·Clinical Research·

Retinal circulation and its role in macular disorders in patients without systemic disease

Priyangshu Chandra, Aditya Sudhalkar, Souvik Mandal, Jay Chhablani

Smt. Kanuri Santhamma Retina Vitreous Centre, L. V. Prasad Eye Institute, Kallam Anji Reddy Campus, L.V. Prasad Marg, Banjara Hills, Hyderabad, Andhra Pradesh 500034, India

Correspondence to: Jay Chhablani. Smt. Kanuri Santhamma Retina Vitreous Centre, L. V. Prasad Eye Institute, Kallam Anji Reddy Campus, L. V. Prasad Marg, Banjara Hills, Hyderabad, Andhra Pradesh 500034, India. jay.chhablani@gmail.com

Received: 2013-12-24 Accepted: 2014-08-22

Abstract

• AIM: To determine whether retinal circulatory changes play a role in the pathogenesis of macular disorders in patients who are otherwise healthy.

• METHODS: Patients with macular disorders that required angiographic imaging were included in this prospective case series. After a complete ocular exam, fluorescein angiography was performed using a standardized technique on the HRA –II (Heidelberg Engineering, Heidelberg, Germany) with special focus on the posterior pole. Only patients with good quality images were included in the analysis. Circulatory parameters recorded included the arm –choroid time, choroid–retinal artery, and finally the retinal artery–vein time. Zonal asymmetry (between the upper and lower zones divided by a line passing through the centre of the fovea) in transit times, if any was also noted. Appropriate statistical analysis was done. Circulation times were compared with age matched historical controls. Changes in retinal dye transit times relative to historical age matched controls, if any, were noted and compared between various disorders.

• RESULTS: A total of 156 eyes of 156 patients (120 males) were included in the study. Mean age: 49.14 ±14.93y. Macular disorders studied were age related degeneration, polypoidal vasculopathy, central serous chorioretinopathy (CSCR) and parafoveal telangiectasia. Delayed circulation time was noted in CSCR patients only.

• CONCLUSION: CSCR patients appear to have delayed arterial filling, retinal circulatory disturbances do not seem to contribute to the pathogenesis of other macular disorders.

• **KEYWORDS:** fluorescein angiography; circulation; parafoveal telangiectasia; idiopathic polypoidal choroidal vasculopathy; age-related macular degeneration; central serous chorioretinopathy

DOI:10.3980/j.issn.2222-3959.2015.03.27

Chandra P, Sudhalkar A, Mandal S, Chhablani J. Retinal circulation and its role in macular disorders in patients without systemic disease. *Int J Ophthalmol* 2015;8(3):585-589

INTRODUCTION

Hickam and Frayser [1] were the first investigators to report that quantification of the retinal circulation would be possible using dye dilution with fundus fluorescence angiography (FFA). The procedure has subsequently changed significantly to the point that it is one of the most important investigations in ocular disease[2-4]. The interpretation of the FFA is primarily based on subjective evaluation of dye transit time in choroid, capillaries, and arteries and finally veins. FFA eventually provides a quantitative and dynamic understanding of the blood circulation pattern in the living ocular vascular system but it does not provide information about retinal function. Specifically, flow and permeability in the retinal and choroidal vessels can be correlated with clinically apparent or unapparent anatomical changes in different pathologies using this technique.

Age appears to have minimal, effect on retinal circulation as does systemic disease such as diabetes [5]. However, retinal macular circulation appears to correlate negatively linearly with age but correlated well with the concurrent decrease in ganglion cells in the human tissue[6,7].

The time from injection to first appearance in retina is said to vary between 12.4±3.41s in normal volunteers [8]. Whether altered retinal circulatory dynamics play any part in the pathogenesis of various macular diseases is as of now, unknown. If a correlation exists, this finding may not only assist in defining eyes at risk but may also help to elucidate the pathogenesis of different macular pathologies.

The purpose of this study is to report an age matched retinal circulation time in different macular pathologies.

