

# Peripheral arterial filling time and peripheral retina fluorescence features in ultra-widefield angiography

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## Abstract

• **AIM:** To evaluate the peripheral arterial filling time (PAFT) and venous filling time (VFT) in eyes without known diseases that may influence filling process using ultra-widefield (UWF) fluorescein angiography (FA), and to review the peripheral retina fluorescence features.

• **METHODS:** A total of 30 eyes of 30 patients were retrospectively reviewed in this observational study. UWF-FA was performed using Optos 200Tx. PAFT and VFT was recorded. The interval between the arterial or venous filling completion and the previous photo was documented. The appearance of the far peripheral retina was described as either granular background fluorescence or mottled fluorescent band or vascular leakage. Terminal vascular patterns was described as loop pattern or branching pattern. Microvascular abnormalities such as arteriovenous shunting, vessels crossing the horizontal raphe, right angle vessels, terminal networks, capillary nonperfusion, drusen or microaneurysms were evaluated.

• **RESULTS:** The normal limits of PAFT was 3.397-8.984s and 4.399-11.753s for VFT. The appearance of the far peripheral retina, defined as granular background (63%), mottled fluorescence (20%), or vascular leakage (17%), was symmetrical between both eyes. Capillary nonperfusion (23%) and microaneurysms (40%) were more frequently found in eyes with loop pattern than in eyes with branching pattern. Other peripheral signs such as right-angle vessels (73%), and terminal networks (80%) were commonly seen on UWF-FA in the normal peripheral retina.

• **CONCLUSION:** The main courses of retinal artery and vein filling time are overlapping with each other on UWF-FA.

Notably, the arterial filling process is completed in the arteriovenous phase rather than the traditionally named arterial phase. There are various manifestations in the peripheral retina of normal eyes.

• **KEYWORDS:** peripheral arterial filling time; venous filling time; ultra-widefield fluorescein angiography; peripheral retina fluorescence features

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## INTRODUCTION

The widespread use of ultra-widefield (UWF) imaging systems has had a significant impact on the diagnose and management of various vitreo-retinal diseases. It allows for recording up to 200° of retina in a single capture, covering approximately 82% of the retina in a single image<sup>[1]</sup>. UWF imaging allows us to see more details of the peripheral retinal vessels, which has not been thoroughly studied before<sup>[2]</sup>. The present standard descriptive parameters are still based on 55° fluorescein angiography (FA) image.

In traditional FA that captured by a single 55° FA image, arterial phase filling is classically described as lasting approximately 2s<sup>[3]</sup>. The presence of arterial forward phenomenon is an indication for artery insufficiency, most frequently seen in retinal artery occlusion and ocular ischemic syndrome. In UWF images, the periphery arterial filling process can be captured, and arterial forward phenomenon can always be seen. Several studies have provided some detailed analyses of the fluorescence features of the far peripheral retina of normal eyes<sup>[3-9]</sup>. But periphery arterial and venous filling features have not been well characterized. Among these studies, only one study has mentioned the mean peripheral arterial filling time (PAFT) and suggests the normal range using 2 standard deviation (SD) to be approximately 4-14s<sup>[3]</sup>. But there is no widely accepted standard for arterial filling phase in UWF images.

In previous studies, many fluorescence features of the far peripheral retina have been described, such as mottled

fluorescent band, ground glass hyperfluorescence, granular hyperfluorescence and vascular leakage<sup>[5,8]</sup>. Terminal vascular patterns was described as loop pattern or branching pattern<sup>[7]</sup>. Other vascular related or non-related signs were also noted and recorded as arteriovenous shunting, vessels crossing the horizontal raphe, right angle vessels, terminal networks, capillary nonperfusion, microaneurysms, and drusen<sup>[3,8]</sup>.

In this study, we aimed to describe the PAFT and venous filling time (VFT) in eyes without known diseases that may influence filling process using UWF FA, in an effort to provide a reference for study and clinical use. In the meantime, we also have reviewed the peripheral retina fluorescence features and discussed the symmetry between two eyes of one person.

