Purtscher Retinopathy: An Alternative Etiology Supported by Computer Fluid Dynamic Simulations

Thomas J. Harrison,1 Cyrus O. Abbasi,2 and Tariq A. Khraishi2

PURPOSE. To explore an alternative etiology for Purtscher retinopathy by literature review and fluid dynamic computational simulations of wall shear stress (WSS) profiles.

METHODS. Computer simulations were developed, incorporating posterior pole retinal microvascular flow parameters, to demonstrate WSS profiles at 90° and 45° angle artery/arteriolar branching.

RESULTS. Computer simulations reveal WSS profiles dependent on artery/arteriolar branching angles. At high flow rates an area of changed WSS and flow swirling and reversal was noted at the proximal fillet of the 90° arteriolar branching. These changes did not appear at the 45° arteriolar branching until the flow rate was increased an additional 30%.

CONCLUSIONS. Computer simulation data, as well as review of the history and clinical findings of Purtscher and Purtscher-like retinopathy, present evidence that an additional etiology for Purtscher retinopathy may be a rheological event at a retinal posterior pole foci of vascular endothelial dysregulation, followed by downstream endothelin-induced vasculopathy. (Invest Ophthalmol Vis Sci. 2011;52:8102–8107) DOI:10.1167/iovs.11-7734

Purtscher retinopathy is a well known, but seldom observed, member of traumatic retinopathies that has defied an exact etiology since it was first described by Purtscher a century ago. Purtscher observed a delayed posterior pole retinopathy with hemorrhages and exudates in males who had sustained head injuries. Shortly after Purtscher’s original description, a similar constellation of findings were described in individuals with compressive chest injuries.2 In the ensuing years Purtscher retinopathy has been associated with a confusing number of seemingly disparate traumatic and nontraumatic diseases.

Clinical findings of Purtscher retinopathy and Purtscher-like retinopathy have been described in numerous articles, reviews, and textbooks. They consist of delayed involvement of the retinal posterior pole layers with ischemic lesions of the superficial nerve-fiber layer (cotton wool spots), infarcts of the retinal posterior pole layers with ischemic lesions of the superficial nerve-fiber layer (cotton wool spots), and dot/blot hemorrhages (deeper retinal layers). Optic nerve edema and hemorrhage are common.

Involvement of the choroid, retinal pigment epithelium is less common, but when it does occur, can be responsible for persistent vision loss.

Studies have shown vascular endothelial response to spatio-temporal gradients of wall shear stress (WSS) effects of downstream vascular autoregulation. Mechanical and toxic microenvironments to which vascular endothelial cells are exposed can result in acute and/or chronic endothelial dysregulation. Other studies provide evidence that the environment to which endothelial cells are exposed is, in part, dependent on the angle of artery/arteriolar branching with flow separation and reversals occurring more readily at obtuse angle branching than that at acute angle branching. These findings suggest that a susceptible focus of vasculopathy may exist upstream in the retinal posterior pole vascular system where Purtscher retinopathy clinical presentations converge.

METHODS

Computer simulations of retinal blood flow were developed using a sophisticated computational dynamics (CFD) code (Academic ANSYS-CFD, Release 12.1; ANSYS Inc., Cannonsburg, PA). In the last 25 years, CFD codes have been used to evaluate the dynamics of both Newtonian and non-Newtonian fluids within a simple or highly complicated environment such as a piston of a combustion engine or, in this case, in the human retinal blood flow system. The code has proved to be a reliable and repeatable tool in studying three-dimensional hemodynamics in complex arterial geometries. CFD works on the basis of finite volume methods, which incorporates the fundamental partial differential Navier–Stokes (NS) equations describing the patterns of blood flow. After constructing a representative model of a complex arterial geometry within the CFD code, the code discretizes the model into many smaller volumes called elements. These elements (usually cubes, tetrahedral, hexahedral, or prisms) are interconnected to each other at their corner points called nodes. By using the divergence theorem, the code converts the volume integrals (NS equations) of the elements into surface integrals. The surface integrals are used to evaluate the flux of blood through all the surfaces of an element. The flux exiting from one element is equal to the flux entering into the adjacent element. Thus, mass is conserved and the laws of conservation of mass are observed. From the numerical solution of the NS equations for all the elements, hemodynamic quantities such as WSS are obtained by the CFD code. Contrary to experimental flow studies, various parameters of the flow model such as blood viscosity, density, and wall roughness can be modified within the code. These convenient capabilities of CFD make it attractive to hemodynamic research groups.

