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# Blood pressure effects on retinal vessel diameter and flicker response: A 1.5-year follow-up

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PURPOSE. *The study examined the influence of individual blood pressure changes over time on retinal vessel diameter and the latter's response to flicker light.*
METHODS. *The diameter of a retinal arterial and venous segment was measured continuously online with a Dynamic Vessel Analyzer in 20 patients twice (mean interval between examinations of 24 months). Eleven patients had no cardiovascular disease. Nine patients had arterial hypertension and were untreated at the time of the first measurement; at the time of the second measurement they were undergoing various antihypertensive therapies. Each test consisted of a 50-s baseline plus three 20-s periods of flicker stimulation followed by an 80-s period of observation. During the examinations the blood pressure was measured at 1-minute intervals.*
RESULTS. *In the hypertension group changes in the mean arterial blood pressure (MAP) correlated significantly with changes in the arterial baseline diameter ($y=-0.1-0.37x$, $r=0.74$, $p_{(increase)}<0.03$). A comparison of the two measurements showed no such relationship in the group of cardiovascularly healthy subjects. The venous baseline and the arterial and venous flicker response did not change significantly in either group between the two measurements and showed no relationship to blood pressure changes.*
CONCLUSIONS. *In hypertensive subjects, long-term therapy-related changes in blood pressure induced a change in the arterial baseline by approximately +3.7 µm/–10 mmHg MAP. An influence of lowering MAP to the arterial flicker response could not be detected. (Eur J Ophthalmol 2006; 16: 560-5)*

KEY WORDS. *Arterial hypertension, Blood pressure, Flicker light, Retinal vessel analyzer, Retinal vessel diameter*

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## INTRODUCTION

Cardiovascular disease ranks at the top of morbidity and mortality statistics of developed countries due to increasing life expectancy and lifestyle factors. A better understanding of pathogenetic processes and the knowledge and diagnosis of as many risk factors as possible are approaches to individualized prevention and early treatment. Systemic arterial hypertension, one of the foremost disease factors in this complex, is known to lead to macro- and microangiopathy. Changes in major vessels, measurable, for example, by the ankle-brachial index or by carotid Doppler sonography, have been well evaluated in terms of their prognostic value for cardiovascular events (1-5). In recent studies it has been shown that diameter changes in major vessels are accompanied by retinal microangiopathy (6-8).

Epidemiologic studies have shown a close relationship

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between hypertension and retinal arteriolar narrowing (7, 9-11). Since the retina is, in ontogenetic terms, a projection of the brain, and retinal arteriolar narrowing has been shown to be an independent prognostic marker of stroke (10), retinal arterial narrowing is seen as a sign of cerebral arteriosclerosis (8). Parameters such as the arteriole-to-venule ratio (AVR) (7, 9, 10) and the arterial diameter at branch points (8) mentioned in the above-cited studies characterize morphologic vascular properties and are used by us in statical retinal vessel analysis. In addition, analysis of serial images of the fundus can be used to determine the behavior of the vessel diameters—whether spontaneous (e.g., pulse-synchronous changes [12]) or induced (by respiratory gas changes [13-15], intraocular pressure changes [16, 17], blood pressure [BP] changes [18, 19], flicker light [20-23]). Parameters of such dynamic vessel analysis reflect the functional properties of retinal vessels. The extent and rate of vessel diameter changes depend on the provocation method. Thus, retinal arteries contract by an average of 5.5% after approximately 2 minutes in response to a BP increase of 24 mmHg brought about by isometric muscle exertion (18). By contrast, retinal vessels dilate by up to 10% within seconds in response to flicker light. It is believed that this response is mediated by the vascular endothelium (24). The endothelium plays a key initial role in the development of cardiovascular disease (25, 26). As a supplement to previous diagnostic techniques, some of which are invasive (27), there is a simple way to examine endothelial function noninvasively in vivo via the retina. A reduced flicker response of retinal arterioles has already been demonstrated in patients with untreated hypertension (28) and in patients with diabetes mellitus (29).

The present study investigated the influence of changes in subjects' BP profile over a period of at least 1 year on retinal vessel diameter and flicker response.