## SUBJECTS AND METHODS

**Ethical Approval** Ethics approval was obtained from the Institutional Ethic Committee of Beijing Tongren Hospital, Capital Medical University. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all examined individuals before UWF FA.

**Study Population** This is an observational, retrospective study conducted in the Department of Ophthalmology, Beijing Tongren hospital, Beijing, China. We retrospectively reviewed UWF FA images from February 2017 to June 10, 2020. Inclusion criteria are eyes without known diseases that may influence filling process. Therefore, eyes with no pathologic diagnosis made, macular epiretinal membrane, macular hole, previous laser treatment for peripheral retina degeneration were included. Most healthy cases were ordered UWF FA to screen for familial exudative vitreoretinopathy (FEVR) but without positive findings. Exclusion criteria were as follows: refractive error over -6.0 diopters (D); patients with concomitant diseases with a recognized potential for retinal vessel pathology, such as diabetic retinopathy, hypertensive retinopathy, retinal vein occlusion, retinal artery occlusion, ocular ischemic syndrome, premature birth history, FEVR, Coats' disease, uveitis, scleritis and sickle cell retinopathy; past history of vitreoretinal surgery and glaucoma; and unanalyzable images owing to poor image quality due to cataract or poor patient cooperation. The presence of myopia, hypertension or diabetes was based on their medical records. Patients who had diabetes mellitus were included only when there was no diabetic retinopathy. The presence of hypertension was distinguished if the patients identified themselves as hypertensive in their medical history or if they had a history of taking antihypertensive drugs. Patients who had hypertension were checked for their blood pressure before the procedure and FA was done if their blood pressure was under 160/90 mm Hg.

**UWF Fluorescein Angiography** The pupil was dilated with 0.5% tropicamide and 0.5% norepinephrine hydrochloride,

and UWF pseudocolor images were captured centered on the fovea using the Optos 200Tx (Optos, Dunfermline, Scotland, United Kingdom). After intravenous administration of fluorescein dye (5 mL of sodium fluorescein 10%, Alcon Pharmaceuticals) through the antecubital vein, UWF images were obtained during the early (35s), middle (1-5min), and late (10min) phases of the angiography. During the middle phase, in addition to a central image centered on the macula, the FA images were steered superiorly, inferiorly, temporally, and nasally to allow clear visualization of the far-peripheral retina.

**Image Analysis** In order to make sure the interval between each image captured during the early phase is short enough not to cause falsely prolonged filling time, UWF images were strictly screened by two readers (She HC and Zhang XF) independently. If there was a discrepancy between the two readers, the images were reviewed again with both evaluators present to render a consensus determination. The interval between the filling completion and the previous photo for arterial and venous filling was recorded respectively.

For qualified UWF images, PAFT and VFT was recorded (Figure 1). PAFT was calculated from the beginning of arterial filling to the completion of arterial trunk filling in temporal peripheral region. VFT was calculated from the beginning of laminar flow of the first vein to the complete filling of all veins. Cilioretinal artery and its drainage vein were distinguished and excluded from the calculation.

For each subject, the appearance of the far peripheral retina was described as either granular background fluorescence or mottled fluorescent band or vascular leakage (Figure 2).

