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Retinal and Choroidal Capillary Perfusion Are Reduced in Hypertensive Crisis Irrespective of Retinopathy

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Purpose: Hypertensive crisis causes end-organ damage through small-vessel damage as described histologically. Noninvasive optical coherence tomography angiography (OCTA) makes it possible to image retinal and choroidal capillaries on a microscopic level in vivo. We quantified eye vessel perfusion changes in hypertensive crisis using OCTA.

Methods: Patients with hypertensive crisis (systolic blood pressure $\geq$180 mm Hg and/or diastolic blood pressure $\geq$110 mm Hg) and age-matched healthy controls were included in the study. OCTA en face 3 $\times$ 3-mm images of the superficial and deep retinal layers and the choriocapillaris were acquired. Outcome parameters included vessel density (VD) and vessel skeleton density (VSD) of the superficial and deep retinal layers, as well as flow voids of the choriocapillaris.

Results: Twenty-eight eyes of 17 patients and 31 age-matched control eyes of 18 healthy subjects were included. VD and VSD of the deep retinal layer were significantly reduced in hypertensive crisis ($P \leq 0.004$). Choriocapillaris signal intensity was more heterogeneous in patients, and flow voids exhibited confluence with a larger average area and a lower absolute count ($P \leq 0.045$). These changes were independent of time since onset of hypertensive crisis and of the presence and extent of retinopathy. Deep retinal changes were associated with renal end-organ failure ($P = 0.045$).

Conclusions: Hypertensive crisis is associated with a significant reduction in retinal and choroidal capillary perfusion based on OCTA findings. These alterations are independent of retinopathy and related to end-organ damage.

Translational Relevance: OCTA might help distinguish hypertensive urgency from hypertensive emergency earlier than currently possible.

Introduction

A hypertensive crisis can be the first manifestation of arterial hypertension or a complication of existing primary or secondary hypertension[1–3] and may cause considerable damage in end organs such as hypertensive retinopathy, nephropathy, or encephalopathy.[2–4]

Hypertensive crises affect 1% to 2% of all patients with essential hypertension,[1,2] and an estimated 5 of 1000 patients in emergency departments present with a hypertensive crisis.[5] This illustrates the relevance of detecting hypertensive crises–related end-organ complications as early as possible due to the high medical and socioeconomic relevance of the disease. Existing histologic studies indicate an association between capillary changes and end-organ failure,[6,7] which renders imaging of the capillary bed clinically relevant. High-resolution imaging of capillaries in vivo, however, remains difficult. The eye is the only organ that allows for direct examination, imaging, and quantitative analyses of vessels using, for example, high-resolution optical coherence tomography (OCT).

OCT is a noninvasive, noncontact imaging method based on local interference between an object's signal and a reference signal.[8,9] It has recently been extended to OCT angiography (OCTA), which allows for the noninvasive visualization of the retinal vasculature by detecting blood flow based on the variability in OCT amplitude and phase signal over time.[10–12]

Hence, with OCTA, high-resolution noninvasive in vivo imaging of retinal capillaries and the choriocapillaris is possible in hypertensive crisis. We examined retinal and choriocapillaris perfusion in patients with hypertensive crisis on OCTA and compared them with healthy controls.

Methods

Subject Recruitment

Ethics approval was obtained from the ethics committee of the University of Bonn (approval ID 089/08). Patients with hypertensive crisis (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg,[4,13–15] episode ≤7 days prior to eye examination) were recruited from the departments of cardiology and ophthalmology of the University of Bonn, Germany. In the patient group, recent estimated glomerular filtration rate (using the Modification of Diet in Renal Disease Study 4 Equation equation) was obtained from the laboratory results available. Age-matched subjects without a history of arterial hypertension were recruited as a control group. Informed consent was obtained from all participants prior to study inclusion. The study adhered to the principles of the Declaration of Helsinki. Exclusion criteria were concurrent retinal or choroidal pathology, history of glaucoma or diabetes, high myopia, and insufficient OCTA image quality for quantification (e.g., media opacities, movement artifacts, signal strength index <7).