## PATIENTS AND METHODS

In a prospective clinical study one eye of each of 20 patients (Tab. I) was examined twice after about 2 years by dynamic vessel analysis. Eleven patients had no cardiovascular disease and were taking no vasoactive medication at either of the examination points. Nine patients came to the first examination with untreated hypertension on referral by their ophthalmologist. At the time of the second examination they were undergoing various antihypertensive therapies initiated by their general practitioners. Ophthalmologic exclusion criteria for the examined eye were clouding of the refractive media, visual acuity of <0.5, astigmatism of >2.0 D, myopia of >7.0 D, ocular disease, a history of eye operations or injuries, and the wearing of contact lenses within the past 24 hours. General exclusion criteria were acute infection, diabetes mellitus, and pregnancy or lactation.

The subjects' clinico-ophthalmologic status was first determined (visual acuity, objective refraction, slit-lamp microscopy, applanation tonometry, funduscopy), and the pupil of the eye to be examined was dilated with tropicamide. The vessel diameter was then measured with a dynamic vessel analyzer (DVA, IMEDOS Germany). At the start of the examination a section of a large parapapillary retinal artery and vein approximately 1 mm in length was marked out by the examiner (Fig. 1). The marked vascular sections were then scanned at a rate of 25 images per second. The position of the edges, the angular offset, and the diameter of the vessel as well as a correction for ocular movements were calculated automatically online. Since the image scale of each eye was unknown, the measured values were expressed in relative units (RUs). These units correspond to micrometers if the examined eye has the dimensions of the standard Gullstrand eye. Due to the pixel size of the CCD matrix and oblique positioning, each single vessel scan was approximately 30 µm long. The measurement accuracy perpendicular to the course of the vessel was <1 µm. The analysis was based on the mean of all scanned segments of the marked vessel section measured over 1 second. The camera was focused, the eye was allowed to adapt, and the uninfluenced vessel diameter was measured for 50 s. This was followed by three 20-s cycles of flicker provocation and an 80-s period of observation. The period from 30 s to 1 s before flicker provocation was taken as the baseline, and the subsequent diameter response was standardized to this. The mean baseline (RUs) and mean flicker dilation (%) were calculated from the three provocation cycles (Fig. 2). The first measurement was carried out by a prototype of the DVA which could detect online only the arterial vessel diameter. The venous segment was measured offline using a SVHS record. In some of these offline measurements the detection of the venous diameter during the flicker period was impossible because of a lack of synchronization (Fig. 2, lowest curve).

The flicker light was generated by 12.5 Hz rectangular-

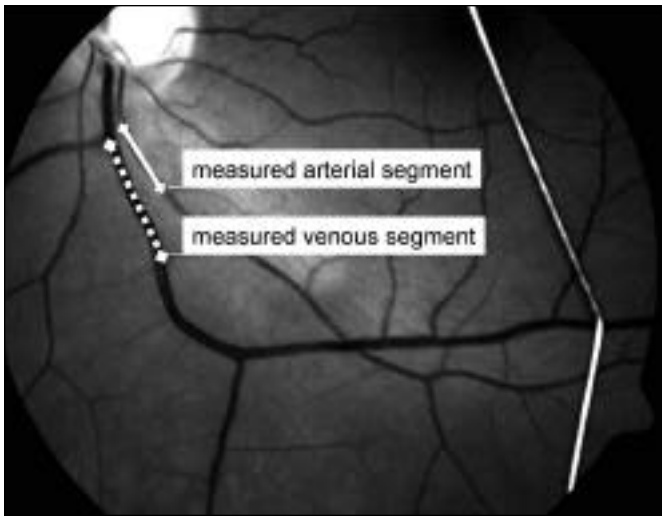


**Fig. 1 -** *Hypertensive patient, K.H., 48-year-old man, image with the inner fixation of the retina camera, selected arterial and venous segment.*

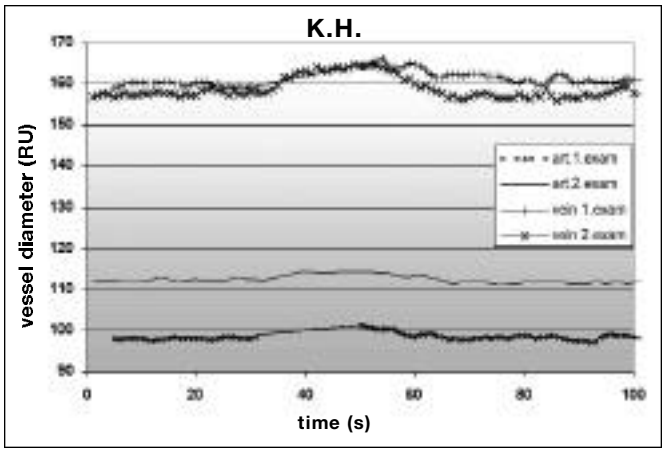


**Fig. 2 -** *Patient K.H., mean flicker response of the retinal vessel segments marked in Figure 1 in the first and second examinations.*