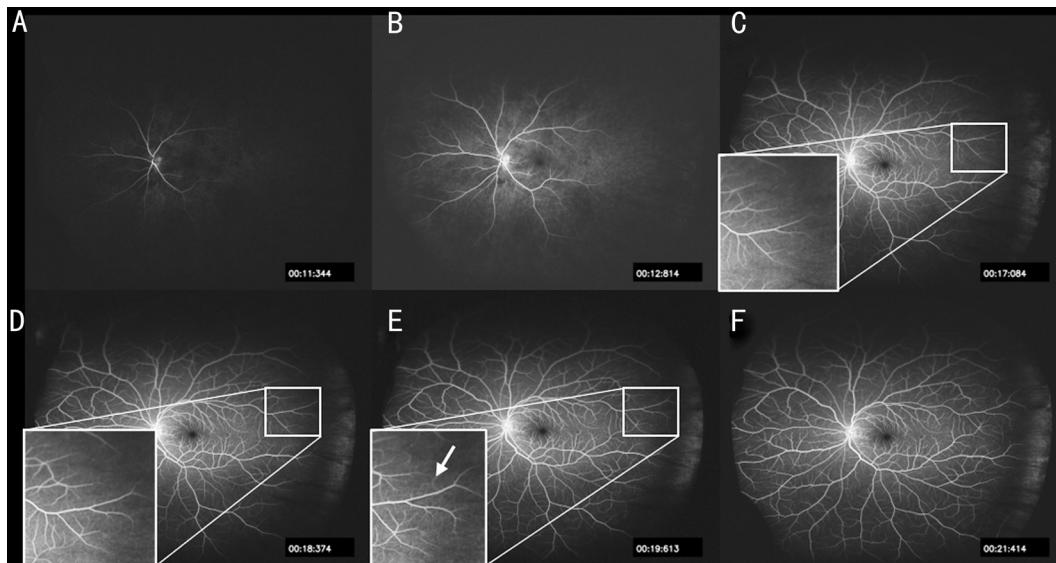
Terminal vascular patterns was described as loop pattern or branching pattern. Loop pattern was defined when most terminal vascular branches ran circumferentially and formed vascular loops (Figure 3A). Conversely, when most vascular endings were ramified and tapered toward the periphery, branching pattern as defined<sup>[7]</sup> (Figure 3B).

Microvascular abnormalities such as arteriovenous shunting, vessels crossing the horizontal raphe, right angle vessels, terminal networks, capillary nonperfusion, drusen or microaneurysms were documented in all subjects (Figure 3C, 3D).

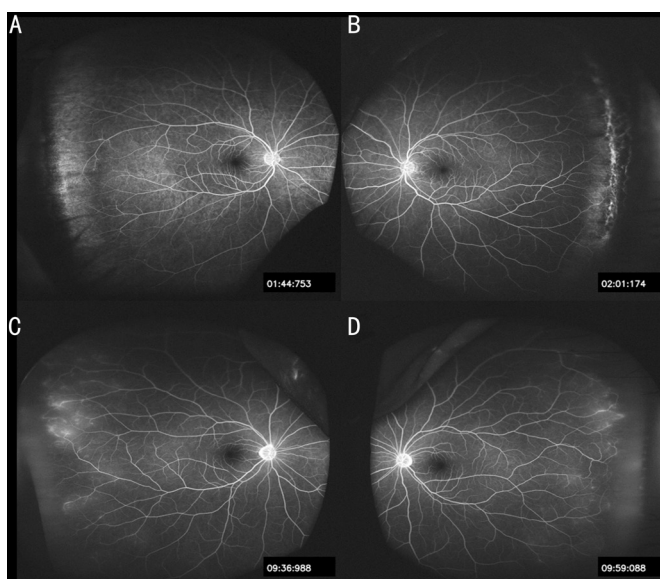
**Statistical Analysis** Statistical analysis was performed using SPSS software for Windows, version 23.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA). Normality of each parameter was evaluated by Shapiro-test, and a  $P$  value  $>0.05$  was considered as normally distributed. The upper or lower limits of normal was defined at the 95% level of agreement by mean  $\pm 1.96 \times SD$ . Finally, we report the normal values based on the normal probability at the 95% level of agreement for the PAFT and VFT.