SUBJECTS AND METHODS

This prospective study was conducted at the L.V. Prasad Eye Institute, Hyderabad. For inclusion, patients were required to

have macular disease that mandated an angiographic exam and were free of systemic disease, vascular or otherwise, that was likely to influence retinal circulatory dynamics (such as diabetes mellitus or hypertension). Patients with fundus images graded to be of poor quality and those likely to be prone to hypersensitive to the fluorescein dye or those who developed a hypersensitivity reaction to the dye during the procedure were excluded. Subgroups were based on age (at 10y intervals) and pathology.

The study was conducted according to the recommendations put forth in the Declaration of Helsinki. The institutional ethics committee approved the study protocol, and all patients provided written informed consent. A complete ocular and systemic history was obtained from all patients. A comprehensive ocular and systemic examination, backed up by laboratory tests wherever applicable was performed.

Angiography The procedure was performed using the HRA-II (Heidelberg Engineering, Heidelberg, Germany) machine. A unique feature of the HRA-2 is the ability to acquire dynamic, high-speed movies (up to 16 frames per second) in both fluorescein and indocyanine green (ICG) angiographies. This is especially important in the initial phase of FFA, when documentation of the early filling stages is important.

Pupillary dilatation for the procedure was achieved with a combination of topical tropicamide (0.5%) and phenylephrine (5%), unless contraindicated, in which case topical cyclopentolate 2% was used.

Color retinal photographs and red-free fundus photographs were obtained before performing the angiography procedure. All the photographs for all patients were taken in 50 degrees in field 2 where macula is at the centre and disc at the edge. In the present study, the measurement area was the edge of the optic disc and around the posterior pole. For analysis, the posterior pole was divided into an upper and lower zone by a line bisecting the disc and the fovea. A note was made of any asymmetry in dye transit between the two zones.

An intravenous catheter was inserted into the antecubital vein; patency was confirmed with intravenous saline. The dye used was 20% sodium fluorescein. An anesthetist was kept on standby with all emergency medications complete with resuscitative equipment ready. The subject was informed of all possible reactions during the procedure and instructed to report immediately if any symptoms arose. The timer was set in motion once the dye reached the vein. The subject was instructed to look at an internal fixation mark to ensure that fixation would be as steady as possible. The initial photographs were taken in the effected eye up to 1min then the camera moved to the other eye and images were captured. Photographs were obtained every second from the moment of complete injection of dye into the vein up until the end of the first minute. Thereafter, photographs were obtained every minute for six minutes. A late photograph was obtained at ten and twenty minutes. The whole examination was carried out as rapidly as possible. After the procedure, all the patients were warned about possible late reactions.

Circulatory parameters recorded included the arm-choroid time, choroid-retinal artery, and finally the retinal artery-vein time. The choroidal phase consists of the period of time between the injection of dye into the cubital vein and its first appearance in the choroid which looks faint, patchy and irregular called "choridal flush". The arterial phase starts when the central retinal artery begun to fill. The phase identified by laminar flow in the veins would be the venous phase.

We studied the relationship between the circulatory parameters and macular disease for a given age and gender.

Statistical Analysis SPSS software version SPSS 15.0 (SPSS Inc., Delaware, USA) was used for the data analysis. Statistical analysis values for all groups and overall are given as mean±SD. Significance differences between the groups in mean values were evaluated using one way ANOVA test. The P values less than 0.05 were regarded as significant.

RESULTS

A total of 156 patients (age range 16-77 years old) with one of the subsequently enumerated macular diseases requiring an angiographic examination were included in the study.

A single observer had performed all the scans and analysis. one hundred and fifty-six eyes of 156 consecutive subjects were enrolled in the study, and 120 patients of this cohort were male. The average age of the patients was 49.14±14.93y.

Patients were categorized based on five common macular pathologies: dry age-related macular degeneration (ARMD), wet ARMD, central serous chorioretinopathy (CSCR), parafoveal telangiectasia (PFT) and idiopathic polypoidal choroidal vasculopathy (IPCV) as per the results of the clinical and angiographic exam. All patients were divided into 7 groups based on their age starting from 10 to 70 years old at 10y interval; Table 1 summaries the baseline characteristics of all patients. The mean choroidal appearance time was 17.83±5.76s, arterial appearance time 20.03±5.89s and mean venous appearance time 23.4±6.03s. Eight patients (wet ARMD, n=2; PFT, n=1; CSCR, n=5) had an arm retina time of more than 30s, 1 patient with CSR was greater than 40s. Subanalysis of these six patients showed that all six had a significantly longer duration of complaints (133.2±33.4d) as opposed to those patients of CSCR who had normal circulation times (43.34±22.4d; P <0.001). The mean retinal circulation time increased with each decade in a linear relation (Figure 1) but no significant correlations were found between age and blood appearance time in different phases, given in Table 2 (choroidal appearance, P=0.155; arterial appearance, P=0.148; venous appearance, P=0.214). Though the circulation time in each decade showed

