REVIEW

Age-related changes in retrobulbar circulation: a literature review

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Abstract

Introduction The advances in research methods used in ophthalmology allow for an increasingly accurate examination of the eyes, as well as the morphology and function of the vessels. Colour Doppler imaging is still the first-line method for the analysis of parameters of retrobulbar circulation. Therefore, the aim of this work was to present the current state of knowledge about anatomical and functional age-related changes in retrobulbar arteries.

Methods A literature search was performed mainly based on the PubMed database.

Results The anatomy of retrobulbar arteries, histological background of age-related vascular changes, age-related changes in retrobulbar blood flow in the ophthalmic artery, central retinal artery, short posterior ciliary arteries, and the reference values for the age-dependent retrobulbar circulation parameters

measured by colour Doppler imaging are discussed in this review.

Conclusion The age of the subject should always be taken into account when interpreting the parameters of retrobulbar blood flow measured by colour Doppler imaging.

Keywords Ageing · Colour Doppler imaging · Ocular blood flow · Retrobulbar circulation

Introduction

Causative treatment relies on a detailed understanding of the aetiology of diseases and the causes of disorders leading to their development. It has been demonstrated that age-related hemodynamic and vascular changes in retrobulbar vessels may induce pathological processes leading to ocular diseases potentially associated with significant visual impairment or irreversible blindness [1, 2]. This hypothesis seems to be confirmed by the increased prevalence of many ocular diseases, in particular, glaucoma, age-related macular degeneration (AMD), and thromboembolic changes in retinal vasculature in older age groups. The prevalence of glaucoma and AMD in the sixth decade of life has been estimated at 2.1% and 2.4%, respectively. Over the age of 75, this rate increases significantly to 8.7% and 13.5%. The anomalies characteristic of AMD were found in up to 90% of the examined subjects

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older than 90 years [3]. In addition, concomitant cardiovascular diseases are often associated with the same risk factors as the development of the above-mentioned ocular diseases. These factors include smoking, hypertension, diabetes, lipid disorders, sedentary lifestyle, as well as genetic determinants [1].

Vascular aetiology is the subject of particularly intensive studies in patients with normal tension glaucoma (NTG) and those with the progression of neuropathy, despite the low intraocular pressure (IOP) values obtained after anti-glaucoma treatment [4, 5]. Patients with glaucoma were diagnosed with decreased blood flow in the retina, choroid, optic disc, as well as in retrobulbar circulation. It has been shown that atherosclerosis and cardiovascular diseases can exacerbate the course and progression of neuropathy in these patients [4]. Moreover, in patients with primary open angle glaucoma, decreased systolic and diastolic blood pressure was described in comparison with healthy controls [5]. These changes can be manifested by the decreased maximum blood velocity and an increased pulsatility index in the retrobulbar circulation with particular emphasis on the central retinal artery (CRA), which is responsible for optic nerve head perfusion [4, 5]. Processes leading to the dysfunction of the vascular endothelium and vasospasm are physiological and attributed to the ageing of the blood vessels, but they are also observed in younger subjects diagnosed with glaucoma [6]. Disorders of the mechanism regulating blood flow in elderly people using hypotensives can lead to the night drops in blood pressure and the progression of neuropathy that is found in the analysis of measurements for visual field [7]. The significance of age-related vascular changes in the development of many ocular diseases associated with visual impairment is even greater considering the fact that the proportion of people aged 65 years and older in Europe is forecast to increase to 25% in 2050 [8].

The advances in research methods used in ophthalmology allow for an increasingly accurate examination of the eyes, as well as the morphology and function of the vessels. Colour Doppler imaging (CDI) is still the first-line method for the analysis of parameters of retrobulbar circulation. This is a non-invasive technique that is based on the Doppler effect. The moving blood morphotic particles reflect the high frequency ultrasound wave generated by the CDI probe. Next, the differences between the direction and

velocity are calculated mathematically and coded in a colour scale. The blood moving in the direction of the probe is red-coloured, while the opposite direction is blue-coloured. The measurement technique was also described in detail by Stalmans et al. [9]. The CDI is a method characterised by a generally high repeatability independent of the time interval between the analysed measurements, but may differ between the analysed retrobulbar arteries. However, the interobserver variability was described to be greater than the intraobserver variability, with the coefficient of variation in healthy individuals ranging from 4.9 to 27.3 and 1.3 to 22.0, respectively [9]. It is also worth noting that variability differs between the analysed blood flow parameters and evaluated arteries. The calculated coefficient of variation is usually higher for peak systolic velocity (PSV) and end-diastolic velocity (EDV), while lower for resistance index (RI). Moreover, the reproducibility increases with training and examiner's experience. This process is longer for small ciliary arteries and shorter for the CRA and the ophthalmic artery (OA). According to these observations, the limitation of the CDI method is the subjective nature of the measurement [9].

Taking the above into account, the aim of this work was to present the current state of knowledge about anatomical and functional age-related changes in retrobulbar arteries.

