Abstract

Since many eye diseases are based vascular factor, it is very important to understand both the vascularization of this area as well as their pathogenesis and management. Regarding the optic nerve (ON), its vasculature plays a decisive role in etiopathogenesis of different forms of optic neuropathy (including glaucoma) as well as other eye diseases. ON vascularization is complex, particular and varies depending its segment.

In the last years new techniques have been developed, or some older were perfected, for examination of oculo-orbital vessels and blood flow of this level. The current techniques for noninvasive examination of ocular blood flow have contributed significantly to understanding the role of ocular hemodynamic in the etiology of various eye diseases.

Keywords: arterial circulation, venous circulation, blood flow, optic nerve

Introduction

The eye is the organ where the blood vessels can be examined directly, through noninvasive techniques. The ocular blood flow is influenced by various factors and their interaction: metabolic products, perfusion pressure, blood gases. Effects and interactions of these factors influence complex and varied the ocular blood flow, requiring its study to elucidate the hemodynamic changes in different diseases.

Research carried out in order to understand ocular blood flow have increased in recent decades, all over the world. The current techniques for noninvasive examination of ocular blood flow have contributed significantly to understanding the role of ocular hemodynamic in the etiology of various eye diseases [1].

In the last years, it was concluded that in glaucomatous optic neuropathy, besides intraocular pressure, there are other factors that influence the disease evolution, including vascular factor would seem to play an important role. A proof of this is the 6th meeting of the World Glaucoma Association (WGA) of 2009, which had as theme “Ocular blood flow in Glaucoma” [1].

Optic Nerve Vascularization

ON vascularization is complex, particular and varies depending its segment: the optic nerve head, consists of the following 4 regions from anterior to posterior aspects: the surface nerve fiber layer, prelaminar region, lamina cribrosa region and retrolaminar region, intraorbital segment (25-30 mm), canalicular segment (9-10 mm), intracranial segment (16 mm) [2,3,4,5], being very rich before entry of central retinal artery in the glob and much poorer thereafter [6].
I. Arterial Circulation
Arterial circulation of ON is achieved through the ophthalmic artery (OA), branch of the internal carotid artery, with origin at the level of anterior wall of C3 regions and with horizontal and anterior direction, which enters in the orbit through the ophthalmic hole along with ON, located lateral and inferior towards it [7]. Subsequently, passes over the ON, having in the front third a parallel trajectory with the medial side of the orbit and passes medial and superior towards ON [8]. OA is divided into ocular and orbital branches [7]. OA ocular branches are [3]: short posterior ciliary artery, long posterior ciliary artery, central retinal artery (ACR) which penetrates ON approximately 10-15 mm posterior to the globe, and after entering the eye is divided into 2 arcade: upper and lower [9].

Typically, between 2 and 4 posterior ciliary arteries (PCA) has an anterior trajectory and will be divided into approximately 10-20 short PCA before entering in the eye [1]. Often, PCA form the two arterial groups: lateral and medial, before branching in short PCA [1]. Short PCA penetrate the perineural sclera for vascularize peripapillary choroid and anterior portion of ON. Some of them can cross the sclera until the choroid level without branch [1]. After Hayreh, PCA along intraorbital path are divided into numerous branches at different distances before entering the eyeball: long PCAs in generally in number of 2- one medial and one lateral- without role in vascularization of ON and short PCAs in number of about 20, which is subdivided into 2 subgroups - paraoptic arteries (for the ON) and distal arteries (for the choroid) [10].

1. The Surface Nerve Fiber Layer
It is the first area irrigated by centripetal model by branches of CRA, which forms at the peripapillary retina [4]. These arterioles go to the optical disc and are called “epipapillary vessels”. Capillary branches of these vessels are continuous with the retinal capillaries at the edge of the optic disc, but they have posterior anastomoses with the prelaminar capillaries of ON [1,3,4,5]. Direct choroidal contribution is not demonstrated at this level [4,5]. When cilio-retinal artery is present (one or more), precapillary branches can contribute to irrigation of temporal sector [1,3,4,5,10]. The number of these arteries is correlated with optic disc size [3].

