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ABSTRACT

**Purpose:** To study changes in retinal microcirculation and the prevalence of chronic paracentral acute middle maculopathy (PAMM) lesions in patients with mild hypertension.

**Design:** Prospective cohort study.

**Participants:** Twenty-seven patients (21 males and 6 females, 50.3 ± 6.3 years) with mild hypertension and with low cardiovascular risk, and 24 healthy subjects (15 males and 9 females, 46.3 ± 13.0 years) were included.

**Methods:** The foveal avascular zone (FAZ) area, vessel density of superficial, and deep capillary plexus were assessed using optical coherence tomography (OCT) angiography. The presence of chronic PAMM lesions was evaluated for both eyes by the revision of cross-sectional OCT images of 6-mm volume scans. A chronic/resolved PAMM lesion was defined as inner nuclear layer thinning with outer plexiform layer disruption.

**Main outcome measures:** Vessel density of superficial and deep capillary plexus and prevalence of chronic PAMM lesions.

**Results:** There was no difference between the hypertensive group and healthy group in demographic and clinical characteristics, vessel density of superficial capillary plexus (48.9 ± 2.4% and 47.8 ± 2.0%, respectively, p = 0.92), vessel density of deep capillary plexus (54.1 ± 3.3% and 54.0 ± 1.8%, respectively, p = 0.93), or FAZ area (0.26 ± 0.13 mm² and 0.23 ± 0.9 mm², respectively, p = 0.37). Chronic PAMM lesions were found in 24 out of 27 (88.9%) hypertensive patients and in 4 out of 24 (16.7%) healthy individuals. The odds ratio for the presence of chronic PAMM lesions in subjects with mild hypertension was 40.0 (p < 0.001).

**Conclusion:** Chronic PAMM lesions are highly prevalent in hypertensive patients and may represent the earliest changes in retinal
microcirculation in patients with mild hypertension, before changes in OCT angiography parameters have become apparent.

**Keywords:** optical coherence tomography angiography; hypertension; paracentral acute middle maculopathy; capillary plexus; vessel density; foveal avascular zone; blood pressure
Introduction

Changes in microcirculation in the end-organs is a key stage of hypertension which leads to cardiovascular complications. Although a number of organs suffer from microcirculatory damage, only the retina allows direct observation of these changes in vivo.

Detailed analysis and quantification of retinal microcirculation have become available upon the introduction of optical coherence tomography angiography (OCTA), which has the potential to improve early diagnosis of hypertension. Using OCTA data, several studies have revealed the decrease in vessel density of superficial and deep capillary plexuses in patients with advanced hypertension\textsuperscript{1,2}. However, the role of OCTA for the diagnosis of mild hypertension remains uncertain.

In a recent paper, we showed that, in patients with unilateral RVO, the healthy eye frequently demonstrated resolved (chronic) paracentral acute middle maculopathy (PAMM) lesions, which may indicate previous episodes of deep retinal capillary ischemia\textsuperscript{3}. This study also found an association of resolved PAMM lesions with hypertension in otherwise healthy individuals, although this was not the purpose of the investigation\textsuperscript{3}. We suggest that deep retinal capillary ischemia appearing as PAMM lesions might be one of the earliest findings associated with an alteration of retinal microcirculation, including that which occurs in hypertension. This is because PAMM represents damage to the deep vascular complex, which is considered the primary site in the progression of retinal ischemia.

In this study, we evaluated retinal microcirculation in patients with mild hypertension using OCTA and focused specifically on the prevalence of chronic PAMM lesions in these patients.