## RESULTS

We retrospectively reviewed 30 eyes of 30 patients (15



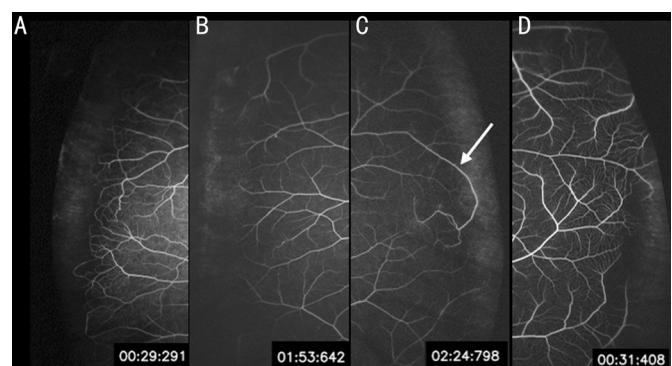
**Figure 1 Representative images for evaluation on the PAFT and VFT in UWF FA** A: PAFT was calculated from the beginning of arterial filling; B: VFT was calculated from the beginning of laminar flow, starting from areas around the papilla; C: The photo previous to the arterial filling end point, arterial forward continues moving; D: The arterial filling end point, arterial forward reached the temporal peripheral retina, and is previous to the next photo in E; E: The peripheral capillary network (arrow) was shown; F: Venous filling end point, laminar flow in the main trunk was disappeared.



**Figure 2 Representative images for evaluation on the appearance of the far peripheral retina** A: Granular background fluorescence; B: Mottled fluorescent, consisted of hyperfluorescent and hypofluorescent components at the far peripheral retina adjacent to the ora serrata; C, D: Vascular leakage, symmetry in subject's two eyes.

males and 15 females) that met the inclusion criteria between February 2017 and April 2020. The mean age was  $37.5 \pm 17.8$ y (range: 7-73y). The summary of the diagnosis and concomitant conditions were listed in Table 1.

In UWF-angiography, arterial forward took several seconds to reach the temporal peripheral retina. The arterial filling end point was decided by the photo previous to the one that the peripheral capillary network was shown (Figure 1D).



**Figure 3 Representative images showing loop pattern, branching pattern, right angle vessel and terminal networks** A: Loop pattern, most terminal vascular branches ran circumferentially and formed vascular loops; B: Branching pattern, most vascular endings were ramified and tapered toward the periphery; C: Right angle vessel, vessel turns back in the direction from which it originated, and away from areas of far peripheral capillary nonperfusion; D: Terminal networks, the small-vessel detail can be clearly seen within the networks in the early-phase, mimicking telangiectasia in Coats' disease.

During the arterial filling process, the vein from the perfused area started to show laminar flow, starting from areas around the papilla. As the filling process continued, each small vein gathered and filled the main trunk vein completely. When the laminar flow in the main trunk was disappeared, the venous filling process was considered over.

In three eyes that cilioretinal artery was present, the venous drainage from the corresponding area was earlier than other



**Table 1 The summary of the diagnosis and concomitant conditions**

Category	Eyes	Percentage
Diagnosis		
Healthy	25	83
ERM	2	7
MH	2	7
Previous laser treatment for peripheral retina degeneration	1	3
Myopia		
Yes (mean±SD: 4.5±1.87 D, range: -2 to -6 D)	5	17
No	25	83
Diabetic mellitus		
Yes	5	17
No	25	83
Hypertension		
Yes	4	13
No	26	87

ERM: Epiretinal membrane; MH: Macular hole.

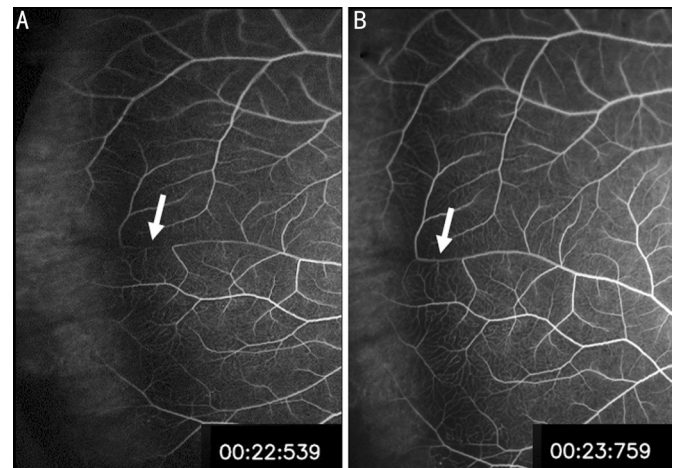
veins in areas that was perfused by central retinal artery. In these cases, the VFT was calculated when laminar flow of the latter was shown. In two eyes, a small segment of vein in the temporal peripheral retina was filled completely after the main trunk vein laminar flow sign was disappeared (Figure 4).

