Hypothesis

Hypothetical proposal for the course of retinal blood vessels in the posterior pole—description and its clinical implications

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ABSTRACT

Background: Branch retinal vein occlusion (BRVO) is the second-most common retinal vascular disorder. Arteriosclerotic changes at the site of obstruction and hemodynamic turbulence within the vessels are considered risk factors. Overcrossing of the vein by an artery has traditionally been considered to increase the risk of BRVO. Recent studies using optical coherence tomography and optical coherence tomography angiography have suggested a higher prevalence of vein-over-artery crossings in this disease. Nevertheless, uncertainty persists as to why some patients, even those with the same disease duration, have varying degrees of venous dilation and develop sufficient collaterals, while others develop substantial ischemia and its sequelae.
Hypothesis: Herein, it is hypothesized that because retinal blood vessels are transparent, tubular, and collapsible conduits coursing over a hollow spherical surface, the changes related to AV crossings over the entire course of a vessel, rather than at any single isolated crossing, could contribute to the risk, natural progression, and outcomes of BRVO. The study analyzed color fundus photographs from two image datasets. The first dataset comprised 100 randomly selected images from the author's own collection at the Rajendra Prasad Center for Ophthalmic Sciences. The second dataset comprised 100 images from the MESSIDOR database; three images were excluded owing to poor focus. Using 394 observations from 197 retinal photographs, four distinct patterns of AV crossing along the course of blood vessels were recognized: (A and B) wicker basket, (C) straight, (D) widely spaced, and (E) indeterminate. The percentages of tight wicker, loose wicker, straight, widely spaced, and indeterminate patterns in the two image sets were 19% (38/200) and 16.5% (32/194), 22.5% (45/200) and 27.8% (54/194), 16.5% (33/200) and 15.5% (30/194), 22.5% (45/200) and 28.4% (55/194), and 19.5% (39/200) and 11.9% (23/194), respectively. Hence, the wicker basket pattern was the most common AV crossing pattern in both image sets.
Conclusions: The wicker basket pattern may provide structural stability and aid in maintaining pressure gradients within the retinal vascular bed. This observation of variable AV relationships at consecutive crossings may improve our understanding of the pathogenesis, natural history, and outcomes of BRVO. Future longitudinal studies including patients at risk of BRVO, or retrospective analyses of patients with BRVO who had ophthalmic examinations and archived fundus images before the vascular event, should verify the relevance of these observed vascular patterns.

KEYWORDS
blood vessel, retinal vessel, branch retinal vein occlusion, hypothesis, observation

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INTRODUCTION

Studies on the various clinical characteristics of retinal blood vessels have been conducted, and excellent descriptions of these vessels are available in the literature [1]. These studies highlight the variability of blood vessels in terms of caliber, color, divisions, and characteristics of arterio-venular (AV) crossings, not only between individuals but also within different regions of the eye [2, 3].

These variations in retinal blood vessel characteristics [4] add a great deal to the subjectivity and interpretation of vascular findings in the clinical setting. For example, the poor correlation between the clinical description of retinal blood vessels and the earlier grades of hypertensive retinopathy has been well documented [5]. Like hypertensive retinopathy, changes within the retinal blood vessels at AV crossings also contribute to the development of branch retinal vein occlusion (BRVO), the second-most common retinal vascular disorder [6, 7]. Most studies on the pathogenesis of BRVO have focused on changes at the point of crossing alone and have highlighted whether the arteriole passed above or beneath the corresponding venule [8, 9].

However, on reviewing the published literature, no studies were found describing AV relationships when there are multiple crossings proximal and distal to the affected crossing. As the retinal vessels traverse the entire surface of the retina, they cross at multiple sites at various distances from the center of the optic nerve head. However, even involving normal individuals, no studies have reported the evaluation of crossing patterns (arterial overcrossing [A/V] or venous overcrossing [V/A]) that occur over the entire course of the retinal vessels.