Figure 1 demonstrates the three-dimensional nature of computer studies from which two-dimensional figures are later derived. Computer results as depicted by Figures 1 though 13 (specifically Figs. 6–13), reveal WSS calculations as a function of blood flow rate and bifurcation angle. Blood properties and flow data are provided in Table 1. Figures 2 to 5 represent composite pictures with points of interest (labeled A through E, Y, and A’ through E’). These points lie along the S1, S2, or S3 line paths. In later figures, WSS values at these

From 1Alaska Retinal Associates, Anchorage, Alaska; and the 2Mechanical Engineering Department, University of New Mexico, Albuquerque, New Mexico.

Supported in part by a Graduate Assistance in Areas of National Need (GAANN) Graduate Fellowship, New Mexico Department of Education (COB).

Submitted for publication April 13, 2011; revised July 15 and August 26, 2011; accepted August 26, 2011.

Disclosure: T.J. Harrison, None; C.O. Abbasi, None; T.A. Khraishi, None

Corresponding author: Thomas J. Harrison, 1301 Vista Morada, Santa Fe, NM 87506; tom_harrison3@hotmail.com.

Copyright 2011 The Association for Research in Vision and Ophthalmology, Inc.
points were important to discuss. S1 is a line path along the main artery base that extends beyond the arteriolar branch above it. S2 is a line path that passes through the proximal fillet, which links the main artery with the branch artery. S3 is a line path that passes through the distal fillet. WSS values were plotted along these three line paths. Please note that the line sense of S3 goes opposite to the blood flow direction in the arteriolar and along the blood flow direction in the main artery. In WSS figures (Figs. 6–11), findings for 90° and 45° branching are superimposed for direct comparison.

RESULTS

Normal Blood Flow

Along S1 (Fig. 6), with normal blood flow conditions (Table 1), there are no significant WSS profile differences between 90° and 45° arteriolar bifurcation angles.

Along S2 (Fig. 7), with normal blood flow, both 45° and 90° branch angle profiles show a sharp increase in WSS at the upstream fillet. For the 90° angle branching, the WSS increase initiates from the main artery shortly before the proximal fillet and reaches a maximum at point E. This maximum value is followed by a sharp decrease in WSS that reaches a minimum at point F. Again along S2 (Fig. 7) and for the 45° WSS profile, the sharp increase in WSS initiates at the artery somewhat before the fillet region and reaches a maximum at point E' followed by a minimum at point F'. The maximum 90° angle WSS is 14.5% higher than the maximum WSS of the 45° angle branch. The minimum 90° branch WSS (at point F) is 34.5% higher than the minimum WSS of the 45° branch (at point F').

For S3, with normal blood flow conditions (Table 1), both 90° and 45° WSS profiles behave similarly (Fig. 8). Of interest is that the WSS value at point B of the 45° angle branch is 25.3% higher than the corresponding value of the 90° branching (point B). The WSS value at point D of the 45° branching is 2.87% higher than the corresponding value of the 90° branching (point D). The first maximum WSS, for the 45° branching at B, is 11.9% lower than the second (global) maximum occurring at D. In addition, for the 90° branching first maximum WSS occurring at B is 27.7% lower than the second (global) maximum occurring at D. Note that the shear stress at points C and C' are zero since these are bifurcation points for the flow streamlines.

Twenty-Five Times Normal Blood Flow

Along S1, for 25 times the normal blood flow rate (Fig. 9), the WSS drop pattern, noted at normal blood flow, reverses. The WSS drop of the 90° branching (point A) is steeper compared with the smoother WSS drop of the 45° branching (point A').

Along S2 (Fig. 7), with normal blood flow, both 45° and 90° branch angle profiles show a sharp increase in WSS at the upstream fillet. For the 90° angle branching, the WSS increase initiates from the main artery shortly before the proximal fillet and reaches a maximum at point E. This maximum value is followed by a sharp decrease in WSS that reaches a minimum at point F. Again along S2 (Fig. 7) and for the 45° WSS profile, the sharp increase in WSS initiates at the artery somewhat before the fillet region and reaches a maximum at point E' followed by a minimum at point F'. The maximum 90° angle WSS is 14.5% higher than the maximum WSS of the 45° angle branch. The minimum 90° branch WSS (at point F) is 34.5% higher than the minimum WSS of the 45° branch (at point F').