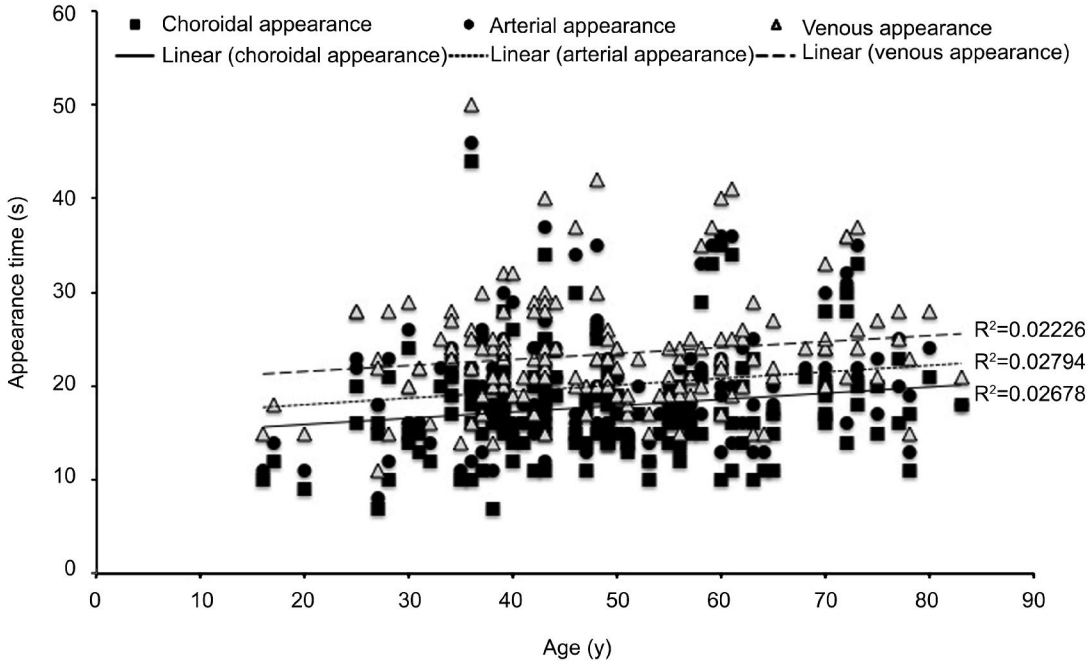

Figure 1 Figure plots the age of the patients against the time at which the dye was first noticed at various loci, *viz.* the choroidal, arterial and venous circulation The Scatter plot showed no significant change in dye appearance time with increasing age.

Table 1 Baseline clinical characteristics of the study groups *n* (%)

Variables	Details
Total subject	156
M	120 (76.92)
F	36 (23.08)
OD evaluated first	85 (54.49)
OS evaluated first	71 (45.51)
Age (mean±SD)	49.14±14.93
Grouping based on age (a)	
10-20	3 (1.92)
21-30	11 (7.05)
31-40	37 (23.72)
41-50	44 (28.21)
51-60	28 (17.95)
61-70	19 (12.18)
70-80	14 (8.97)
Grouping based on pathology	
Wet ARMD	52 (33.33)
Dry ARMD	11 (7.05)
CSCR	59 (37.82)
PFT	16 (10.26)
PED	15 (9.62)
IPCV	3 (1.92)

OD: Right eye; OS: Left eye; SD: Standard deviation; ARMD: Age-related macular degeneration; CSCR: Central serous chorioretinopathy; PFT: Parafoveal telangiectasia; PED: Pigment epithelial detachment; IPCV: Idiopathic polypoidal choroidal vasculopathy.

increased, intraretinal circulation time showed to be uniform in all decade. There was also no significance difference found between the disease groups in different phase shown in Table 3 (choroidal appearance, P=0.734; arterial appearance, P=0.773; venous appearance, P=0.891). In 71 patients (45.51%) there was no disparity in dye transit between the two zones. In 49 patients (31.41%), the upper part of the retina showed earlier transit, whereas in 36 (23.08%) patients the lower part filled up first. Mean dye transit times for all macular diseases (age wise distribution) is shown as Table 4.