Material and methods

All patients were informed about the aim and design of this study and signed informed consent for the use of the data obtained during the cardiological and ophthalmic examination for the study. The study followed
the ethical standards stated in the Declaration of Helsinki and was approved by the Local Ethics Committee. All participants were referred from the cardiological department after comprehensive cardiological examination and categorized into two study groups, patients with mild hypertension and healthy participants. Hypertensive patients had been referred to the cardiological department by a general physician if hypertension was suggested. Healthy volunteers were recruited during a routine medical examination and had an additional cardiological examination as a part of the study. The main inclusion criterion for hypertensive patients was mild hypertension defined as Grade I hypertension (systolic blood pressure of 140-159 mm Hg and diastolic blood pressure of 90 - 99 mm Hg) with low risk of cardiovascular events (a calculated 10 year Systematic COronary Risk Evaluation (SCORE) system risk of <1%) according to the definitions of the European Society of Hypertension (ESH)/European Society of Cardiology (ESC). All blood pressure measurements, including that of healthy participants, were performed by ambulatory blood pressure monitoring in the cardiological department. The conclusion as to the presence/absence of mild hypertension was made by a cardiologist. Other inclusion criteria for both groups were age 35 - 60 years and both eyes available for OCTA examination. Exclusion criteria were hypertension worse than mild, or any other concomitant systemic diseases, including diabetes mellitus, best-corrected visual acuity less than 20/20, myopia higher than 6.0 D, hyperopia higher than 2.0 D, any pathology of the posterior eye segment, strength signal index lower than 70, quality of OCTA scans less than Q7, and significant motion artefacts on OCTA images. All hypertensive patients were receiving antihypertensive therapy with either an angiotensin converting enzyme inhibitor or an angiotensin-2 receptor blocker.

All participants received a comprehensive ophthalmic examination, including OCT examination using RTVue-XR Avanti (Optovue, Fremont,
CA, software version 2017.1.0.150). Angio Retina 3 mm (304 2×B-scans each of 304 A-scans) and HD Angio Retina 6 mm (400 2×B-scans each of 400 A-scans) volume scans centered on the center of the macula were obtained for both eyes of each participant. The main OCTA parameters, including superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density as well as foveal avascular zone (FAZ) area from right eyes, were extracted from 3×3 mm OCTA scans and used for analysis. Only default segmentation was used to evaluate OCTA parameters for both SCP and DCP. Six-mm volume OCTA scans were used only for identification of chronic PAMM lesions. For this, all cross-sectional images of the 6-mm volume scan were scrolled and carefully reviewed in AngioVue software by two masked specialists (D.S.M. and M.A.B.), independently. A chronic/resolved PAMM lesion on a cross-sectional image was defined as the area of the inner nuclear layer thinning associated with outer plexiform layer disruption (elevation) as described previously. Since, in contrast to large classical PAMM lesions, the actual changes of outer plexiform layer in such small resolved/chronic PAMM lesions are not fully understood, the term “disruption” was used as a descriptive characteristic of findings on cross-sectional OCT images. Additionally, for each eye, we evaluated the slab constructed using two segmentation lines of the outer plexiform layer with -9 µm and 0 µm shift (Figure 1). As was shown earlier, such a thin slab highlights outer plexiform layer disruption as being sharply delineated black areas (eFigures in the Supplement). The presence of at least one chronic PAMM lesion, even in one eye of a participant, confirmed by two specialists upon cross-sectional and en face images simultaneously was sufficient for an individual to be considered as having chronic PAMM lesions. Readings for systolic and diastolic blood pressure (as well as the conclusion on the presence of mild hypertension) were provided by a cardiologist after all patients had completed the ophthalmic examination.
MedCalc 18.4.1 (MedCalc Software) was used for statistical analysis. The results are expressed as the mean ± standard deviation. An independent samples t-test was performed for continuous variables (age, FAZ area, SCP vessel density, and DCP vessel density) and Fisher’s exact test was used to compare binary variables (gender). The odds ratio was calculated for the presence of chronic PAMM lesions in one eye of hypertensive patient versus the healthy age-matched individual. The interrater correlation coefficient (kappa) was calculated for categorization of patients as having the chronic PAMM lesions or not and for the number of the chronic PAMM lesions identified. Statistical significance was defined as $P < 0.05$.