PAFT and VFT followed normal distribution, and the mean, SD, range (minimum-maximum) and normal limits were listed in Table 2.

The mean value of the interval between the arterial filling completion and the previous photo was 1.866s (25-75 percentiles: 1.219-2.318s). The mean value of the interval between the venous filling completion and the previous photo was 2.531s (25-75 percentiles: 1.274-3.604s).

The granular background fluorescence appeared in the early phase and increased in intensity in the mid phase, showed no leakage in the late phase, and faded out gradually (Figure 2A). The mottled fluorescent consisted of hyperfluorescent and hypofluorescent components at the far peripheral retina adjacent to the ora serrata (Figure 2B). The hyperfluorescent component appeared early in the angiography, increased in intensity gradually, and stained with fluorescein in the late phase without leakage. Vascular leakage type can easily defines as dye leaked from the vessels of the peripheral retina in the early phase, became very intensive in the mid phase, and gradually appeared fuzzy in the late phase<sup>[5]</sup> (Figure 2C, 2D).

Vessels crossing the horizontal raphe was referred to inferior arcade or superior arcade crossing the horizontal meridian as it progresses into the periphery<sup>[3]</sup>. Right angle vessel was defined if vessel turns back in the direction from which it originated, and away from areas of far peripheral capillary nonperfusion<sup>[3]</sup> (Figure 3C). Terminal networks were frequently seen in the early-phase on UWF angiography. The small-vessel detail can be clearly seen within the networks, mimicking telangiectasia



**Figure 4** A small segment of vein in the temporal peripheral retina was filled completely after the main trunk vein laminar flow sign was disappeared.

**Table 2 Normal limits for peripheral arterial and venous filling time**

Parameter	Mean	SD	Range (min-max)	Normal limits
PAFT, s	6.186	1.428	4.141-9.531	3.397-8.984
VFT, s	8.076	1.876	4.288-11.920	4.399-11.753

PAFT: Peripheral arterial filling time; VFT: Venous filling time.

in Coats' disease<sup>[3]</sup> (Figure 3D). Microaneurysms should be differentiated from drusen which was independent of the vasculature and generally demonstrate brighter fluorescence in the far periphery<sup>[3]</sup>. Arteriovenous shunting presented as thoroughfare channel or preferential channel was not detected in the study. Capillary nonperfusion is a common sign in angiography and often accompanied by terminal networks and microaneurysms<sup>[3]</sup>.

The summary of the far peripheral retina fluorescence features was listed in Table 3. Among 5 eyes that was categorized as vascular leakage, 2 of them were myopes, with the refractive error of -6 and -5.5 D. Due to retrospective nature of this study, the early phase of the contralateral eye was not always recorded, so the appearance of the far peripheral retina in the contralateral eye was not listed here. However, we reviewed the middle and late phases of the contralateral eye in order to discuss the symmetry between the two eyes. The appearance of the contralateral eye was always in consistent with the study eye.

## DISCUSSION

With the widely application of UWF angiography, we have been able to observe the peripheral retina in much more detail. But it is also important to verify the normal arterial filling time when interpreting the result, since we are observing the filling process from a much larger angle of view. With the expansion of the captured area, the peripheral arterial filling process can now be seen and the PAFT is quite different from that captured by traditional 55° angiography. Our study showed that PAFT

**Table 3** The summary of the far peripheral retina fluorescence features

Category/subgroup	Number of cases	Percentage
The appearance of the far peripheral retina		
Granular background fluorescence	19	63
Mottled fluorescent band	6	20
Vascular leakage	5	17
Terminal vascular patterns		
Loop pattern	9	30
Branching pattern	21	70
Other peripheral signs		
Arteriovenous shunting	0	0
Vessels crossing the horizontal raphe	3	10
Right angle vessels	22	73
Terminal networks	24	80
Capillary nonperfusion	7	23
Drusen	3	10
Microaneurysms	12	40

was 3.397-8.984s in eyes without known diseases that may influence filling process. This normal range was narrower than that reported by a previous study, which is 4-14s calculated using 2 SDs<sup>[3]</sup>.

