions as Fourier analysis argues against the existence of hidden patterns of transient diameter changes in the two-minute recordings used for the frequency analyses.

The results of previous studies suggest that relative changes in the diameter of retinal arterioles are similar at different branching levels,[23] and that absolute diameter changes therefore decrease with increasing branching level. This may explain the larger powers of oscillations in the LF and the HF bands in the larger arterioles than in the macular and peripheral arteriolar branches and confirm that these frequencies of diameter changes between 1.4 to 4.2 cycles/minute (period lengths of 14–42 seconds) are physiologically important for flow control.[18] The increase in the arterial blood pressure induced by isometric exercise broadened the frequencies where the power of diameter oscillations was increased to include the VLF band. This may be a response to the increased tension in cells in the vascular wall secondary to the increased intravascular pressure.[24] Conversely, the power of all frequency bands at all three arterial vessel types were reduced during flicker stimulation, where the lack of significance of the responses in the VLF band in peripapillary and macular arterioles may be the result of higher variability of the measurements. A previous study found a lack of effect of isometric exercise on diameter oscillations of retinal arterioles in diabetic patients.[5] This may be related to loss of autoregulation and underlines the significance of describing this phenomenon under normal conditions.

The fact that peripheral arterioles showed less dilation to flicker stimulation, more reduction in Fourier power, and less reduction in hydraulic resistance than the macular arterioles confirm previous studies of differences in autoregulation,[25] oxygen saturation,[26] and ischemic conditioning[12] among macular and peripheral arterioles in normal persons. This argues that vasomotion may contribute to the differences in response potential of retinal vascular disease in the macular area and the retinal periphery.[5,27] However, it remains to be investigated whether vasomotion and the derived effects on the retinal microcirculation are affected differently in the macular area and the retinal periphery in retinal vascular disease.

Altogether, the study has shown a lack of short-term propagation of diameter changes along peripapillar retinal arterioles. Furthermore, the amplitudes of arteriolar vasomotion were found to increase when the vessels contracted secondary to isometric exercise and to decrease when the vessels dilated secondary to flicker stimulation, which also reduced the hydraulic conductance in larger and macular arterioles. The results confirm the complexity of the regulation of retinal blood flow and can be used as a basis for studying pathological vasomotion in retinal vascular disease.

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References

1. Mitsui R, Hashitani H. Synchrony of spontaneous Ca2+ activity in microvascular mural cells. *J Smooth Muscle Res*. 2020;56(0):1–18.
2. Cole WC, Gordon GR, Braun AP. Cellular and ionic mechanisms of arterial vasomotion. *Adv Exp Med Biol*. 2019;1124:297–312.
3. Hessellund A, Jeppesen P, Aalkjaer C, Bek T. Characterization of vasomotion in porcine retinal arterioles. *Acta Ophthalmol*. 2003;81:278–282.