2. The prelaminar region
Irrigation is insured mainly by short PCAs through direct branches or Zinn-Haller circle (when is present). Branches of arterioles and capillaries form a diffuse network around and inside nerve fascicles [5]. There are studies that support the existence of branches from peripapillary choroidal vessels (10% of vascularization of this area) [1,4,10]. The capillaries of this region are complex and are continues with the capillary bed from the surface of nerve fibers layers and the level of laminar region.

Circle of Zinn-Haller
It was described by Haller in 1754 and Zinn in 1755 as an incomplete anastomotic arterial circle located at the sclera level, and consists from anastomoses of short PCAs around of ON head [1,3,4,10]. At the eyes with Zinn-Haller circle well developed, arterial branches from this supply both the prelaminar, laminar regions [1] as well as retrolaminar region by recurrent branches [10]. Olver et al., described the circle of Zinn-Haller as a microscopic, intrascleral, elliptical, microvascular anastomosis formed by branches of the medial and lateral paraoptic short PCAs [10].

3. The laminar region
Entire vascularisation is provided by branches of short PCAs and Zinn-Haller circle [3,4,10]. Occasionally, from peripapillary choroid can leave small arterioles [4]. At this level, the capillaries are organized as a dense capillary plexus, forming a highly vascularized structure at the ON head [10]. The capillaries of this region are continues with the capillaries of retrolaminar region.

4. The retrolaminar region
Vascularization of this region is double: peripheral, centripetal vasculature provided by pial vessels with origins at the Zinn-Haller circle, short PCAs and from the choroidal peripapillary region [1,4,10]; may also participate pial branches from CRA and other orbital arteries; axial, centrifugal vasculature, present in 75% of cases, consisting of branches (from 1 to 8) of CRA. Axial vasculature, when is present, is not as developed as the peripheral [4,10]. May also participate capillary from laminar region [4].

In conclusion PCA, directly or via choroidal peripapillary branches or short PCAs (or Zinn-Haller circle when is present), is the only vascular source for the prelaminar and laminar regions and the main source (if not only) for retrolaminar region [10].

PCA Watershed Zones
When a tissue is supplied by two or more end-arteries, the border between the territories of distribution of any two end-arteries is called a “watershed zone”. These areas with poor vascularisation, which makes them vulnerable to ischemia. The important role of these zones becomes obvious in cases where the perfusion pressure from one or more end-arteries belonging to the same area decreases. The location of the watershed zones at this level varies according to the number of the PCAs and their locations [10].
5. Intraorbital part of the ON
Is subdivided, according to the place of penetration of CRA in ON, in 2 sub-segments: anterior and posterior [10].

Anterior subsegment disposes of 2 vascular systems: the peripheral system (centripetal) and axial system (centrifugal). The peripheral system is always present, arterial vascularization of peripheral fiber of ON being ensured through the arteries coming from the vascular system of the pia mater, most of them being branches of the OA [4], peripapillary choroid, Zinn-Haller circle, CRA and other orbital arteries [10]. Branches from OA penetrate the dura at 10-12 mm from the glob to participate in the formation pial system [4]. Recurrent branches of PCAs and juxta-papillary choroidal are added to pial vascularization [4]. The axial (centrifugal) system is present in 75% of ON; central parts of ON are supply by intraneurial arterioles with the pial origin [6] and intraneurial branches (in number of 1-8) of CRA [6,10].

Posterior subsegment presents a peripheral centripetal vascular system represented by pial vascular plexus, consisting of multiple small collateral arteries, with origin often at the OA level and rarely in other orbital arteries. In 10% of cases there may be an axial centrifugal vascular system consists of intraneurial branches of the CRA [10].