Image Acquisition

OCTA images were acquired using a swept-source OCTA device with 100,000 A-scans per second at a 1040- to 1060-nm central wavelength (Zeiss PLEX Elite 9000; Carl Zeiss Meditec, Dublin, CA, USA). The scan size was a 3 × 3-mm cube centered on the macula. Automatic segmentation algorithms of the device were used and manually corrected if necessary before exporting the OCTA en face images of the superficial retinal layer (encompassing the nerve fiber layer, ganglion cell layer, and the inner plexiform layer), the deep retinal layer (encompassing the inner nuclear layer, outer plexiform layer, and the Henle fiber layers), and the choriocapillaris layer (10–40 µm below retinal pigment epithelium (RPE)-fit segmentation) following the current vessel nomenclature for OCTA images.[16] For the images of the deep retinal layer and the choriocapillaris, superficial vessel projections were removed by the software provided by the device manufacturer (PLEX Elite 9000 software version 2.0.0.42943, Zeiss PLEX Elite 9000; Carl Zeiss Meditec, Dublin, CA, USA).

Image Analysis

The open-source image-processing software Fiji,[17] which is based on ImageJ[18] (version 1.51w; National Institutes of Health, Bethesda, MD, USA), was used to quantify the perfusion parameters. In a first step, the en face images of the superficial and deep retinal layer were binarized with an automatic thresholding algorithm ("Li" algorithm[19] for superficial layers and "Moments" algorithm[20] for deep layer, with the assumed perfused vessel structures displayed in white). Vessel density (VD) was calculated for the binarized images.[21] The binarized images were skeletonized, and vessel skeleton density (VSD), which "adjusts" for differences in vessel diameter and is putatively more responsive to alterations of small vessels, was calculated.[21] In addition, the vessel diameter index (VDI) was calculated, describing the relation of vessel diameter to total vessel length (for formulae, please see supplementary file).[21] For the choriocapillaris layer, mean signal intensity and standard deviation of mean signal intensity were analyzed. Additionally, choriocapillaris flow voids were calculated. For this purpose, the choriocapillaris en face OCTA images were binarized using the Phansalkar local thresholding algorithm (radius: 50 px, approximating 150 µm[22]). The number of coherent areas (interpreted as flow voids) was counted, and their individual sizes were determined. Mean numbers of flow voids per eye and their respective absolute and relative sizes were calculated. Additionally, the number of flow voids was binned according to their size. Since the flow void frequency versus size relationship followed a power law distribution, a linear regression line was fitted to the logarithm of the original values to describe the distribution as previously described.[22]

Statistical Analysis

The data were prospectively collected and statistically analyzed with IBM SPSS Statistics for Windows, version 25 (IBM Corporation, Armonk, NY, USA) and R version 3.5.0 (R Core Team, Vienna, Austria). Between- and within-group comparisons were done using the Mann-Whitney U test due to the limited sample size and data distribution requirements being met. Multiple regression analysis was performed to assess the association of clinical signs, measures of kidney function, and OCTA parameters. For this purpose, OCTA variables with Spearman correlation coefficients >0.5 and $P < 0.05$ were included in regression models as independent variables. Due to

Table. OCTA Variables (Mean ± Standard Deviation) Acquired in Patients and Control Subjects

Characteristic	Patients	Control Subjects	*P* Value
Superficial retinal layer			
Vessel density	0.303 ± 0.030	0.310 ± 0.027	0.387
Vessel skeleton density	$7.5 \times 10^{-8} \pm 6.9 \times 10^{-9}$	$7.7 \times 10^{-8} \pm 4.2 \times 10^{-9}$	0.145
Vessel diameter index	4,044,250 ± 318,855	4,027,524 ± 221,147	0.574
Deep retinal layer			
Vessel density	0.086 ± 0.021	0.103 ± 0.019	**0.004**
Skeleton density	$4.7 \times 10^{-8} \pm 6.1 \times 10^{-9}$	$5.2 \times 10^{-8} \pm 5.0 \times 10^{-9}$	**0.002**
Vessel diameter index	1,829,463 ± 269,663	1,967,183 ± 182,722	0.064
Choriocapillaris			
Mean signal intensity	74.2 ± 10.0	75.9 ± 10.5	0.682
Standard deviation of signal intensity	22.8 ± 4.6	19.7 ± 1.7	**0.002**
Mean number of flow signal voids	3167 ± 941	3679 ± 416	**0.045**
Mean size of flow signal voids	99 ± 49	71 ± 26	**0.025**
Mean slope of flow void regression line	−1.9 ± 0.2	−2.1 ± 0.3	**0.011**
Mean ordinate intercept of flow void regression line	7.2 ± 0.7	7.8 ± 0.6	**0.009**

P Values printed in bold are below the level of significance ($P < 0.05$).

the exploratory nature of the study, no adjustment for multiple comparisons was performed. For regression analysis, we used linear mixed models with a random intercept per patient.