**Results**

In total, 68 participants were enrolled and 51 were included in the study, 9 and 8 participants were excluded due to ophthalmological and systemic exclusion criteria, respectively. Twenty-seven hypertensive patients (21 males and 6 females, 27 eyes) with a mean age of 50.3 ± 6.3 years and 24 healthy age-matched subjects (15 males and 9 females, 24 eyes) with a mean age of 46.3 ± 13.0 years were included in this case-control observational study. There were no statistically significant differences in the male-to-female ratio ($p = 0.21$, exact Fisher test) and age ($p = 0.18$, t-test) between study groups. The mean systolic blood pressure in hypertensive and healthy group was 141.0 ± 16.9 and 124.8 ± 10.1 mm Hg, respectively. The mean diastolic blood pressure in hypertensive and healthy group was 93.0 ± 11.0 and 82 ± 5.2 mm Hg, respectively.

Vessel density in SCP of hypertensive patients and healthy individuals was 48.9 ± 2.4% and 47.8 ± 2.0%, respectively ($p = 0.92$). Vessel density in DCP of hypertensive patients and healthy individuals was 54.1 ± 3.3% and 54.0 ± 1.8%, respectively ($p = 0.93$). Mean FAZ area in hypertensive patients and healthy individuals was 0.26 ± 0.13 mm$^2$ and
0.23 ± 0.9 mm², respectively (p = 0.37) (Figure 2). No hypertensive vascular changes were noted during fundoscopy.

Chronic PAMM lesions were found in 24 out of 27 hypertensive patients (88.9%) and in 4 out of 24 healthy participants (16.7%). In hypertensive patients, chronic PAMM lesions were found in 25 right and 20 left eyes. In healthy individuals, PAMM lesions were found in 3 right and 3 left eyes. There was no statistically significant difference in the distribution of the lesions between right and left eyes, neither in hypertensive patients (p = 0.29) nor in healthy individuals (p = 0.65). The odds ratio for the presence of at least one chronic PAMM lesion in one eye of the hypertensive patient compared to the age-matched healthy individual was 40.0 (95% CI 8.0 - 200.1, p < 0.001) (Figure 3). The mean number of chronic PAMM lesions in the eyes of hypertensive patients was 1.5 ± 1.8 (range 1 to 4) and 1.7 ± 0.8 (range 1 to 3) in the eyes of healthy subjects if any. The chronic PAMM lesions were distributed mostly outside the perifovea. There were no acute lesions detected. There were no cases of disagreement between the specialists in the categorization of patients as having PAMM lesions or not. The interrater correlation coefficient (kappa) was 1.0 (95% CI 1.0 to 1.0). The interrater correlation coefficient for the number of PAMM lesions identified was 0.98 (95% CI 0.97 to 0.99).

**Discussion**

In this study, we evaluated retinal microcirculation in patients with mild hypertension. No statistically significant changes were found to the main OCTA parameters compared to age-matched controls, including vessel density in superficial and deep capillary plexus as well as the FAZ area. However, patients with mild hypertension were more likely to demonstrate chronic PAMM lesions. This leads us to conclude that detectable quantitative changes in retinal vessel density are not the earliest signs of hypertension. These results agree with our previous study, where resolved (chronic) PAMM lesions were associated with hypertension in
otherwise healthy subjects\textsuperscript{3}. However, the odds ratio for resolved PAMM lesions in patients with hypertension was substantially higher in the current study than reported previously (40.0 versus 5.6)\textsuperscript{3}. This difference could be anticipated since the diagnosis of hypertension in the current study was established by a comprehensive cardiological examination rather than being extracted from electronic medical records. Thus, in a previous study, some healthy patients who demonstrated resolved PAMM lesions might have had undiagnosed hypertension. Simultaneous association of resolved PAMM lesions with both retinal vein occlusions and hypertension is reasonable since hypertension is one of the most important risk factors for retinal vein occlusions.