6. Canalicular part of the ON
There are different opinions regarding blood supply of this area. After Hayreh, vascularization of this segment is provided by AO by collateral branches, usually between 1 and 3. These branches reach to the ON traversing the conjunctiva sheath which covers the nerve at this level. There are no axial vascular system at this level [10].

7. Intracranial part of the ON
There are many controversies regarding vascularization of this segment. In summary, it is provided by branches from: internal carotid artery, anterior cerebral artery, anterior communicating artery, OA. Pial arterioles become capillary and cross the pial septum until ON axis [4,10].

II. Venous circulation
Venous circulation of the ON head is provided especially by central retinal vein (CRV) [10], parallel to with homonymous artery inside of ON [1,3]. Small venules draining from superficial nerve fibers layer to choroid (optico-ciliary veins) [4].

Vessels of prelaminar region draining to peripapillary choroidal veins (VCR, at this level, communicates with choroidal circulation). There is no venous equivalent for Zinn-Haller circle. Veins of nerve trunk go one part in CRV and other part in a central posterior vein [6].

Intraorbital region drains mainly into the CRV. Pial veins located at the pia mater mostly open at the CRV. CRV is formed at the optic disc level through the union a number of different retinal veins, and go posterior through the axis of ON, temporal by the CRA. CRV goes through part of ON before heading out it, in orbit. Therefore, venous blood is drained most of the cavernous sinus and to a lesser extent to the orbito-facial and orbito-pterygoid network [6].

Angioarchitecture of the optic nerve
Since 1903 has been described by various investigators. Vascularization of ON is identical to the brain. All arteries of ON provides its vasculature through the pial vascular plexus which acts like a “distributing centre for the vessels”. The vessels entering the nerve from the pia take a covering of the pia and glia with them, which forms the septal system of the nerve. The angioarchitecture in the region of the lamina cribrosa has been described as comprising numerous, small, very close and transversely elongated meshes, a very dense capillary plexus 10–20 mm in diameter which makes this part of the ON head a highly vascular structure. Intraorbital segment presents anastomoses between OA branches to the surface of ON and anastomoses between intraneurial branches inside of ON. Longitudinal vessels are connected irregular with transverse vessels that go in different directions forming in longitudinal section “mesh nets” with irregular forms. Intracanalicular segment has a similar angioarchitecture with intraorbital segment, becoming increasingly complicated as cranial segment approach, losing the difference between longitudinal and transverse vessels. Intracranial segment has a double angioarchitecture: in the distal part, compared with previous segment, longitudinal vessels become prominent, and the transverse vessels become rare; in the proximal portion, especially lateral side, vessels are less dense. At the ON level, capillaries extending throughout its length, with anastomoses between them, and above anastomoses with retinal capillaries [10].

Vascular wall structure
Vascular wall is made up of 3 concentric layers, histologically different, from inside to outside: tunica intima, media and adventitia.

Tunica intima is made up of endothelial layer, subendothelial layer and internal elastic lamina. Endothelial layer has a single row of cells (simple squamous epithelium), ovoid shape, with the long axis parallel to the long axis of the vessel, placed on the basal lamina. Their numbers differ depending on the size of vessel: at vessels with the small caliber one endothelial cell is sufficient to cover the circumference of the lumen;
at the greater vessels their number is directly proportional to their size. In the endothelial cells from arteries level exist Palade corpuscles (ribosomes) who containing von Willebrand factor [11], with a role in clot formation. Subendothelial layer is made up of lax conjunctive tissue and smooth muscle cells disposed longitudinally. Internal elastic lamina is made up of elastin, with fenestrated aspect (“mesh”), allowing diffusion of the substances. Is more developed in the arteries of muscular type.

Tunica media consists of smooth muscle cells and external elastic lamina. Smooth muscle cells are arranged in the concentric layers, disposed helicoidal, among which finding elastic fibers (better developed in the arteries of elastic type), type III collagen fibers and proteoglycans. Postcapillary vessels have not medium tunic, which was replaced by pericytes.