For S3, with normal blood flow conditions (Table 1), both 90° and 45° WSS profiles behave similarly (Fig. 8). Of interest is that the WSS value at point B of the 45° angle branch is 25.3% higher than the corresponding value of the 90° branching (point B). The WSS value at point D of the 45° branching is 2.87% higher than the corresponding value of the 90° branching (point D). The first maximum WSS, for the 45° branching at B, is 11.9% lower than the second (global) maximum occurring at D. In addition, for the 90° branching first maximum WSS occurring at B is 27.7% lower than the second (global) maximum occurring at D. Note that the shear stress at points C and C' are zero since these are bifurcation points for the flow streamlines.

TABLE 1. Utilized Dimensions of the 90° and 45° Bifurcations; Natural Retinal Blood Flow/Velocity, Density, and Dynamic Viscosity; and Calculated Reynolds Number and Entrance Length within the Main Vessels of the 90° and 45° Bifurcations

<table>
<thead>
<tr>
<th>Vessel Dimensions</th>
<th>Diameter (μm)</th>
<th>Length (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90° Main vessel (MV)*</td>
<td>110</td>
<td>3300</td>
</tr>
<tr>
<td>Side branch (SB)12</td>
<td>65</td>
<td>1040</td>
</tr>
<tr>
<td>45° MV*</td>
<td>110</td>
<td>3300</td>
</tr>
<tr>
<td>SB12</td>
<td>65</td>
<td>1040</td>
</tr>
</tbody>
</table>

Retinal Blood Flow (RBF) and the Inlet Velocity at the MVs

RBF into MVs13 = 6.66E-10 m³/s
Area of MVs13 = 9.503E-09 m²
MV inlet velocity13 = 0.0702 m/s

Density and "Dynamic" Viscosity

Density14 = 1060 kg/m³
Dynamic viscosity15,16 = 1.05 cP
Maximum dynamic viscosity15,16 = 5.70 cP

Reynolds Number and Entrance Length (Le)

Reynolds number17 = 7.790
Le within the MVs18 = 5.141 μm

Along S2, for 25 times the normal blood flow rate (Fig. 10), WSS patterns similar to those occurring with normal blood flow conditions are noted. However, for the 90° branching, after reaching a maximum WSS value at point E, the WSS does not directly drop to a minimum value as seen with normal blood flow. Rather, it drops to a minimum at point X, followed by a small WSS increase to point Y, and then decreases to a second (global) minimum at point F. The occurrence of this WSS behavior is due to swirling blood flow observed in the 90° branching angle at high flow levels (Fig. 3), which is not observed at normal blood flow (Fig. 2). This swirling pattern is not seen in the 45° branching unless the blood flow is increased an additional 30%.

Along S3, for 25 times the normal blood flow rate (Fig. 11) and for both 45° and 90° angle branching, a sharp increase in WSS values is noted at B' and B. Point B' of the 45° branching is 43.9% higher than the corresponding value for the 90° branching at point B. After the two lines drop to zero at the distal fillet points C' and C, the WSS sharply increases and reaches a second (local) WSS maximum at points D' and D. At this point the 45° branching is 6.36% higher than the 90° branching. Further, for the 45° branching, the first (global) maximum WSS occurring at B' is 35.1% higher than the second (local) maximum occurring at D'. Note that under normal blood flow conditions (Fig. 8), the WSS at B' is 11.9% lower than that of point D'. Thus, the WSS pattern has reversed. For the 90° branching the first maximum WSS occurring at B is only slightly (0.19%) lower than the second maximum occurring at D. Under normal blood flow conditions (Fig. 8), the WSS value at point B is 27.7% lower than that at point D, whereas at 25 times normal blood flow both values (for points B and D, Fig. 11) are almost equal.

**DISCUSSION**

The etiology of Purtscher and Purtscher-like retinopathy has been investigated chiefly by focus on a specific disease or set of diseases in which Purtscher retinopathy has been observed. Review of these diseases suggests they fall into three categories: toxic and/or obstructive emboli, intravascular volume surges, and intracephalic shock waves.

Presently, retinal arteriolar and capillary embolism with microinfarction is considered the most acceptable etiology for Purtscher retinopathy and there is pathologic and experimental evidence to support this hypothesis. 19–22

A serious argument against end organ capillary embolization as the only etiology for Purtscher retinopathy is the occurrence of Purtscher retinopathy in nonembolic syndromes, head trauma, and chest compression injuries. In addition the delayed clinical signs of Purtscher retinopathy would be more typical of nonembolic toxic ischemia rather than embolic vascular obstructive disease.