HYPOTHESIS

Because retinal blood vessels are transparent, tubular, and collapsible conduits coursing over a hollow spherical surface [10], it is likely that AV crossings along the entire course of the retinal vessels, rather than any single crossing, would influence the structural and hemodynamic stability of the retinal vascular bed. Herein, it is hypothesized that the changes related to AV crossings over the entire course of a vessel, rather than at any single crossing, could contribute to the risk, natural progression, and outcomes of patients with BRVO.

EVALUATION OF THE HYPOTHESIS

This cross-sectional study aimed to determine the patterns of retinal vascular AV crossings at the optic nerve head and at three successive major crossings in the posterior pole. The study analyzed color fundus photographs from two image datasets. The first dataset comprised 100 randomly selected images from the author's own collection (2014 – 2020) at the Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences (AIIMS), New Delhi, India. The second dataset comprised 100 images from the MESSIDOR database. The MESSIDOR database is publicly accessible and can be used for academic work after obtaining permission [11, 12]. Permission to use MESSIDOR database images was obtained through e-mail correspondence. Because only de-identified images were captured over several years in the past (retrospective), and a publicly available image set was used for the study, official ethics approval was obtained at the departmental level to publish the outcomes of this study.

Only images with clear media and sharp focus were selected for evaluation. The MESSIDOR database images were de-identified; hence, information regarding age and sex was not obtainable. However, in the author's selected image set, the patient ages ranged from 24 to 56 years. Fifty-eight (58%) images were from men, and 53 (53%) were of the right eye. Fundus images consisted of photographs taken for diabetic retinopathy screening and included images with no diabetic retinopathy (i.e., normal fundus) and those with mild retinopathy. No patients with any form of vascular occlusion were included. Three images from the MESSIDOR database were excluded owing to poor focus; therefore, 97 images from the database were ultimately included in the analysis. All 100 photographs from the author's image set were adequately clear for analysis (captured using either the Zeiss FF 450^{plus} camera [Carl Zeiss Meditec AG, Jena, Germany] or Topcon Maestro2 camera [Topcon Healthcare, NJ, USA]). Thus, a total of 197 images were included in the final analysis. The courses of the superotemporal and inferotemporal vessels were analyzed separately. Therefore, 394 (197 × 2) retinal vascular divisions were evaluated to classify AV crossing patterns.

All images were viewed on a 17-inch laptop screen (HP Pavilion; HP Inc., Palo Alto, CA, USA) with high resolution. For the author's patients, evaluations of the anterior segment using a slit-lamp (Model BQ 900; Haag Streit, Koniz, Switzerland), the posterior segment using an indirect ophthalmoscope (Heine Omega Indirect ophthalmoscope; Heine Optotechnick GmbH & Co., Germany), and intraocular pressure using non-contact tonometry (Nidek NT-4000; Nidek Co. Ltd., Gamagori, Japan) were routinely performed after capturing fundus images.

The patterns of entry and exit of the retinal arteriole and venule, respectively, at the optic nerve head were categorized based on the acuteness of the divergence/convergence of the superior and inferior divisions toward the optic cup. When the major superotemporal and inferotemporal vessels acutely converged or diverged at their locations over the optic nerve head, they were designated as V type (Figure 1A and Table 1). When the two major trunks curved gradually into each other, they were designated as U type (Figure 1B and Table 1). The AV crossing pattern (A/V or V/A) was documented at four levels: over or at the optic nerve head, and at three successive major crossings along the superotemporal and inferotemporal divisions. First- and second-order vessels were defined according to a previously described method [13]. Each was coded numerically: 1, arteriole crossing over the venule; 2, venule crossing over the arteriole; 3, absence of any AV crossing; and 4, indeterminate (when only two crossings instead of all four crossings were evident in the image). Furthermore, the AV crossings were classified into types A–E, as outlined in Table 1. Types A and B were characterized as tight wicker basket and loose wicker basket patterns, respectively (Table 1).