Tunica adventitia is made up of fibroblasts, type I collagen fibers and elastic fibers oriented longitudinally. Depending on the proportion of various elements of the wall structure, arteries are divided into: elastic and muscle [7].

At the microcirculation level, the balance between blood flow and intraluminal pressure is provided by arteriolar tone, precapilare sphincter, pericytes and capillary tone and smooth muscle fibers from veins. Capillary pericytes can substitute role of precapilare sphincters where they are missing.

As regards nature of endothelium, capillaries and can be fenestrated and nonfenestrated. Fenestrated capillaries (present in most organs) allow passage of large molecules, particularly proteins. Nonfenestrated capillaries, present at the retinal and ON head level, do not allow diffusion of substances from plasma into surrounding tissue [3,5] and have junctions type tight between endothelial cells, achieving the blood-ocular barrier [5]. Capillaries of the retina and ON are devoid of precapillary sphincters but have many pericytes. These pericytes act as vascular smooth muscle genuine, reacting to the presence of CO2, O2 levels and adenosine concentration. These capillaries are equipped to intervene in the control of blood flow to the ON head through the mechanism of “metabolic autoregulation”. In contrast, choroidal capillary bed (coriocapillary) consists of fenestrated capillaries and rare pericytes [3].

Examination of vascularization and blood flow to the ON
In the last years new techniques have been developed, or some older were perfected, for examination of oculo-orbital vessels and blood flow of this level. Some remained in the experimental stage, others have found clinical application.

Pulsatility measurement devices
Ophthalmodynamometry (ODM): is an indirect measurement of the systolic and diastolic blood pressure in the CRA; a contact lens equipped with a pressure sensor measuring increased intraocular pressure (IOP); CRA diastolic pressure is considered to be equal to IOP onset; maximum value of IOP corresponds ACR systolic pressure [1].

Ophthalmodynamography (ODG): measured pressure in OA; the eye is cover with an elastic membrane which exerts pressure on the whole orbit; similar to blood pressure measurement with sphygmomanometer, pulsation is transmitted from the orbit through the membrane in the device, and recorded on a diagram [1].

Oculo-oscillo-dynamography (OODG): improves the previous techniques, determining directly pulsation within either retinal or choroidal vascular bed.

Pulsatile Ocular Blood Flowmetry (POBF): measures IOP in real time, without perturbing it, through a modified pneumotonometer connected to the computer. Ocular blood flow varies during the cardiac cycle, influencing IOP value, with a peak during the systole and a decrease in the diastole. Quantifying IOP pulsation associated cardiac cycle, allows the calculation of pulsatile component of ocular blood flow (done approximately 200 measurements/sec) [1,3,10].

Interferometry: highlighted directly the pulsation of the retinal level, using a laser beam who is divided into two fascicles (one to retina and one for cornea) [1,3].

Laser devices
LDF (Laser Doppler Flowmetry): method was first described in 1992 by Riva et al., evaluates blood flow to the ON head: the laser beam measuring blood flow at a depth greater than 520 μm, corresponding to the CPA [1,3,10].

SLDF (Scanning Laser Doppler Flowmetry): is the only device that measures vascular flow in absolute units. By combining the advantages of fundus camera and the Doppler effect, may reveal velocity, diameters and vascular tracts [1,10].

LSF (Laser Speckler Flowgraphy): noninvasive technique first used by Japanese researchers which examines the blood flow to the ON head, the laser beam reaching depths of 0.5-1 mm. Based on the phenomenon of “interference” seen when a light source such as laser scans a reflective surface [1,3,10].

Scanning Laser ophthalmoscope (SLO): technique based on LDF; the devices using a confocal optical system, which leads to obtaining a high quality image of the fundus [1,10].

HRF (Heidelberg Retinal Flowmeter): technique based on LDF, which has adapted a confocal laser
scanning system which allows a greater depth examination. Can provide images of peripapillary retina and neuro-retinal ring [1,3,10].

HRT (Retinian Tomography Heidelberg): Evaluates blood flow to the neuro-retinal ring [1].