Anatomy of retrobulbar arteries

The OA is the first branch of the internal carotid artery after it passes through the cavernous sinus. [It emanates from the C6 ophthalmic (supraclinoid) segment of the internal carotid artery.] The OA is responsible for the perfusion of all intraorbital structures. The lumen of the OA is 0.7–1.4 mm [10, 11]. Branches of the OA are characterised by high individual variation and may also differ between the left and right sides in the same individual. The OA enters the orbit through the optic canal on the inferolateral part of the optic nerve. Here, the OA branches into the supraorbital artery and the supratrochlear artery. Then, it turns to the opposite side of the optic nerve, running in the superomedial direction. In most cases (73.7% of the right eyes and 84.2% of the left eyes), the OA crosses the optic nerve from above, at the point defined as the OA 'angle' by

Fig. 1 Anatomy of the ophthalmic artery and the central retinal artery

Hayreh (1962). Next, the OA runs on the medial aspect of the optic nerve and the lateral aspect of the superior oblique and inferior part of the medial rectus muscle. This part of the OA is called the ‘bend’ [11] (Fig. 1).

The CRA has been described as the first artery branching off the OA in 26.3% of the right eyes and 47.4% of the left eyes. In some cases, the CRA and the medial posterior ciliary artery (MPCA) may diverge at the same level of the OA. The CRA has an outer diameter of 0.4–0.9 mm and about 0.2 mm in the lumen [12]. The CRA enters the optic nerve 5.3–14.1 mm from the eyeball on its inferomedial side. It runs further to the retina inside the optic nerve. The CRA supplies blood to the superficial layers of the optic nerve and the optic disc. The CRA in its terminal segment does not form a rich network of connections and runs together with the central retinal vein [11]. Disorders in the CRA result in reduced retinal flow and ischaemia within the neuroretinal rim [1].

The deeper layers of the optic nerve receive blood from the posterior ciliary arteries (PCAs) [13]. The PCAs, after diverging from the OA, run in the anterior direction, and, before entering the eyeball, they branch into about 10–20 short posterior ciliary arteries

(SPCAs) with an internal lumen of 0.1–0.2 mm. SPCAs are responsible for the perfusion of the anterior segment of the optic nerve, its prelaminar part, and the peripapillary part of the choroid. The numerous longitudinal branches of PCAs penetrate the sclera in the medial, lateral and superior parts of the optic nerve. PCAs also form numerous transverse branches that encircle the optic nerve. SPCAs supply blood to the choroid. They also form the Zinn–Haller arterial circle around the point where the optic nerve leaves the eyeball. Disorders in the perfusion of the optic nerve may be involved in the development of ischaemic glaucomatous neuropathy or optic disc oedema [11].

The vascularisation of the lamina cribrosa comes from the choroidal vessels and SPCAs. Other parts of the optic nerve, laminar and extralaminar, receive blood from SPCAs and sometimes from meningeal arteries that branch into the CRA before the entry of the CRA into the optic nerve [13]. Processes associated with the ageing of the body may change the flow parameters in retrobulbar arteries, and sometimes also lead to the narrowing or occlusion of blood vessels [11, 14].

Histological background of age-related vascular changes

The wall in the retrobulbar arteries is an extension of the elastic internal carotid artery. On the outer side, it is formed mainly by collagen fibres of the adventitia, which create a scaffold for a vessel inside the soft orbital tissues. The media is formed by circumferentially arranged smooth muscle cells and a small number of support cells. The lumen of the vessel is limited by the inner membrane formed by endothelial cells and pericytes attached to the basal membrane. Individual layers are separated from each other by external and internal elastic membranes [1, 14–16].

With age, the vascular wall is remodelled, and the medial and inner layers become thicker, which consequently reduces the flexibility of the vessel and increases its rigidity. Deposits of collagen and glycosylated proteins are also formed in the vessel wall [15]. As shown by the Blue Mountain Eye Study [16], age is an independent risk factor for the reduced diameter of blood vessels.

With age, the basal membrane of the vascular wall also becomes thicker [17]. This process may be more strongly pronounced in pathological conditions such as hypertension or diabetes. Increased thickness of the basal membrane may impair the transport of nutrients and metabolites. These processes are potentially attributed to an increased activity of the polyol pathway and the accumulation of polyhydric alcohols, which are the products thereof, as well as an increased synthesis of enzymes responsible for the formation of the basal membrane [17].

The endothelium is the inner layer of the vessel wall, consisting of a single cell layer. With age, the number of endothelial cells and pericytes is generally reduced [17]. These cells react to physical and chemical stimuli, regulate the tone and diameter of the vessel through the release of nitric oxide (NO) and endothelin-1, modify immune and inflammatory responses, and are also responsible for the activation of platelets and clotting (thrombosis). In addition, they release vasoactive substances in response to humoral, neuronal and mechanical stimuli. Other substances released by endothelial cells include bradykinin, histamine, acetylcholine, and prostacyclin. Endothelial cell dysfunctions or their failure result in abnormal regulation of the diameter and tone of blood vessels [1].