These codes were entered into a Microsoft Excel worksheet on the Microsoft Windows® 10 (Office 2021) platform (Microsoft Corp., Redmond, WA, USA), and simple descriptive statistical tests were carried out to determine the frequencies of various AV crossing patterns. The patterns were classified into four categories: wicker basket pattern (alternation after one or two similar crossings) (Figure 2A and Table 1), straight course (no alternation seen over three successive crossings) (Figure 2B and Table 1), widely spaced (fewer crossings could be analyzed because the central retinal vessels took a very divergent course after exiting the optic nerve head) (Figure 2C and Table 1), and indeterminate (peripheral crossings could not be analyzed because of non-capture within the available image field (Figure 2D and Table 1).

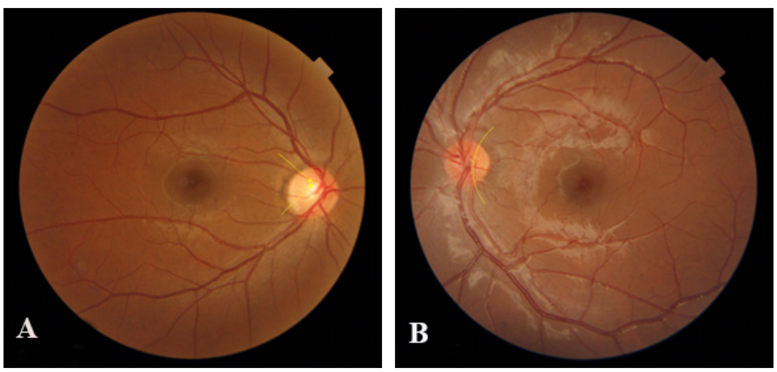

Figure 1. (A, B) Patterns in the superotemporal and inferotemporal vessel relationships at the optic disc. In (A), the major branches (both arterioles and venules) converge at an acute angle (V type, yellow arrows), while in (B), they do not converge but curve into each other (U type, yellow arc).

Table 1. Summary of the different patterns of arterio-venular (AV) crossings as the major vessels course along the posterior retina

Vascular pattern at the optic nerve head
V pattern (Figure 1A): the two trunks meet at an acute angle close to the optic nerve head.
U pattern (Figure 1B): the two trunks curve into each other at the optic nerve head.
Course of blood vessels (patterns from the optic disc outward)
Type A: alternating pattern at consecutive AV crossings (tight wicker basket pattern)
A1: one venous overcrossing between two arteriolar overcrossings (1-2-1) (**Figure 2A**)
A2: one arteriolar overcrossing between two venous overcrossings (2-1-2)
Type B: alternating pattern after two similar crossings (loose wicker basket pattern)
B1: one venous overcrossing following two consecutive arteriolar overcrossings (1-1-2 or 2-1-1)
B2: one arteriolar overcrossing following two consecutive venous overcrossings (2-2-1 or 1-2-2)
Type C: no alternating overcrossing seen over three expected AV crossings (1-1-1 or 2-2-2) (straight pattern) (Figure 2B)
Type D: widely spaced in regions normally expected to show crossing (if middle 2 values are 3) (widely spaced pattern) (Figure 2C)
Type E: only two crossings evident (indeterminate) (Figure 2D)

Note: These definitions have been set for the first time by the author of the manuscript.

Tables 2 and 3 summarize these observations (n = 394). The percentages and frequencies of tight wicker (A), loose wicker (B), straight (C), widely spaced (D), and indeterminate (E) patterns in the two image sets were 19% (38/200) and 16.5% (32/194), 22.5% (45/200) and 27.8% (54/194), 16.5% (33/200) and 15.5% (30/194), 22.5% (45/200) and 28.4% (55/194), and 19.5% (39/200) and 11.9% (23/194), respectively (Tables 2 and 3). Hence, the wicker basket pattern (A and B) was the most common pattern of AV crossing observed in both image sets.

The importance of structural and hemodynamic stability of the retinal vascular tree in maintaining the neurosensory retina cannot be overemphasized [14]. Vascular flow within retinal blood vessels may follow some of the principles of fluid dynamics, such as Laplace's law [14, 15]. These physical laws, in addition to the cellular composition and neurovascular control of the retinal blood vessels, help to explain the maintenance of steady vascular flow and pressure gradients within the major and minor branches, as well as in the capillary bed [16]. Dysregulation of one or more of these elements—part of the Virchow triad—is a primary element in the pathogenesis of retinal vascular occlusions, particularly BRVO [17].