Results

Twenty-eight eyes of 17 patients (7 women, 10 men) and 31 eyes of 18 age-matched controls (8 women, 10 men) were included. There was no significant difference in mean age between patients (56 ± 19 years) and controls (52 ± 16 years, $P = 0.578$). Maximum systolic and diastolic blood pressures measured noninvasively in the patient group during hypertensive crisis were 250 mm Hg and 141 mm Hg, respectively. Mean logMAR best-corrected visual acuity was 0.1 in the patient group, and 10 (36%) of the eyes had clinical signs of hypertensive retinopathy (narrowed arterioles, arteriovenous nicking, retinal hemorrhages, retinal exudates, cotton wool spots, retinal edema). Patients were on blood pressure–lowering drugs, including renin-angiotensin-aldosterone system inhibitors (13 participants, 76%), calcium channel antagonists (10, 59%), β-blockers (7, 41%), α-adrenergic substances (4, 24%), and diuretics (3, 18%).

Microvascular perfusion was significantly impaired in the deep retinal layer, and choriocapillaris perfusion was more heterogeneous in hypertensive crisis (Table). VD and VSD of the deep retinal layer were decreased in the patient group (Fig. 1), and choriocapillaris flow voids were also significantly larger and more heterogeneous in patients with hypertensive crisis (Fig. 2). Maximum systolic blood pressure in the patient group was significantly associated with the standard deviation of the choriocapillaris signal intensity ($\beta = 4.8$; 95% confidence interval [CI], 0.4–9.3). In a subgroup analysis of eyes without macular edema and respective age-matched controls (48 eyes of 30 participants), VD and VSD of the deep retinal layer were decreased in patients ($P = 0.013$ and $P = 0.011$, respectively). The standard deviation of the choriocapillaris signal intensity was also significantly more heterogeneous in patients in this subgroup compared with controls ($P = 0.007$).

In multiple regression analysis of the overall cohort, all OCTA parameters were independent of time since onset of hypertensive crisis. We calculated a sum score of the conventional features of hypertensive retinopathy as visualized by funduscopy (1 point for each arteriovenous crossing signs, retinal hemorrhages, retinal exudates, cotton wool spots, papilledema). The resulting score representing retinal involvement was independent of the OCTA parameters assessed. VDI of the deep retinal layer was significantly associated with estimated glomerular filtration rate as a proxy for renal end-organ failure ($\beta = 2.9 \times 10^{-5}$; 95% CI, 7.3×10^{-7} to 5.8×10^{-5}).

Discussion

We found a significantly impaired deep retinal and choriocapillaris perfusion using OCTA in patients with

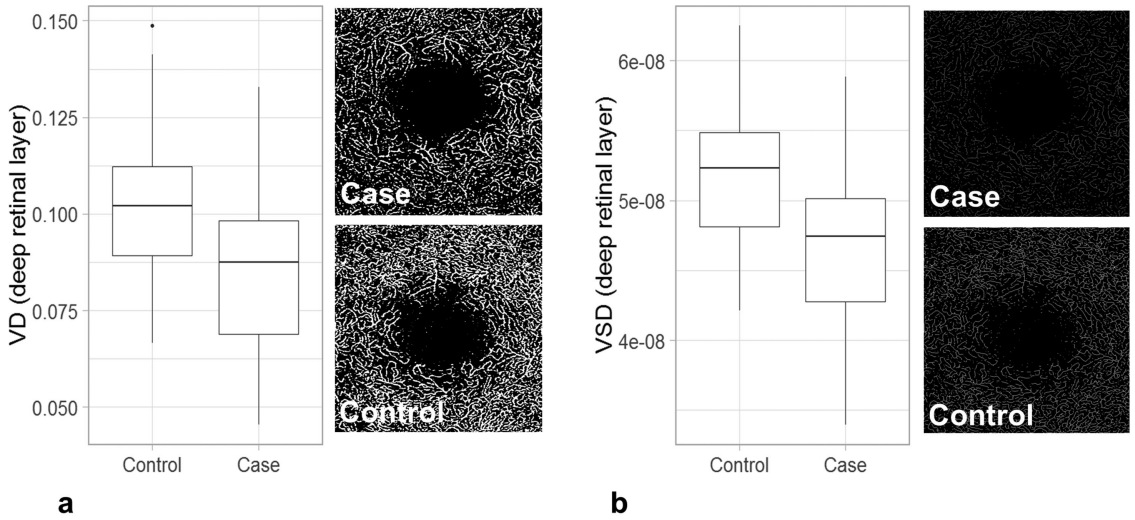

Figure 1. Vessel density (a) and vessel skeleton density (b) values of the deep retinal layer in subjects with hypertensive crisis and controls with examples of binarized (a) and skeletonized (b) OCTA images. Values more than 1.5 times the interquartile range from the quartiles were considered outliers according to Tukey's rule.[31]