The fact that Purtscher retinopathy occurs rarely, bilaterally, unilaterally, and associated with many disparate diseases suggests an unusual and complex interaction of vascular anatomic and physiological events.

**Retinal Microvascular System**

The inner retinal microvascular system has three aspects, which makes it uniquely vulnerable to endothelial dysregulation. It is, unlike the choriocapillaris, a terminal vascular complex, unfenestrated, and autoregulated. The microvascular system of the inner retina is derived from the central retinal artery.
and is a terminal system with no anastomoses outside the retina. Branches from the central retinal artery form two capillary plexi, one within the ganglion cell layer and the other in the inner nuclear layer. Rarely do capillaries from these plexi extend into the outer plexiform layer. At the fovea, the layers of the inner retinal thin to form the foveal pit. At this point there are no inner retinal vessels.

Inner retinal vascular endothelia respond to mechanical, hormonal, and chemical flow stimuli by the production of autoregulators, among which are nitric oxide, prostacyclin, and endothelin peptides to achieve downstream vascular balance.23,24

Endothelial dysregulation, as seen in atherosclerosis, hypertension, diabetes, and hypercholesterolemia as well as in cases of dysregulatory spatiotemporal variations of WSS, results in reduced production of nitric oxide as well as increased production of endothelins, which results in downstream vasoconstriction.25

**Wall Shear Stress**

Vascular equilibrium, in a closed autoregulated system such as the inner retinal microvascular system, depends on being able to sense local blood flow dynamics. This signal transduction process is mediated through vascular endothelial cells.26 Endothelial cells respond to spatiotemporal gradients of flow affecting downstream vascular autoregulation.27,28 Wall shear stress as the relation between force (pressure) and the longitudinal/axial force becomes the key mechanosignal transducer of information between the blood and the vessel wall.26

**Retinal Microcirculation Geometry**

Microcirculation system bifurcation angles have been shown to begin with obtuse branching and then develop to acute angles as the system progresses into capillaries.29 The retinal microcirculation is no exception. The India ink preparations of Paul Henkind29 reveal the artery/arteriole branchings in the retinal posterior pole to be predominantly at right or obtuse angles, as opposed to the periphery where there is a broad capillary network of acute angle dichotomous branchings.29,30 Apple and Rabb31 describe the retinal posterior pole vascular system to bend sharply and vertically into the retina.

Variable wall shear stress throughout the vascular system, especially at vessel branching, results in complex chains of rheological events that can produce areas of disease predilection. Data from studies of cardiac lesions,32,33 intracranial aneurysms,34 abdominal aneurysms,35 and atherosclerotic plaques36 show the effect of vascular culprit areas, vulnerable to rupture, atherosclerosis, and trauma.

**Retinal Vascular Endothelium**

Vascular endothelial dysregulation with endothelin production as part of Purtscher and Purtscher-like retinopathy has been suggested by some authors.28 Blood, in disease situations, to which retinal endothelial cells are exposed, contains potential endothelial dysregulatory substances that have been known to be associated with Purtscher-like retinopathy. These toxic aggregations do not necessarily need to be embolic at terminal capillaries, but can cause upstream endothelial dysregulation.
by way of WSS alterations, augmenting cellular aggregation and cellular adherence to retinal vascular endothelium.

Endothelin peptides are powerful vasoconstrictors that are normally produced by vascular endothelium. In disease states, dysregulated endothelium overproduces these vasoconstrictive substances. Endothelin-1 is found systemically elevated in septic and endotoxic shock syndromes, such as renal failure, hemolysis, elevated liver enzymes and low platelet of “HELLP” syndrome, elevated liver enzymes and low platelet of “HELLP” syndrome,46 and adult Still disease.45 It is with these systemic diseases, associated with abnormal systemic endothelin, that Purtscher retinopathy is associated.

**Optic Nerve**

One of the more universal aspects of Purtscher and Purtscher-like retinopathy is optic nerve involvement. Hayreh40 has demonstrated that the vascular supply of the optic nerve is variable and individualistic. It is logical to assume that the branching angles of optic nerve vascular supply would follow the usual obtuse to acute angle configuration of vascular microsystems.4,5 Studies have shown that the optic nerve head is autoregulated and is thereby susceptible to endothelial direction.41 Optic nerve vascular homeostasis follows the same vascular homeostasis of retinal vessels, that is, a balance dependent on factors emerging from upstream endothelium.