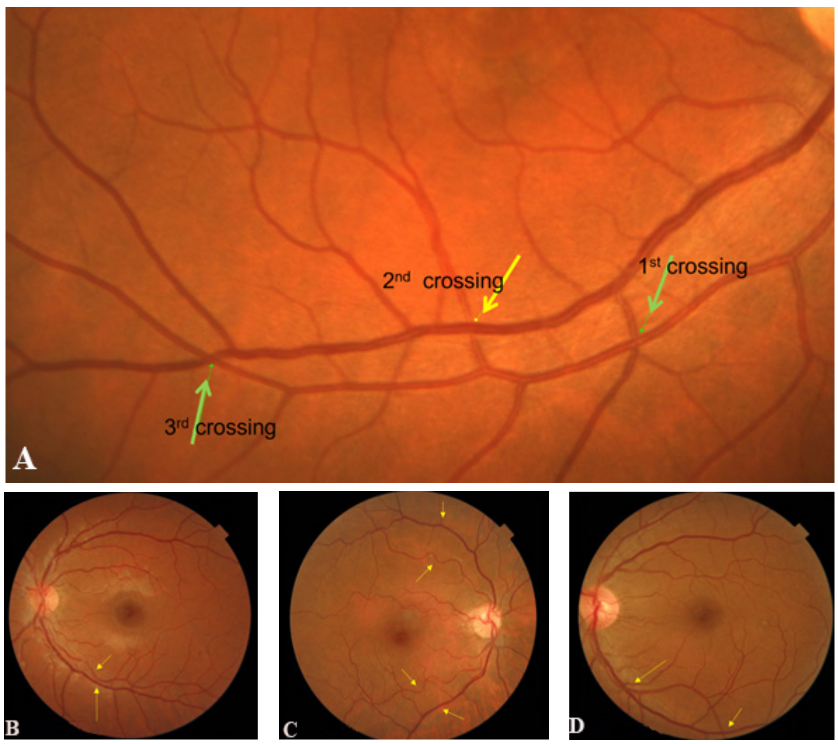

Figure 2 (A-D) Various patterns of retinal vascular course based on the nature of consecutive arterio-venular crossings: wicker basket pattern (A, magnified view), straight pattern (B, along inferotemporal arteriole and venule), widely spaced pattern (C, both upper and lower vessels), and indeterminate (D, along inferotemporal arteriole and venule).

Table 2. Frequencies of retinal vascular course patterns based on pattern type observed in the two image sets

Pattern type	Image set 1 (AIIMS) (n = 200)	Image set 2 (MESSIDOR database) (n = 194)
A1, n (%)	25 (12.5)	22 (11.3)
A2, n (%)	13 (6.5)	10 (5.2)
B1, n (%)	33 (16.5)	40 (20.6)
B2, n (%)	12 (6.0)	14 (7.2)
C, n (%)	33 (16.5)	30 (15.5)
D, n (%)	45 (22.5)	55 (28.4)
E, n (%)	39 (19.5)	23 (11.9)

Abbreviations: n, number of observations; %, percentage. Note: For details regarding the retinal vascular course patterns used to establish categories A1, A2, B1, B2, C, D, and E, refer to Table 1; AIIMS, This dataset comprised 100 randomly selected images from the author's own collection at the Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences (AIIMS) archive; MESSIDOR database, This database is publicly available and can be used for academic work after obtaining permission [11, 12].

Table 3. Frequencies of retinal vascular course patterns based on course type observed in the two image sets

Course type	Image set 1 (AIIMS) (n = 200)	Image set 2 (MESSIDOR database) (n = 194)
Wicker basket (A and B), n (%)	83 (41.5)	86 (44.3)
Straight (C), n (%)	33 (16.5)	30 (15.5)
Widely spaced (D), n (%)	45 (22.5)	55 (28.4)
Indeterminate (E), n (%)	39 (19.5)	23 (11.9)

Abbreviations: n, number of observations; %, percentage. Note: For a definition of each course type, refer to Table 1; AIIMS, This dataset comprised 100 randomly selected images from the author's own collection at the Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences (AIIMS) archive; MESSIDOR database, This database is publicly available and can be used for academic work after obtaining permission [11, 12].