Doppler OCT (Optical Coherence Tomography): New generations of OCT: time-domain (TD-OCT) and spectral-domain (SD-OCT) increased performance of the classic OCT. SD-OCT provides three-dimensional images of the intraretinal microstructure through a faster scanning and with a higher resolution (18,000 measurements/sec, with an axial resolution of 5 mm) than TD-OCT (400 measurements/sec with an axial resolution of ~10 mm). Experimental is used High-speed ultrahigh-resolution OCT (UHR OCT): 25,000 measurements/sec, with an axial resolution of 3.5 mm. The new technologies can measure speed and volume of blood flow to the branches of the retinal vessels and the size of these vessels. The development of these techniques attempts to obtain Doppler structural information and oximetry during the same scan [1,3,5].

Doppler ultrasound: useful in the diagnosis of multiple primary or secondary vascular diseases of the eye and orbit [12].

Color Doppler imaging (CDI): can examine the OA, CRA and CRV, short PCAs, superior ophthalmic vein, measuring the velocity of vascular flow and resistance vascular index at their level. The principal parameters measured are: peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI) and resistivity index (RI) [1,3,10,12,13].

Transcranial Doppler ultrasound: non-invasive method, used since 1982 by Rune Aaslid, currently has multiple uses, including examination AO [7,10].

Angiography

AFG (Angiofluorography): used in ophthalmology for 50 years, shows the in vivo vascularization of ON head, retina and choroid (less) [10,14]. The contrast substance, fluorescein, is a nontoxic chemical compound, with bright fluorescing properties, which is injected IV. Blue excitation light (λ=465-490 nm), acting on the fluorescein, unbound of plasma proteins, resulting in a yellow-blue light (λ=520-530nm). Can be performed an analysis: sequential - is examined the angiogram frame by frame highlighting its phases: prearterial, arterial, arteriovenous and venous; anatomical- are observed layers and zones of posterior pole; morphological [5,14].

Scanning Laser AFG: is obtained high quality images with a wide field, in which can be examined vascular diameters and tracks in dynamics (real time) [1,3,10].

Indocyanine green angiography (ICG): is performed using a SLO device that will highlight presence of the contrast agent bound to plasma proteins (indocyanine), injected IV, at the eye vessels level, mainly the choroidal [3,5,10].

Magnetic resonance angiography = angio-RM (MRA): complete, noninvasive method for examining intra- and extracranial circulation; the most used technique is the “time of flight” (TOF), with two possibilities data acquisition for imaging: two-dimensional (2D-TOF) and three-dimensional (3D-TOF) [7]. Another technique used is “phase contrast pulse sequences” [15].

Computed tomography angiography= angio-CT (CTA): performed 1mm sections, viewed by MIP technique (maximum intensity projection) [7,15].

“Dynamic ultra-widefield” angiography Optos P200MA: offers a very broadly field and high quality examination [5].

Oximetry

Retinal oximetry: noninvasive method that measures the oxygen saturation of hemoglobin in retinal structures using digital images [1,3].

Magnetic Resonance Oximetry: is based on the paramagnetic properties of oxygen and its ability to influence the relaxation rate (1/T¹). Posterior vitreous oxygenation is used to determine the retinal oxygenation.

Direct examination

Examination of the ON head within fundus analyzing by: direct ophthalmoscopy, indirect ophthalmoscopy, fundus biomicroscopy with different lenses, fundus camera (is obtained stereoscopic images).

Disorders in which it is involving vascularization of ON

Vascular disorders of the ON head

Central retinal vein occlusion (RVO): histopathological thrombosis occurs at the lamina cribosa of the CRV [5,12,13], or at the branch of it.

Central retinal artery occlusion (RAO): after occlusion location can be divided into: CRA occlusion, occlusion of the branch of CRA, cilio-retinal artery occlusion, occlusion combined CRA and CRV [5,12,13].