DISCUSSION

With the present system, all circulation times can be calculated objectively and uniformly. The injection system comprises of small amount of dye and a saline flush, which allow a complete morphological evaluation of retinal circulation. The time frames considered include the time required for the injection of dye to reach the choroid then retinal artery and subsequently to the vein. The filing time is much shorter in the region of the posterior pole concentric to the fovea and longest in the peripheral parts of the retina[9].

Numerous studies have described arterial, capillary circulation time on different ocular pathologies in patients with systemic disorders [10-12]. The current study has attempted to focus on macular disease in patients without systemic disorders. Our data also showed reduction of circulation time with increasing age though the trend is not significant in our study. The reduction rate was shown to be 9.9% percent per decade by Groh *et al*[6] which is very close to our value 12%. It is well known that increasing age is associated with changes of the morphology of blood vessels [13]. The decrease of retinal circulation obsered with effect of age was already suppoted by the morphological changes already stated earlier. Laatikainen and Larinkari [14] reported significant increase of foveal avascular zone due to the atrophy of macular capillaries with increasing age. Gao and Hollyfield[15] showed that there is a 16% reduction of cells between the second and

Table 2 Mean circulation time of different phase in different age group with standard deviation (SD)

Age group	Mean choroidal appearance time±SD	Mean arterial appearance time±SD	Mean venous appearance time±SD
10-20	10.33±1.52	12±1.72	16±1.73
21-30	15.8 ±5.78	18.2±6.49	22.4±7.5
31-40	17.89 ±6.21	19.97 ±6.17	23.28±6.2
41-50	18.22 ±4.79	20.47 ±5.33	23.81±5.61
51-60	18.73±5.46	20.87±5.83	23.93±6.09
61-70	18.94±6.07	21.52±5.68	24.1±5.98
71-80	20.28±6.3	22.57±6.39	26.28±6.43
P	0.155	0.148	0.214

Table 3 Mean circulation time of different phase in different diseased group standard deviation (SD)

Disease group	Mean choroidal appearance time±SD	Mean arterial appearance time±SD	Mean venous appearance time±SD
Wet ARMD	17.22±5.51	19.28±5.68	22.79±5.78
CSR	18.23±6.22	20.53±6.39	23.88±6.62
PFT	19.61±3.86	21.46±3.88	24±4.26
IPCV	15.03 ±5.03	17.66±5.13	20.66±4.5
Dry ARMD	18±17.36	20.18±7.26	23.54±7.22
PED	17.25±5.17	19.91±5.51	25.664.63
P	0.734	0.773	0.891

Table 4 Mean dye transit times for all macular diseases (age wise distribution, as applicable)

Age group	Wet AMD			CSR			PFT		
	C	A	V	C	A	V	C	A	V
10-20	N/A	N/A	N/A	N/A`	N/A	N/A	N/A	N/A	N/A
21-30	N/A	N/A	N/A	15.8 ±5.8	18.2±6.4	22.4±7.5	N/A	N/A	N/A
31-40	N/A	N/A	N/A	17.9 ±6.2	19.9 ±6.2	23.3±6.2	N/A	N/A	N/A
41-50	N/A	N/A	N/A	N/A	20.4±5.3	23.8±5.6	20.2 ±4.7	22.8±5.1	
51-60	18.7±4.9	19.8±5.8	23.8±6.0	N/A	N/A	N/A	19.7±5.4	20.8±5.8	23.93±6.1
61-70	16.4±6.0	19.4.±5.6	22.1±5.9	N/A	N/A	N/A	18.9±6.1	21.52±5.7	24.1±5.8
71-80	17.5±5.2	19.8±5.4	22.4±6.4	N/A	N/A	N/A	N/A	N/A	N/A
Age group	IPCV			Dry AMD			PED		
	C	A	V	C	A	V	C	A	V
10-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
21-30	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
31-40	N/A	N/A	N/A	N/A	N/A	N/A	17.8 ±5.2	19.7 ±6.1	26.9±6.1
41-50	N/A	N/A	N/A	N/A	N/A	N/A	18.1 ±4.7	19.4±5.3	24.2±4.3
51-60	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
61-70	15.5±4.5	17.8±5.6	20.3±5.1	18.9±5	20.5±4.7	24.5±5.2	N/A	N/A	N/A
71-80	N/A	N/A	N/A	17.6±6.3	19.5±5.2	23.2±4.6	N/A	N/A	N/A