BRVO, the most common retinal vascular disorder after diabetic retinopathy, has a varied presentation and natural course [18, 19]. In BRVO, the affected AV crossing has been studied often and in detail, and reports of differing patterns of AV relationships at the affected crossing have been published [18]. Some patients, despite a venule of similar caliber being occluded, develop adequate collateral vessels and have no appreciable sequelae from the occlusion, while others experience substantial complications such as ischemia and neovascularization, macular ischemia, or macular edema [20]. However, the reasons for the differing responses to similar levels of occlusion remain poorly understood.

The A/V crossing pattern is more common in eyes with BRVO than in normal eyes [21, 22]. A histopathological study showed increased stratification of the basement membrane and abrupt focal narrowing within the venule of the A/V crossing compared to the V/A crossing [23]. Those authors ascribed basement membrane stratification to hemodynamic stress on the venular wall and considered this to also contribute to the higher risk of BRVO associated with A/V crossing than with V/A crossing [23]. Hyperplasia of the extracellular matrix, including the adventitial sheath at the point of contact between the two vessels, is common to both types of crossings [23]. The thick extracellular matrix at the AV crossing has been used as a plane of surgical decompression in BRVO [24].

Recently, studies of AV crossings using optical coherence tomography (OCT) have confirmed earlier histopathological observations of an abrupt directional change and focal narrowing in the vein [25]. Using thin OCT slices, no evidence of compressive effect of the artery on the vein was observed [25]. This is contrary to the findings of previous reports indicating that rigid arterioles are likely to exert compression on thin-walled veins [26, 27]. In addition, OCT and OCT angiography studies suggest that BRVO in regions where the vein crosses over the artery is more common than previously reported [9, 28]. The patterns of change at causative and non-causative AV crossings in patients with BRVO and healthy controls was also recently studied using OCT angiography [29]. However, this author found no reports of how consecutive AV crossings behave from one crossing to the next. This study found that the alternating (wicker basket) pattern was the most common pattern of the AV-crossing relationship as the vessels progressed from the optic nerve head toward the posterior retina. The author believes that this pattern provides the most structural stability as the vessels course within the inner retina and line the hollow sphere. It is also likely that AV relationships along the entire course of the blood vessels, rather than at any single crossing, would influence flow characteristics such as turbulence, influencing the risk, location, severity, and natural history of BRVO. Based on these initial observations in individuals without vascular occlusion, further studies involving patients with BRVO are being considered.

A major limitation of this study is that it was undertaken by only one observer and at single time point, with no means to assess inter-observer or intra-observer variability; thus, further studies are needed to address this limitation. However, because the MESSIDOR database images, which are available to all researchers with permission, was also used in the analysis, other readers may independently ascertain the observed values provided in this report. The current study proposes a hypothesis regarding the course of retinal blood vessels. The clinical relevance of these observed vascular patterns and the associated risk of retinal vascular events could be further investigated in longitudinal studies with larger sample sizes, longer follow-up periods, and involvement of apparently healthy individuals who develop retinal vein occlusions. Another investigatory option would be the retrospective assessment of individuals with retinal vascular events who had prior routine ophthalmic examinations and archived fundus images.

CONCLUSIONS

Four distinct patterns of AV crossings along the course of retinal blood vessels were recognized: wicker basket (alternating), straight, widely spaced, and indeterminate, with the wicker basket pattern as the most common. The author hypothesizes that studying the AV crossing relationship over the entire course of the retinal vasculature, rather than focusing on the affected crossing alone, may improve our understanding of the pathogenesis, natural history, and outcomes of patients with major BRVO.

ETHICAL DECLARATIONS

Ethical approval: Permission to use MESSIDOR database [11, 12] images was obtained through e-mail correspondence. Because only de-identified images were captured over several years in the past (retrospective), and a publicly available image set was used for the study, official ethics approval was obtained at the departmental level to publish the outcomes of this study.
Conflict of interests: None.

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