hypertensive crisis. To our knowledge, this is the first report showing impaired retinal and choroidal perfusion in hypertensive crisis. At present, patients with hypertensive urgency and hypertensive emergency can hardly be distinguished before clinical signs of end-organ damage such as renal failure become apparent. Noninvasive investigation of the retinal and choroidal microvasculature based on OCTA could aid differentiation of hypertensive urgency and emergency as well as identify patients at risk of developing severe systemic complications associated with hypertensive emergencies.

Our results support the hypothesis that microvascular damage is present in patients with hypertensive crisis and correspond with studies in patients with chronic systemic hypertension in whom reduction of retinal capillary density has previously been shown.[23–27] Chua et al.[23] found significant correlations between blood pressure and glomerular filtration rate, on one hand, and retinal capillary density on OCTA, on the other hand, in 77 subjects with chronic hypertension. They hypothesized that arteriolar narrowing due to atherosclerosis could lead to a loss of the retinal vascular autoregulation and capillary rarefaction. Takayama et al.[24] analyzed the choriocapillaris in patients with chronic hypertension and healthy volunteers and found a significant correlation between OCTA endpoints and funduscopic changes according to the Keith-Wagener-Barker classification. However, these studies describe patients with moderate chronic elevation of blood pressure, whereas in our study, only patients with recent highly elevated blood pressure levels ≥180 mm Hg systolic and/or ≥110 mm Hg diastolic were included. The pathophysiology of hypertensive crisis is not entirely understood, but differences from the development of chronic hypertension have been noted since hypertensive crises occur in both normotensive and hypertensive individuals.[4,28] Acute microcirculatory changes in hypertensive individuals might therefore differ from chronic changes, which makes it important to investigate both disease entities.

Historically, several studies have investigated the diagnostic value of funduscopic examination in hypertensive patients.[2,29,30] Even though associations between signs of hypertensive retinopathy (including retinal hemorrhages, exudates, and papilledema) and organ impairment have been described, funduscopic signs had only a low predictive value for end-organ damage.[2] Yet, OCTA allows rapid high-resolution imaging of capillaries at the ocular fundus and enables us to detect abnormalities at the microanatomic level. In our patients, especially the perfusion of the deep retinal capillaries was impaired, which is not readily visible in ophthalmoscopy. Moreover, the choriocapillaris perfusion was impaired and presented as more heterogeneous with fewer, yet larger flow void areas compared with healthy controls. Furthermore, changes of retinal flow patterns were significantly associated with renal end-organ failure. We propose that these changes and their dynamics might identify patients at risk for developing end-organ failure (i.e., hypertensive emergencies) earlier than it is currently possible.