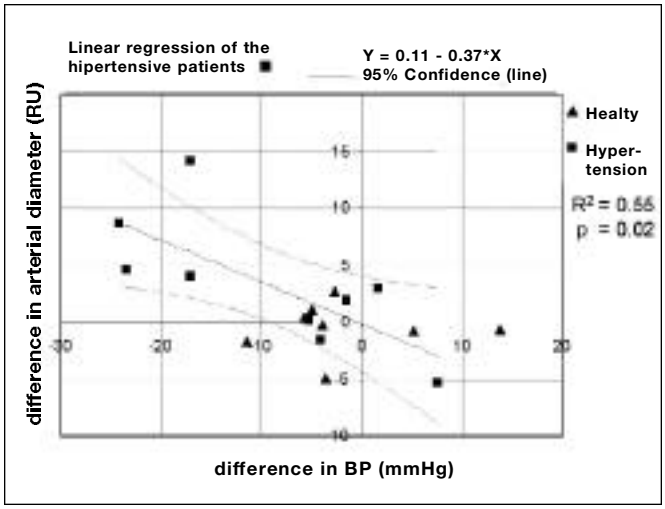


**Fig. 3 -** *Changes in mean blood pressure and arterial baseline values.*

wave interruption of the green test light of the RVA (530–600 nm, irradiance at the fundus approximately 1.96 x $10^{-4}$ W/$cm^2$) over the entire 30° field of view of the retinal camera. The mean arterial systemic BP was derived from the systolic and diastolic BP values measured at 1-minute intervals during the examination ($BP_{mean} = BP_{diast} + 1/3\ [BP_{sys} - BP_{diast}]$).

The Wilcoxon test and regression analysis were applied for statistical analysis. The study was approved by the Ethics Committee of the Thuringia State Medical Board. All the participants had given their informed consent in writing.

## RESULTS

### *Blood pressure during the examinations*

The BPs did not differ significantly between the first and second examinations either in the subgroup of normotensive subjects or in the group of hypertensive subjects. The latter finding is due to the fact that in the small sample size one patient did not exhibit any BP reduction despite antihypertensive therapy, while another patient actually showed a further increase in BP.

### *Baseline vessel diameters*

The baseline values of the measured arterial and venous segments did not differ significantly between the two examinations in either of the two groups (Tab. II). For the change in the arterial baseline diameter in the group of hypertensive subjects, however, a close correlation was found with changes in mean systemic BP (Fig. 3):

$$y = -0.1 - 0.37x,\ r = 0.74,\ p_{(increase)} < 0.03$$

No such correlations were observed in the healthy group or in respect to the venous baseline.

### *Flicker response*

No significant change in the mean arterial and venous flicker response was found in either of the two subgroups or in the group as a whole. Nor was a significant correlation found between changes in BP and changes in arterial or venous flicker-induced dilation.

## DISCUSSION

The relationship between BP and retinal vessel diameter has been extensively investigated in a number of studies. Thus, in epidemiologic studies, the sum of all measured parapapillary arterial vessel diameters decreased by 2.0% and that of venous diameters by 0.3% with every 10 mmHg rise in MAP (30). These values represent a momentary state of a large population but provide no information on changes in vessel diameter as a function of changes in MAP. A brief rise in MAP by >20 mmHg in healthy subjects induced by muscular exertion led to arterial constriction of 2.4% per 10 mmHg MAP rise (18) and 2.2% per 10 mmHg MAP rise (31). Drug-induced reduction of systemic BP in healthy subjects to markedly hypotensive levels with sodium nitroprusside 2.0 µg/kg/min dilated arterial and venous segments by approximately 4.5% per 10 mmHg fall in MAP (32). This myogenic reaction of retinal vessels, which occurs within minutes, is known as the Bayliss effect. It is an autoregulatory mechanism that protects downstream vascular beds from hypertensive pressure peaks. However, this autoregulatory capacity of the vascular bed declines markedly with advancing age (33). It has also been shown that the Bayliss effect is reduced in diabetic retinopathy to a degree depending on the disease stage (31). Very few studies have been published on vessel diameter changes associated with long-term BP changes. Thus, retinal arterial constriction of 2.8 µm per 10 mmHg MAP was measured in pregnant diabetic women from the first to third trimesters (34). After delivery the vessel diameters returned to first-trimester values. It is notable that no rela-