In this study, subjects were strictly selected to make sure the interval between each shot did not cause too much bias. We focused on the temporal arterial filling features mainly, since the distance between the optic disc and ora serrata was longest in the temporal quadrant, as well as the temporal retina was easier to be captured<sup>[4]</sup>.

Traditional 55° angiography was divided into five phases: pre-arterial (choroidal flush), arterial, arteriovenous, venous and late (or recirculation) phase<sup>[10]</sup>. The arterial phase begins 1-2s after choroidal filling. During this phase, arteries are bright, but the veins remain dark. In the arteriovenous phase, dye spreads to the pre-capillary arterioles, the capillaries and the postcapillary venules, resulting in a laminar flow pattern in the filling venules. In the venous stage, veins are gradually filled completely, and the fluorescence begins to reduce progressively. In the late phase, arteries and veins are virtually devoid of fluorescein, any leakage or pooling starts to show. In some books, when maximum concentration of fluorescein occurred 20-25s after injection, the peak phase was named<sup>[11]</sup>. And the arteriovenous phase is named as early arteriovenous phase, while after peak phase, late arteriovenous phase was called instead of venous phase<sup>[12]</sup>. Those staging of FA were based on the limited view of fundus camera. UVW FA have given us the chance to observe the retinal vessel filling process from a much wider angle of view. We have noticed that the retinal veins do start filling about 2.21±1.17s later after the retinal arteries start filling, but the artery does not complete filling before the veins start filling. The main courses of retinal

artery and vein filling time were overlapping with each other. Therefore, there is hardly independent retinal artery phase when observing from the whole retina. Though in each area of the retina, as observed from 55° angiography, the retinal artery fills first, then the capillaries and the veins. It should be noted that in UWF angiography, arterial filling process is completed in the arteriovenous phase or early arteriovenous phase rather than the traditionally named arterial phase. On UWF angiography, the retinal artery starts filling earlier than the veins, and the retinal veins complete filling later than the arteries, like we have observed in the 55° angiography. But it actually takes the retinal artery about 4-9s to complete its filling in normal subjects on UWF angiography. Therefore, on UWF angiography we have to interpret arterial forward phenomenon carefully.

Our study showed that VFT to be 4.399-11.753s. VFT did not differ much compared to traditional 55° angiography, since venous drainage finally returned to main trunk of central retinal vein around optic disc. However, we noticed that in two eyes, a small segment of vein in the temporal peripheral retina was filled completely after the main trunk vein laminar flow sign was disappeared. It is not sure whether this delayed filling is pathologic, as no related vascular abnormality existed in the distal area.

UWF angiography allows us to see the fluorescence features of the far peripheral retina in the early phase. The significance of these manifestations remains unknown. More research needs to be done to answer the question that whether they are facts that has always existed, or they are subclinical early manifestations of diseases.

The appearance of the far peripheral retina was categorized as granular background fluorescence, mottled fluorescent band and vascular leakage in this study. It is believed that granular background fluorescence and mottled fluorescent band might be a normal sign at the far peripheral retina. Granular hyperfluorescence may result from unevenly distributed retinal pigment epithelium (RPE) cells in the far peripheral retina<sup>[5,8]</sup>. Mottled fluorescent bands appeared in the far peripheral retina adjacent to the ora serrata, where neuroepithelial cells migrate to non-pigment epithelial cells. And the mottled appearance was cause by unevenly distributed pigment in RPE cells<sup>[5,8,13]</sup>. In previous studies, a ground glass hyperfluorescence type was also mentioned. It is speculated that the ground glass hyperfluorescence may result in greater transmission of subjacent choroidal hyperfluorescence due to RPE thinning and is commonly seen among 84.34%-87.93% of study eyes<sup>[3,8]</sup>. In Shah *et al's*<sup>[3]</sup> study, the picture illustrating ground glass hyperfluorescence could be easily confused with granular background fluorescence or mottled fluorescent. Since ground glass hyperfluorescence is a common feature in

the far peripheral retina and could be overlapped with granular hyperfluorescence or mottled fluorescent, we prefer to use the category applied by Lu *et al*'s<sup>[5]</sup> study, and the ground glass hyperfluorescence type was not separated into a single category in this study.