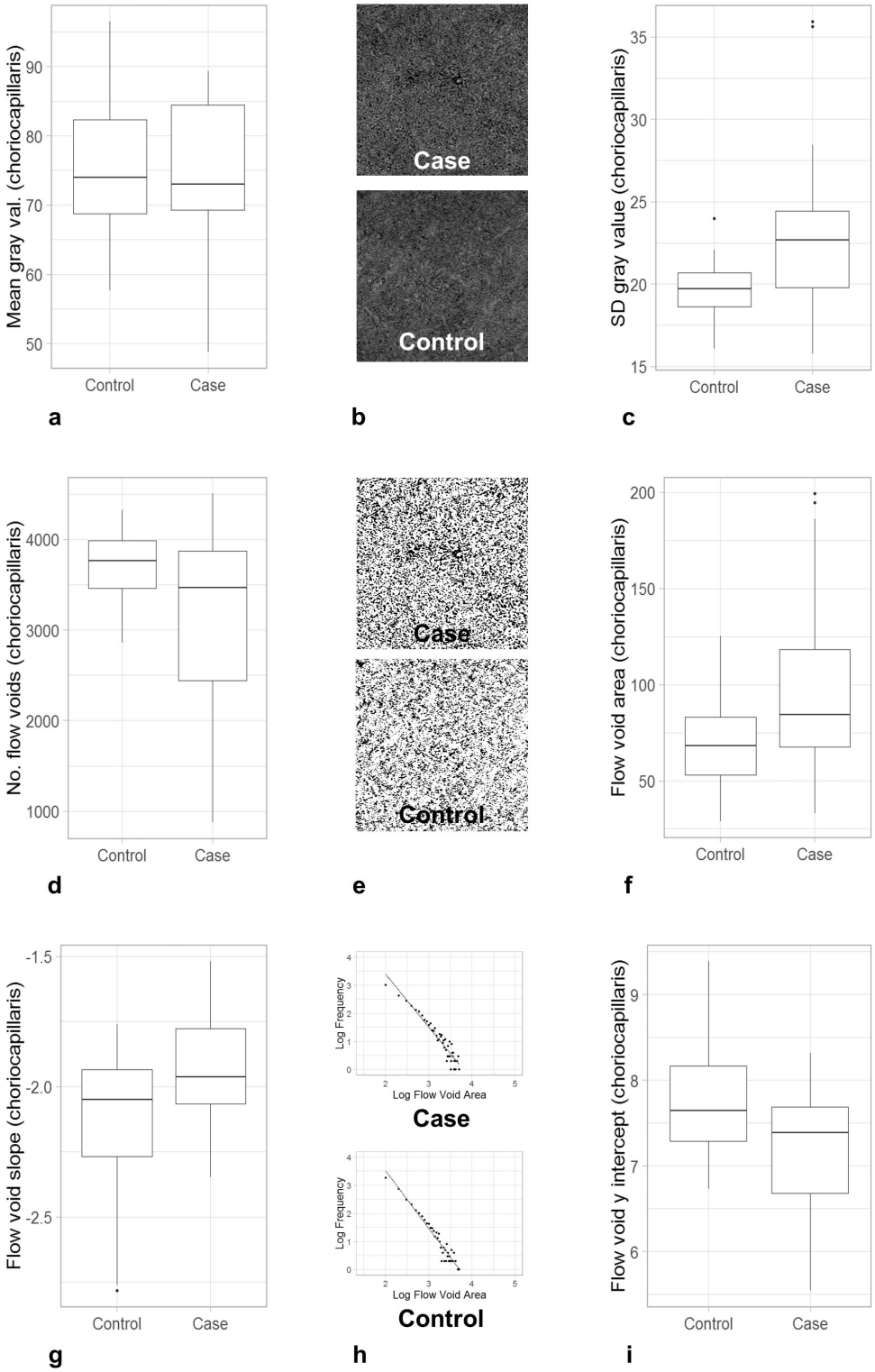

Figure 2. Boxplots showing choriocapillaris flow parameters in subjects with hypertensive crisis and controls (a, c, d, f, g, i), and exemplary raw (b) and binarized OCTA images of the choriocapillaris (e) with flow voids shown in *black* and the logarithmic choriocapillaris flow void distributions with *regression lines* (h) used to analyze slope and ordinate intercept. Values more than 1.5 times the interquartile range from the quartiles were considered outliers according to Tukey's rule.[31]

To our knowledge, we present the first OCTA study in individuals after recent hypertensive crisis. Strengths of our study include the comprehensive ocular phenotyping and the in-depth analysis of both retinal and choriocapillaris flow parameters, the analysis of high-resolution 3 × 3-mm OCTA en face images that provide more details than OCTA images with larger fields of view, and an interdisciplinary approach. Limitations of our study include the relatively small sample size, the lack of laboratory testing, and availability of blood pressure measurements for our control group. As we did not follow participants up over time, we cannot comment on whether any of the observed changes were reversible. This needs to be assessed in future studies.

In conclusion, we found impaired retinal and choriocapillaris perfusion in patients with recent hypertensive crisis. Future studies on longitudinal changes of the microcirculation in the course of hypertensive crises and the clinical usefulness of OCTA parameters to detect patients at risk for end-organ failure are warranted.