Elevated blood pressure is the most important preventable cause of general mortality and mortality from cardiovascular diseases\textsuperscript{6}. A linear association between the elevation of blood pressure and the risk of cardiovascular events including stroke, myocardial infarction, and sudden cardiac death has been shown for all age groups\textsuperscript{6}. The risk of cardiovascular events is in turn associated with the damage of microcirculation in end-organs\textsuperscript{7}. However, direct observation of microvessels in vivo is available only in the eye, and particularly in the retina, where the evaluation of the vessels is standardized and reproducible. The result of the evaluation of retinal vessels may be extrapolated to general end-organ damage and may provide the basis for early diagnosis of hypertension.

Measurement of vessel diameter is a standard approach for the evaluation of retinal vessels and includes different modifications and techniques\textsuperscript{8,9}. This approach is mostly based on evaluating relatively large retinal vessels. However, changes in large retinal vessels do not occur as early as those in the capillary bed. OCTA has recently allowed fine quantitative analysis of the retinal microcirculation in vivo. In fact, in advanced hypertension, OCTA shows the alteration of retinal
microcirculation as a decrease of vessel density in the superficial and deep capillary plexuses\textsuperscript{1,2}. It is worth stressing that this applies mainly to advanced or poorly controlled hypertension. At the same time, Chua J. and coauthors showed that only the deep capillary plexus suffers in milder hypertensive cases, while the superficial capillary plexus remains unchanged\textsuperscript{10}. This data agrees with the high prevalence of chronic PAMM lesions in patients with mild hypertension in our study and with the suggestion that the deep capillary plexus is highly vulnerable to ischemic damage\textsuperscript{11}. Analysis of the evolution of retinal ischemia in retinal arterial occlusions has shown that the earliest ischemic changes occur at the level of the deep capillary plexus and appear as PAMM lesions\textsuperscript{12}. This fact is explained by decreased tissue oxygenation at the venous pole of retinal microcirculation when blood flow is slowed by the arterial/venous occlusion. This seems logical since, when erythrocyte transit time is decreased, extraction of oxygen at the arterial level of the capillary bed increases, leading to ischemia at the venular level. We suggest that the higher vulnerability of the deep capillary plexus also applies in the chronic remodeling of retinal microcirculation, where transient hypoperfusion in small arterial branches results in focal PAMM lesions.

PAMM was firstly described by the group of Sarraf D. as an idiopathic isolated alteration of retinal microcirculation at the level of the deep capillary plexus and was distinguished from acute macular neuroretinopathy\textsuperscript{11}. Further, Nemiroff J. and coauthors, based on OCTA data, confirmed the flow deficit in the DCP in PAMM lesions\textsuperscript{12}. Similar lesions were described in a number of studies in patients with a broad spectrum of ocular and systemic conditions, including central retinal artery occlusion, branch retinal artery occlusion, central retinal vein occlusion, Purtcher’s retinopathy, sickle-cell disease, hormonal therapy, and diabetes mellitus\textsuperscript{11,14-17}. We conclude, therefore, that PAMM is not a distinct condition, but rather a clinical finding in the broad spectrum of vascular
The high prevalence of chronic PAMM lesions in hypertensive patients strongly supports this suggestion. Moreover, this fully agrees with the fact that arterial hypertension is a universal risk factor for many retinal diseases. However, it remains unclear if chronic PAMM lesions are associated with other retinal conditions considered non-ischemic where hypertension is already known to be a significant risk factor, such as central serous chorioretinopathy and age-related macular degeneration. We found no difference in the vessel density of superficial and deep capillary plexus, or the FAZ area, between hypertensive patients and age-matched controls. This seems to conflict with previous studies which have reported a decreased vessel density and increased FAZ area in hypertension. However, in our study, we exclusively selected only mild hypertensive patients with low cardiovascular risk and with minimally affected microcirculation. Additionally, in our patients, there was a discrepancy between the presence of chronic PAMM lesions, which represent deep capillary ischemia, and unchanged vessel density of the deep capillary plexus. We believe that several facts explain this discrepancy. Firstly, the number and area of chronic PAMM lesions are relatively small and their contribution to changes in OCTA metrics is therefore limited. Secondly, as suggested by Nemiroff J. and coauthors, ischemia-reperfusion may be responsible for both ischemic injury in PAMM and preservation of microcirculation in acute PAMM lesions. Although, for chronic PAMM lesions, the loss of perfusion in the deep capillary plexus is considered inevitable, in small lesions this may not be as discernible as in large classical lesions. Thirdly, the chronic PAMM lesions were distributed mostly outside the perifovea and may not affect the vessel density metric within the central 3-mm region. A detailed analysis of chronic PAMM lesion with high-resolution OCTA (using 3-mm scans) might clarify the vascular changes in those lesions. However, this was not done in our study because
the study design did not include 3-mm OCTA scans centered on the lesions. Furthermore, this analysis could not be performed after completion of the study since the lesions were distributed almost exclusively outside the area covered by 3-mm scans. Therefore, further studies on the microvascular anatomy of these lesions are warranted. Finally, if PAMM lesions appear before the decrease in vessel density and FAZ enlargement, this would represent one of the earliest and mildest forms of ischemic retinal injury associated with hypertension.