4. Hessellund A, Aalkjaer C, Bek T. Effect of cyclic guanosine-monophosphate on porcine retinal vasomotion. *Acta Ophthalmol*. 2006;84:228–233.
5. Bek T, Jeppesen P, Kanters JK. Spontaneous high frequency diameter oscillations of larger retinal arterioles are reduced in type 2 diabetes mellitus. *Invest Ophthalmol Vis Sci*. 2013;54(1):636–640.
6. Yu D-Y, Cringle SJ, Yu PK, Balaratnasingam C, Mehnert A, Sarunic MV, An D, Su E-N. Retinal capillary perfusion: spatial and temporal heterogeneity. *Prog Retin Eye Res*. 2019;70:23–54.
7. Intaglietta M. Vasomotor activity, time-dependent fluid exchange and tissue pressure. *Microvasc Res*. 1981;13:131–136.
8. Federspiel WJ, Sarelius IH. An examination of the contribution of red cell spacing to the uniformity of oxygen flux at the capillary wall. *Microvasc Res*. 1984;27:273–285.
9. Bek T. Diabetic maculopathy caused by disturbances in retinal vasomotion. A new hypothesis. *Acta Ophthalmol Scand*. 1999;77;376–380.
10. Petersen L, Bek T. Diameter changes of retinal arterioles during acute hypoxia in vivo are modified by the inhibition of nitric oxide and prostaglandin synthesis. *Curr Eye Res*. 2015;40:737–743.
11. Kaya MY, Petersen L, Bek T. Lack of effect of nitroglycerin on the diameter response of larger retinal arterioles in normal persons during hypoxia. *Graefes Arch Clin Exp Ophthalmol*. 2016;254:277–283.
12. El Dabagh Y, Petersen L, Pedersen M, Bek T. Reduced baseline diameter and contraction of peripheral retinal arterioles immediately after remote ischemia in diabetic patients. *Graefes Arch Clin Exp Ophthalmol*. 2019;257:2095–2101.
13. Garhofer G, Bek T, Boehm AG, et al. Use of the retinal vessel analyzer in ocular blood flow research. *Acta Ophthalmol*. 2010;88:717–722.
14. Jeppesen P, Gregersen PA, Bek T. The age-dependent decrease in the myogenic response of retinal arterioles as studied with the Retinal Vessel Analyzer. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:914–919.
15. Mehlsen J, Jeppesen P, Erlandsen M, Poulsen PL, Bek T. Lack of effect of short-term treatment with amlodipine and lisinopril on retinal autoregulation in normotensive patients with type 1 diabetes and mild diabetic retinopathy. *Acta Ophthalmol*. 2011;89:764–768.
16. Tilma KK, Bek T. Topical treatment for 1 week with latanoprost but not diclofenac reduces the diameter of dilated retinal arterioles in patients with type 1 diabetes mellitus and mild retinopathy. *Acta Ophthalmol*. 2012;90:750–755.
17. Parthimos D, Edwards DH, Griffith TM. Minimal model of arterial chaos generated by coupled intracelluar and membrane Ca2+ oscillations. *Am J Physiol*. 1999;227(3):H119–H144.
18. Liu S, Zhao L, Liu Y. The origin of vasomotion and stochastic resonance in vasomotion. *Front Bioeng Biotechnol*. 2022;10:819716.
19. Petersen L, Bek T. Post-hypoxic constriction of retinal arterioles is impaired during nitric oxide and cyclo-oxygenase inhibition and in diabetic retinopathy without retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2017;255:1965–1971.
20. Stefanova A. Coupled oscillators: Complex but not complicated cardiovascular and brain interactions. *IEEE Eng Med Biol Mag*. 2007;26(6):25–29.
21. Mateo C, Knutsen PM, Tsai PS, Shih AY, Kleinfeld D. Entrainment of arteriole vasomotor fluctuations by neural activity is a basis for blood-oxygenation-level-dependent "resting-state" connectivity. *Neuron*. 2017;96:936–948.
22. Holowatz LA, Thompson-Torgersen CS, Kenney WL. The human cutaneous circulation as a model of generalized microvascular function. *J Appl Physiol*. 2008;1:370–1372.
23. Ernst C, Aalkjaer C, Bek T. ATP induced calcium signaling activity in perivascular cells differ at different vascular branch levels in the porcine retina. *Microvasc Res*. 2022;139:104256.
24. Arciero JC, Secomb TW. Spontaneous oscillations in a model for active control of microvessel diameters. *Math Med Biol*. 2012;29:163–180.
25. Skov Jensen P, Jeppesen P, Bek T. Differential diameter responses in macular and peripheral arterioles may contribute to the regional distribution of diabetic retinopathy lesions. *Graefes Arch Clin Exp Ophthalmol*. 2011;249:407–412.
26. Jørgensen CM, Bek T. Lack of differences in the regional variation of oxygen saturation in larger retinal vessels in diabetic maculopathy and proliferative diabetic retinopathy. *Br J Ophthalmol*. 2017;101:752–757.
27. Bek T. Translational research in retinal vascular disease. An approach. *Acta Ophthalmol*. 2019;97(5):441–450.

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