The percentage of vascular leakage in this study (16.7% of 30 eyes) was similar to Lu *et al*'s<sup>[5]</sup> study (19.8% of 101 eyes) but lower than Wang *et al*'s<sup>[8]</sup> study (32.5% of 166 eyes) and Seo and Kim<sup>[7]</sup> study (50.0%-24.1% among three groups in 242 eyes). The low rate of vascular leakage found in this study may be due to the reason that we included only one eye of the subject, while other studies included mainly both eyes. In our study, the contralateral eye has the same fluorescence features as the study eye in all quadrants, but no chief complaint was made. The leakage may be caused by peripheral vitreous adhesion or intermediate uveitis as suggested by previous researchers<sup>[5,8]</sup>. We tend to believe that vascular leakage seen in the peripheral retina using UWF angiography should not be considered as pathologic if the both eyes have identical configuration and no related chief complaint such as floaters was made. A follow-up observation should be suggested but excessive examination and over treatment should be avoided.

In our study, loop pattern was seen in 30% of study eyes. However, microvascular abnormalities such as capillary nonperfusion and microaneurysms were more frequently found in eyes with loop pattern (both 5/9=55.6%) than in eyes with branching pattern (2/21=9.5% for nonperfusion and 7/21=33.3% for microaneurysms). It is hypothesized that peripheral oxygenation status was related to the peripheral vascular pattern and microvascular abnormalities<sup>[7]</sup>. A hypothesis related to retinal vascular development was proposed by previous researchers to explain this phenomenon<sup>[7,14]</sup>.

The percentage of other peripheral signs listed in Table 3 was similar to previous reports<sup>[3]</sup>. These features may indicate the possibility of subclinical capillary damage, however, they were noted commonly<sup>[3,7]</sup>.

Several limitations should be noted in this research. First, the sample size is relatively small since this is a retrospective study and it is hard to find patients ordered UWF angiography but comparatively healthy in the eye<sup>[15]</sup>. Also, we have selected subjects strictly to make sure the intervals between each shot was short enough not to cause unreliable results. If a recording function is available in the future on the UWF angiography system, the sample size can be easily expanded, and the filling time calculation should be more precise. Second, a wide range of ages (7-73y) was included in this study. It is known that younger people may have faster blood circulation than older people<sup>[11]</sup>. Theoretically, a larger sample size is needed to establish a normal value. Since our result was similar to the previous study, which is 4-14s (mean±2 SDs)

in 31 patients aged 42-92y, it should be considered useful in clinical reference. Third, the ocular perfusion pressure is influenced by blood pressure and intraocular pressure (IOP). As a retrospective study, blood pressure and IOP value was not regularly recorded. However, subjects with high blood pressure before angiography procedure (over 160/90 mm Hg) and eyes with glaucoma history were excluded.

In summary, we introduced the normal limits of PAFT and VFT in eyes without known diseases that may influence the filling process by UWF angiography. With a widened image, we find that the arterial filling process is completed in the arteriovenous phase or early arteriovenous phase rather than the arterial phase. Sluggish segmental venous flow could be seen in the peripheral retina. The appearance of the far peripheral retina of both eyes was symmetrical. Other peripheral signs such as right-angle vessels, terminal networks and capillary nonperfusion were commonly seen by UWF angiography in normal peripheral retina.

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**Authors' contributions:** Conceptualization: She HC; Methodology: Zhang XF, Zhang YP; Formal analysis and investigation: Zhang XF, She HC; Writing-original draft preparation: Zhang XF; Writing-review and editing: She HC; Funding acquisition: She HC; Resources: Zhou HY, Jiao X; Supervision: She HC.

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**Conflicts of Interest:** She HC, None; Zhang XF, None; Zhang YP, None; Jiao X, None; Zhou HY, None.

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