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References

1. Ipek E, Oktay AA, Krim SR. Hypertensive crisis: an update on clinical approach and management. *Curr Opin Cardiol*. 2017;32:397–406.
2. Aggarwal M, Khan IA. Hypertensive crisis: hypertensive emergencies and urgencies. *Cardiol Clin*. 2006;24:135–146.
3. Rodriguez MA, Kumar SK, De Caro M. Hypertensive crisis. *Cardiol Rev*. 2010;18:102–107.
4. Varounis C, Katsi V, Nihoyannopoulos P, Lekakis J, Tousoulis D. Cardiovascular hypertensive crisis: recent evidence and review of the literature. *Front Cardiovasc Med*. 2017;3:51.
5. Pinna G, Pascale C, Fornengo P, et al. Hospital admissions for hypertensive crisis in the emergency departments: a large multicenter Italian study. *PLoS One*. 2014;9:e93542.
6. Nonaka K, Ubara Y, Sumida K, et al. Clinical and pathological evaluation of hypertensive emergency-related nephropathy. *Intern Med*. 2013;52:45–53.
7. Chester EM, Agamanolis DP, Banker BQ, Victor M. Hypertensive encephalopathy: a clinicopathologic study of 20 cases. *Neurology*. 1978;28:928–939.
8. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254:1178–1181.
9. Podoleanu AG. Optical coherence tomography. *J Microsc*. 2012;247:209–219.
10. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express*. 2012;20:4710–4725.
11. Cohen SY, Miere A, Nghiem-Buffet S, Fajnkuchen F, Souied EH, Mrejen S. Clinical applications of optical coherence tomography angiography: what we have learnt in the first 3 years. *Eur J Ophthalmol*. 2018;28:491–502.
12. Spaide RF, Klancnik JM, Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015;133:45–50.

13. Park SK, Lee DY, Kim WJ, et al. Comparing the clinical efficacy of resting and antihypertensive medication in patients of hypertensive urgency: a randomized, control trial. *J Hypertens*. 2017;35:1474–1480.
14. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
15. Bender SR, Fong MW, Heitz S, Bisognano JD. Characteristics and management of patients presenting to the emergency department with hypertensive urgency. *J Clin Hypertens (Greenwich)*. 2006;8:12–18.
16. Campbell JP, Zhang M, Hwang TS, et al. Detailed vascular anatomy of the human retina by projection-resolved optical coherence tomography angiography. *Sci Rep*. 2017;7:42201.
17. Schindelin J, Arganda-Carreras I, Frise E, et al. Fiji: an open-source platform for biological-image analysis. *Nat Methods*. 2012;9:676–682.
18. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods*. 2012;9:671–675.
19. Li CH, Tam PK. An iterative algorithm for minimum cross entropy thresholding. *Pattern Recognition Lett*. 1998;19:771–776.
20. Tsai W. Moment-preserving thresholding—a new approach. *Comput Vis Graphics Image Process*. 1985;29:377–393.
21. Kim AY, Rodger DC, Shahidzadeh A, et al. Quantifying retinal microvascular changes in uveitis using spectral-domain optical coherence tomography angiography. *Am J Ophthalmol*. 2016;171:101–112.
22. Spaide RF. Choriocapillaris flow features follow a power law distribution: implications for characterization and mechanisms of disease progression. *Am J Ophthalmol*. 2016;170:58–67.
23. Chua J, Chin CWL, Hong J, et al. Impact of hypertension on retinal capillary microvasculature using optical coherence tomographic angiography. *J Hypertens*. 2019;37:572–580.
24. Takayama K, Kaneko H, Ito Y, et al. Novel classification of early-stage systemic hypertensive changes in human retina based on OCTA measurement of choriocapillaris. *Sci Rep*. 2018;8:15163-018-33580-y.
25. Chua J, Chin CWL, Tan B, et al. Impact of systemic vascular risk factors on the choriocapillaris using optical coherence tomography angiography in patients with systemic hypertension. *Sci Rep*. 2019;9:5819-019-41917-4.
26. Pascual-Prieto J, Burgos-Blasco B, Avila Sanchez-Torija M, et al. Utility of optical coherence tomography angiography in detecting vascular retinal damage caused by arterial hypertension. *Eur J Ophthalmol*. 2019;1120672119831159.
27. Donati S, Maresca AM, Cattaneo J, et al. Optical coherence tomography angiography and arterial hypertension: a role in identifying subclinical microvascular damage? *Eur J Ophthalmol*. 2019;1120672119880390.
28. Zanotti-Cavazzoni SL. *Critical Care Medicine*. 3rd ed. Philadelphia, PA: Mosby; 2008:723–733.
29. Shantsila A, Lip GYH. Malignant hypertension revisited—does this still exist? *Am J Hypertens*. 2017;30:543–549.
30. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004;351:2310–2317.
31. Chambers JM, Cleveland WS, Kleiner B, Tukey PA. *Graphical Methods for Data Analysis*. Wadsworth, Belmont, CA, 1983:35.