Flammer and others42,43 have made the observation that vascular endothelial dysregulation syndrome with diffusion of endothelin to the optic nerve head results in vasconstriction and increases the risk for venous occlusion as well as weakening the blood–brain barrier. They suggest that the pathogenesis of glaucomatous optic neuropathy is due, in part, to vascular endothelial dysregulation.

Literature suggests that endothelial dysregulation with an outpouring of vasoconstrictive endothelins, with or without embolization, may produce Purtscher retinopathy. Clinical characteristics of Purtscher retinopathy point to a posterior pole focus of dysregulation, where blood flow patterns allow damage at critical endothelial areas (i.e., the 90° angle branching as noted in the above-cited computer simulations). Irregular blood flow with flow separation and retrograde flow, under traumatic circumstances, may result in endothelial dysregulation.

**Limitations**

Involvement of choroid, retinal pigment epithelium, and macula have been reported in cases of Purtscher retinopathy. Often these findings are associated with head injury where ancillary trauma can be incriminated. However, there are cases of nontraumatic disease such as toxic embolization, cellular aggregation and adhesion, as well as vasoconstrictive and vasooclusive events, where choroid and macular disease have been described.44 Although vision recovery is not uncommon in cases of Purtscher retinopathy, chronic vision loss secondary to macular and retinal pigment epithelium damage does occur. More commonly permanent visual loss is secondary to optic atrophy. These unusual findings should not detract from the above-proposed hypothesis, but rather be considered as pathology that has occurred in association with classic Purtscher retinopathy, but not necessarily related to the pathophysiology of endothelial dysregulation.

The effect of intracerephalic shock wave is affected by many variables, such as media density, shock vector direction, magnitude of trauma, and others. These complex variables, as related to Purtscher retinopathy, attest to the rarity and multiple clinical presentations after head trauma. The preceding computer programs were not developed to demonstrate a profile for intracerephalic shock waves as they encounter a perpendicular arteriolar branch as opposed to a profile for an encounter with a dichotomous acute angle branch. Further computer simulation studies are planned to investigate the extravascular shock wave effect on endothelial dysregulation.

To elicit wall shear stress flow disruptions within our computer models, flow rates were increased 25 times above the normal flow rate. Our purpose was to demonstrate that at extremes of flow, 90° angle branchings, common to the retinal posterior pole, are more susceptible to flow disturbances and subsequent endothelial dysregulation than are 45° angle branchings. By keeping flow rates constant, although high, we were able to more accurately compare, as a single variable, branching angles.

There is thought that the retinal vascular Reynolds number is too low to reach disturbed flow conditions. However, our study shows that, although the retinal Reynolds number is linear with retinal blood flow rate (from the definition of Reynolds number), the increase of WSS with Reynolds number (or, alternatively, flow rate) is nonlinear. In fact, it rises more rapidly at the rate of a third-order polynomial (Figs. 12, 13). This suggests that WSS values, especially at bifurcation regions as shown here, are very sensitive to changes in the blood flow rate; these changes may be responsible for Purtscher retinopathy.

**Treatment Avenues**

The above-cited hypothesis provides evidence for research into an avenue of treatment for Purtscher retinopathy. Endothelin receptor antagonists are now being tested for treatment of a variety of conditions, including pulmonary hypertension, congestive heart failure, renal failure, cancer, cerebrovascular disease, hypertensive retinopathy, and glaucoma. A productive avenue of research may be to evaluate endothelin receptor antagonists in the management of Purtscher and Purtscher-like retinopathy.
CONCLUSIONS

It is difficult not to incriminate capillary embolic occlusion in the etiology of Purtscher retinopathy, and indeed the syndrome does involve occlusive end organ vasculopathy as noted by fluorescein, experimental, and pathologic evidence. These studies cannot be ignored. However, limiting our perspective to capillary emboli ignores a number of perplexing contradictions associated with this rare disease and suggests a comprehensive etiology has been incompletely described.

The preceding computer simulation studies of WSS profiles comparing 90° angle vs. 45° arteriolar branching reveal an area, at the 90° angle artery/arteriolar branching, where the margin between physiological and disruptive flow is narrow. It is at this culprit junction where endothelial dysregulation, under stressful conditions, is more likely to occur. Computer dynamic flow simulations, in addition to literature review, suggest that a possible additional pathophysiology that initiates Purtscher retinopathy, within a milieu of embolization, volume surges, and extravascular shock waves, may be an inner layer retinal posterior pole rheological event that results in vascular endothelial dysregulation. This endothelial dysregulation with pathogenetic release of endothelins may contribute to downstream occlusive vasculopathy of Purtscher retinopathy.

References