C: Choroidal appearance of dye; A: Arterial appearance of dye; V: Venous appearance of dye; N/A: Not applicable in that age group as there were no patients in the specific age group.

sixth decade of life. This reduction in cellular content may account for decreased demand, and hence delayed circulation.

Coronary circulatory dysfunction and other vascular disorders like diabetes do have an effect on the circulation time [16-18]. This confounder, however was eliminated from our study by exclusion of patients with said circulatory disorders. Differences in image analysis methods can produce variation in measurements (mean arm-retina time was 11.2 ±3.3s, arterio-venous time 1.45 ±0.4s) [17]. Gender has been shown not to influence initial arterial circulation times [19]. Ocular laterality too does not seem to alter circulation times [20]. Our study appears to suggest that retinal circulatory transit times do not seem to influence macular disease in the absence of systemic dysfunction. Of the 9 patients who had delayed circulation times, 6 patients had CSCR. This has been reported earlier in patients with CSCR [21] Although the precise etiology of the delayed filling is unclear, it might well

be, along with capillary and venous congestion the cause of choroidal ischemia and subsequent retinal pigment epithelial (RPE) hyperpermeability [22]. What actually leads to delayed filling is unknown. CSCR has been linked to increased steroid levels. That steroids cause circulatory disturbances and increased permeability is known [23]. However, it is important to note that only six patients had this finding, and subanalysis revealed a longer duration of disease (more than 6mo) in these six patients. The current value of this observation is uncertain. Larger sample size would be required to prove this observation. There was no difference in transit times between the two zones in any of the studied macular disorders, nor did zonal asymmetry correlate with any macular disease. Recent publications give good insight into the physiology and pathophysiology of retinal circulation[3,24].

Limitations of this study include the inability to obtain proper photographic images every time in an angiographic sequence because of patient related factors, such as poor co-operation. Although a single investigator performed all angiographies, it is possible that delays in image capture could contribute to loss of vital angiographic frames. Also it would have been ideal to incorporate patterns of fluoresceine angiography, ICG angiography, confocal scanning laser ophthalmoscopy and Doppler flowmetry to measure choroidal circulation into the study. For instance, the pathology in CSCR is at the level of the RPE/choroid, ICG angiography is superior to fluorescein angiography in characterizing the choroidal circulation. This applies to polypoidal vasculopathy as well.

This study was designed to determine the retinal circulation times in some of the more common macular pathologies with systematically "healthy" subjects in different age groups. The study, additionally, gives us information on the effect of age on the various early phases of the angiogram in patients of Indian ethnicity and that they are similar to historical controls from different ethnic groups. We can also conclude that except perhaps for CSCR patients (wherein the role of delayed filling is uncertain), retinal circulatory disturbances cannot generally account for the pathogenesis of various macular disorders.

ACKNOWLEDGEMENTS

Conflicts of Interest: Chandra P, None; **Sudhalkar A,** None; **Mandal S,** None; **Chhablani J,** None.