**TABLE I -** CHARACTERISTICS OF THE STUDY GROUPS, MEAN ± SD

| Parameter | Normal BP (N) | Hypertensive subjects (H) | Significance of N – H difference |
|---|---|---|---|
| Number | 11 | 9 | NS |
| Age, y | 48.1 ± 12.4 | 50.6 ± 13.3 | NS |
| Female | 6 | 6 | NS |
| Interval between examinations, mo | 27.4 ± 5.3 | 19.6 ± 3.7 | < 0.001 |
| Blood pressure first examination, mmHg | 105.0 ± 12.4 | 109.6 ± 9.5 | NS |
| Blood pressure second examination, mmHg | 100.8 ± 9.0 | 100.4 ± 11.3 | NS |

BP= Blood pressure

**TABLE II -** FLICKER RESPONSE PARAMETERS (Mean ± SD)

| Parameter | Normal BP (N) | Hypertensive subjects (H) |
|---|---|---|
| Arterial baseline first examination (RUs) | 116.7 ± 9.8 | 116.1 ±12.7 |
| Arterial baseline second examination (RUs) | 114.5 ± 8.4 | 119.4 ± 12.3 |
| Arterial dilation first examination (%) | 5.8 ± 2.9 | 4.4 ± 2.4 |
| Arterial dilation second examination (%) | 5.5 ± 3.5 | 3.4 ± 2,3 |
| Venous baseline first examination (RUs) | 142.1 ± 19.2 | 152.6 ± 16.6 |
| Venous baseline second examination (RUs) | 151.9 ± 19.3 | 150.6 ± 22.9 |
| Venous dilation first examination (%) | 5.2 ± 1.8 | 5.1 ± 1.2 |
| Venous dilation second examination (%) | 5.7 ± 3.6 | 4.6 ± 2.0 |

BP = Blood pressure

**TABLE III -** COEFFICIENT OF VARIATION (%) OF THE BASELINE ARTERIAL DIAMETER AND THE ARTERIAL FLICKER DIALATION, MEASUREMENTS OF IDENTICAL VESSEL SEGMENTS BY DVA

| Interval | 15 min* | 1 h† | 2 h‡ | 1 mo† | 1 mo‡ |
|---|---|---|---|---|---|
| Baseline | 2.6 | 1.4 | 1.0 | 1.8 | 2.2 |
| Flicker dilation | | 0.75 | | 0.91 | |

*(32), †(35), ‡(36) DVA = Dynamic vessel analyzer

tionship between retinopathy stage and vessel diameter changes was found in pregnant women, whereas smoking reduced the autoregulatory vessel response. The change from baseline of 3.7% per 10 mmHg blood pressure reduction measured in our study in hypertensive subjects corresponded well to the results from induced myogenic autoregulation in healthy subjects, the epidemiologic averages, and observations in pregnant women. In our cardiovascularly healthy comparison group no such relationship was found between in-study BP measurements and the arterial baseline diameter. An explanation could be the superposition in healthy subjects of other regulatory systems, e.g.. an intact NO release mechanism in the epithelium, on BP-induced diameter responses. This is also suggested by the smaller flicker-induced arterial dilation measured in hypertensive subjects in comparison to healthy subjects (Tab. II). The antihypertensive treatment of our patients was very different and therefore changes of vessel diameter were not specific but caused probably by the BP lowering. The long-term reduction of arterial constriction as the BP of a hypertensive subject normalizes suggests a reduction of hypertensive vessel damage and is in keeping with the known risk reduction for cerebral and vascular events. Whether this is the case for all patients with arterial hypertension remains unclear, as does the influence of the duration of hypertension and specific therapies.

The changes in retinal arterial diameter caused by changes of systemic BP are small. They were significant detectable in former time by analysis of single images only in larger study populations fundus. Dynamic vessel analysis uses online series of images and is characterized by small variances of diameter values (see Tab. III). Therefore the used method seems to be sensitive enough to measure small individual changes of the retinal vessels. Regardless of the methodic advantages, the small study population, different therapies of the hypertensive patients, and only two examinations in the trial course are limitations of the presented study. The results should encourage further clinical trials for an improved observation of microvascular damage due to hypertension.

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