The limitations of this study include 1) the limited number of participants and 2) the skewed male-to-female ratio (0.29) of the study population. Although the last fact requires precaution when applying our findings to the natural population, both study and control groups were matched regarding age and gender. Furthermore, the fact that a few healthy individuals demonstrate PAMM lesions remains unexplained. It could be that the definition for hypertension and the threshold for retinal ischemic injury may not overlap completely, not least since retinal ischemia is a multifactorial event. A longitudinal study might help to establish if hypertension could occur in these individuals in future.

In conclusion, this study showed that hypertension is strongly associated with the presence of small chronic PAMM lesions in an otherwise healthy population. These lesions can be found in the eyes of patients with mild hypertension without detectable changes in OCTA parameters and, therefore, may facilitate early diagnosis of hypertension.

Appendix

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.17632/j7g3fh6vnm.1
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Figure 1. A representative example of en face optical coherence tomography image used for detection of chronic paracentral acute middle maculopathy lesions. A. The en face image constructed with a 9-µm slab at the lower border of the outer plexiform layer. B. A cross-sectional scan shows the position of segmentation lines of the outer plexiform layer with -9 µm and 0 µm shift.

Figure 2. Representative optical coherence tomography angiography (OCTA) images in healthy individual and hypertensive patient. A. En face and cross-sectional images from the right eye of the healthy individual demonstrates no paracentral acute middle maculopathy (PAMM) lesions. B. En face and cross-sectional images from the right eye of the hypertensive patient shows multiple chronic PAMM lesions. C. OCTA image in superficial capillary plexus in the healthy individual. D. OCTA image in superficial capillary plexus in the hypertensive patient. E. OCTA image in deep capillary plexus in the healthy individual. F. OCTA image in deep capillary plexus in the hypertensive patient. Vessel density parameters (yellow insets in C - F) in the healthy individual and hypertensive patient are within the normal range. Foveal avascular zone area in the healthy individual and hypertensive patient is 0.23 mm² and 0.26 mm², respectively.

Figure 3. En face and cross-sectional optical coherence tomography images from the mild hypertensive patient and healthy individual. A. En face image from the left eye of the mild hypertensive patient constructed with a 9-µm slab at the lower border of the outer plexiform layer (OPL) demonstrates multiple chronic PAMM lesions appearing as dark areas (white arrowheads). B. Cross-sectional scan through chronic paracentral
acute middle maculopathy (PAMM) lesions shows multiple areas of the inner nuclear layer thinning and OPL disruption (white arrowheads) which correspond to the dark areas on the en face image. The dashed line represents the position of the cross-sectional scan. C. En face image from the right eye of the healthy individual constructed with a 9-µm slab OPL shows no disruption of OPL. D. Cross-sectional scan through the center of the fovea. The dashed line represents the position of the cross-sectional scan.
**Highlights**

Chronic (resolved) paracentral acute middle maculopathy lesions are highly prevalent among mildly hypertensive patients and have an odds ratio of 40.0 of being found in hypertensive patients versus age-matched controls.