REFERENCES

1 Hickam JB, Frayser R. Aphotographic method for measuring the mean retinal circulation time using fluorescein. *Invest Ophthalmol* 1965; 4(5): 876-884

2 Gess AJ, Fung AE, Rodriguez JG. Imaging in neovascular age-related macular degeneration. *Semin Ophthalmol* 2011;26(3):225-233

3 Puro DG. Retinovascular physiology and pathophysiology: new experimental approach/new insights. *Prog Retin Eye Res* 2012;31(3):258-270

4 Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM. Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. *Am J Ophthalmol* 2013;155(6):1038-1044

5 Nagaoka T, Sato E, Takahashi A, Sogawa K, Yokota H, Yoshida A. Effect of aging on retinal circulation in normotensive healthy subjects. *Exp Eye Res* 2009;89(6):887-891

6 Groh MJ, Michelson G, Langhans MJ, Harazny J. Influence of age on retinal and optic nerve head blood circulation. *Ophthalmology* 1996;103 (3):529-534

7 Grunwald JE, Piltz J, Patel N, Bose S, Riva CE. Effect of aging on retinal macular microcirculation: a blue field simulation study. *Invest Ophthalmol Vis Sci* 1993;34(13):3609-3613

8 Wolf S, Arend O, Reim M. Measurement of retinal hemodynamics with scanning laser ophthalmoscopy: reference values and variation. *Surv Ophthalmol* 1994;38 Suppl:S95-100

9 Hickam JB, Sieker HO, Frayser R. Studies of retinal circulation and A-V oxygen difference in man. *Trans Am Clin Climatol Assoc* 1959;71:34-44

10 Zhao J, Frambach DA, Lee PP, Lee M, Lopez PF. Delayed macular choriocapillary circulation in age-related macular degeneration. *Int Ophthalmol* 1995;19(1):1-12

11 Kang G, Lee J. Retinal circulation times in branch retinal vein occlusion. *Korean J Ophthalmol* 1995;9(2):107-110

12 Kubicka-Trzaska A. Macular microcirculation blood flow in patients with age related macular degeneration treated with photodynamic therapy and transpupillary thermotherapy. *Klin Oczna* 2007;109(4-6):138-141

13 Nguyen TT, Wang JJ, Wong TY. Retinal vascular changes in pre-diabetes and prehypertension: new findings and their research and clinical implications. *Diabetes Care* 2007;30(10):2708-2715

14 Laatikainen L, Larinkari J. Capillary-free area of the fovea with advancing age. *Invest Ophthalmol Vis Sci* 1977;16(12):1154-1157

15 Gao H, Hollyfield JG. Aging of the human retina. Differential loss of neurons and retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci* 1992;33(1):1-17

16 Arend O, Wolf S, Remky A, Sponsel WE, Harris A, Bertram B, Reim M. Perifoveal microcirculation with non-insulin-dependent diabetes mellitus. *Graefes Arch Clin Exp Ophthalmol* 1994;232(4):225-231

17 Bertram B, Wolf S, Fiehofer S, Schulte K, Arend O, Reim M. Retinal circulation times in diabetes mellitus type 1. *Br J Ophthalmol* 1991;75(8): 462-465

18 Koc S, Ozin B, Altin C, Altan Yaycioglu R, Aydinalp A, Muderrisoglu H. Evaluation of circulation disorder in coronary slow flow by fundus fluorescein angiography. *Am J Cardiol* 2013;111(11):1552-1556

19 Schwartz B, Kern J. Age, increased ocular and blood pressures, and retinal and disc fluorescein angiogram. *Arch Ophthalmol* 1980;98 (11): 1980-1986

20 Laux U, Eckert G, Pauschinger P. Synchronous determination of retinal circulation times in both eyes. *Ann Ophthalmol* 1979;11(5):777-780

21 Kitaya N, Nagaoka T, Hikichi T, Sugawara R, Fukui K, Ishiko S, Yoshida A. Features of abnormal choroidal circulation in central serous chorioretinopathy. *Br J Ophthalmol* 2003;87(6):709-712

22 Iida T, Kishi S, Hagimura N, Shimizu K. Persistent and bilateral choroidal vascular abnormalities in central serous chorioretinopathy. *Retina* 1999;19(6):508-512

23 Ichiseki T, Matsumoto T, Nishino M, Kaneuji A, Katsuda S. Oxidative stress and vascular permeability in steroid-induced osteonecrosis model. *J Orthop Sci* 2004;9(5):509-515

24 Kur J, Newman EA, Chan-Ling T. Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. *Prog Retin Eye Res* 2012;31(5):377-406