Chronic glaucoma (hypertensive, especially the normotensive): in the last years have made many prospective studies that have demonstrated retinal, choroidal and retrobulbar circulation problems. Also, glaucomatous optic neuropathy was associated with abnormal ocular perfusion pressure, nocturnal hypotension, disc hemorrhage, migraine and aging of blood vessels. Chronic ischemia of ON leads to loss of retinal ganglion cells, independent of IOP value. Reduction of ocular perfusion pressure may be secondary to elevated IOP, or may represent the first cause of impaired ON in glaucoma. Also, chronic ocular ischemia can induce vascular impairment of self-
regulation and its incapacity to reduce IOP and maintaining adequate ocular perfusion pressure [3,12,13,16].

**Ocular hypertension**

**Retinal detachment**

**Optic neuropathies:** may be divided into 2 groups: vascular neuropathies (anterior ischemic optic neuropathy = AION, Horton’s disease, complicated drusen) and inflammatory neuropathies (demyelinating diseases, systemic disorders - sarcoidosis) [13]. Hayreh divides optic neuropathy according to the arterial source in: anterior ischemic optic neuropathy (AION) which refers to the anterior portion of the ON supplied by the PCA circulation and which is subdivided into arteritic and non-arteritic; posterior ischemic optic neuropathy (PION) involving the rest of the optic nerve not supplied by the PCA circulation and which is subdivided into arteritic, non-arteritic and surgical (peri- or postsurgical) [10].

**Effect or orbital space-occupying lesions**

*Cavernous hemangiomas:* mostly occur in young adults, in the retrobulbar intraconal space [13].

*Capillary hemangioma:* usually diagnosed in infants [13].

*Orbital varices:* affected veins change during Valsalva’s maneuver (expands and the flow stops), or when the head is leaned [13.17].

*Orbital Cellulitis:* bacterial infection (common: staphylococcus, streptococcus or Haemophilus) of the orbital fatty tissue.

*Orbital lymphoma* [13]

*The ON glioma:* leads to reduced flow and increased impedance indices in CRA through the pressure exerted on the sheath of ON [12].

*Orbital tumor invasion* [10].

**Other disorders**

*Carotid artery stenosis:* causes a decrease in blood flow to the CRA, OA, or both when the degree of stenosis is more than 70% and a change of flow in occlusions (because of supply OA from external carotid, through activation of anastomoses between periorbital arteries, with origin in external carotid artery and OA) [7,12,13]. When carotid stenosis is over then 90%, perfusion of the OA level decreases by 50%, resulting in ocular ischemic syndrome [5].

*Carotid-cavernous fistulas (posttraumatic or spontaneous):* shunts between the arterial and venous system [17]. It is characterized by: CRV is enlarged with reverse flow (or bidirectional) and “arterial blood” and supraorbital vein with reversed flow [12.13]; increase the eye pressure [17].

*Arteriovenous malformations:* vein caliber, velocity and flow direction changed [12.13].

**Diabetes Mellitus**

*Arterial hypertension:* depending on the degree of impairment of vascular bed, hypertension can cause: hypertensive retinopathy, optic neuropathy and choroidopathy [5].

**Conclusions**

Since many eye diseases are based vascular factor, it is very important to understand both the vascularization of this area as well as their pathogenesis and management. Regarding the optic nerve (ON), its vasculature plays a decisive role in etiopathogenesis of different forms of optic neuropathy (including glaucoma) as well as other eye diseases.

For now do not have perfect technique should examine blood flow to the ON level. Ophthalmologists need of techniques readily accessible, safe, reliable, non-invasive and repetitive in the current practice for examination patients with glaucoma, ischemic optic neuropathy or other vascular disorders of the ON. Also, due to the discovery nocturnal hypotension involvement in the development and progression of non-arteritic AION and glaucoma, is required a method that can monitor blood flow to the ON head continuously/frequently over a period of 24 hours (or more) and particularly during sleep.

The lack of these technologies make management of ischemic diseases of the ON and, implicitly, to prevent blindness a difficult task [10].

**References**