Nitric oxide is synthesised in the vascular endothelium by NO synthase (NOS) and has a relaxing effect on smooth muscle cells. Oxidative stress and disorders of NO synthesis can result from atherosclerosis, dyslipidaemia or hyperglycaemia in an ageing body. These diseases, as well as hyperhomocysteinaemia or accompanying cardiovascular conditions, are associated with an increased serum concentration of the enzyme arginase, an endogenous inhibitor of NO synthase [1].

Ageing is also associated with an impaired response to acetylcholine-induced relaxation, reduced activity of NOS, and reduced availability of NO. As a consequence, there is an increase in vascular tone and an increased response to vasoconstrictive factors. It seems that the mechanism regulating blood flow within retrobulbar vessels is similar to that in peripheral circulation. On the other hand, choroidal circulation is strongly affected by the concentration of NO and endothelin-1, while retinal circulation is not controlled externally and depends on the levels of NO, NADP, endothelin-1, VEGF and cGMP [1, 14]. Loss of endothelial cells associated with ageing was also found in choriocapillaries, and is one of the first anomalies observed in patients with AMD [17].

Oestrogens, through oestrogen receptors located in the vascular endothelium, stimulate the increased release of NO and prostaglandin-12, substances with a vasorelaxing effect, as well as inhibit the vasoconstrictive effect of endothelin-1. Because of this mechanism, the use of hormone replacement therapy (HRT) in postmenopausal women may reduce the incidence of cardiovascular events [18]. Ageing is also associated with an increase in the level of the membrane attack complex (MAC), which is responsible for the non-specific immune response and subsequent cell lysis. Intensification of the process is observed in the choroid of patients with AMD [19].

The change in capillary structure associated with age leads to the narrowing of vessels. As a consequence, the diameter, stiffness and integrity of the vessels are reduced. This process stabilizes blood flow velocity in the atherosclerotic vessel, but at the expense of a decreased total vessel diameter and the volume of flowing blood. Structural changes in vessels and impaired autoregulation of blood flow reduce the supply of oxygen and nutrients to the ocular structures, as well as decrease the rate at which metabolites are eliminated from them [1].

The contents of elastin and smooth muscle fibres within the vessel wall decrease with age. Experiments demonstrated a 35% and 42% reduction in the parameters of ocular blood flow in aged rats compared to young and adult animals. In addition, the study revealed a significant increase in vascular resistance in the ocular vessels of aged rats, but not in cerebral vessels. This experiment confirms the local nature of age-related changes in ocular blood flow, as well as the possible autonomic regulation of vascular response to changes in the course of the ageing process [14].

Age is an independent factor in the reduction of retinal vascular diameter. A greater intensity of this process was found in subjects with hypertension, while younger patients experienced a greater reflex vasoconstriction. This may result from the increased rigidity of vessel walls and their lower susceptibility to deformation in the elderly compared to younger patients with atherosclerosis. After the age of 40, the size of the foveal avascular zone within the retinal macula increases. A gradual reduction in the number of choriocapillaries and the thickness of the choroid is observed in subjects between the first and tenth decade of life [1]. The influence of selected age-related factors on retrobulbar blood flow assessed by CDI is summarised in Table 1.

Age-related changes in retrobulbar blood flow

The ophthalmic artery (OA)

It has been demonstrated that ageing is associated with a decreased EDV at the unchanged values of PSV in the OA. Changes in blood flow velocity result in an increased vascular resistance index (RI) in the OA [20]. This process was also reported by other authors [21], who demonstrated a relationship between RI, age of the examined subjects, and the values of arterial blood pressure. An increased RI in the analysed group was associated with an increased systolic blood pressure (SBP) and a decreased RI with an increased diastolic blood pressure (DBP). In addition, an increased DBP correlated with an increased EDV, which consequently led to a reduced RI in the analysed group. Similarly, increased SBP and PSV induced an increase of RI in the OA [21]. These observations confirm age-related vascular remodelling. Structural changes lead to a reduction in the diameter of vessels

Table 1 Changes in retrobulbar arteries blood flow in colour Doppler imaging under selected conditions related to ageing

Condition	Colour Doppler imaging changes				
	PSV ^a decrease	EDV ^b decrease	PI ^c increase	PI decrease	RI ^d increase
Age [15]	CRA ^e , OA ^f , TPCA ^g , MPC ^h	CRA, OA, TPCA			CRA, OA, TPCA
Age and sex [20]		OA, TPCA, MPC			OA, TPCA, MPC
Age in women [32]	CRA, OA	CRA, TPCA			CRA, TPCA
Arterial hypertension [33–35]	CRA, OA, TPCA, MPC	CRA, OA, TPCA, MPC	CRA, OA, TPCA, MPC		CRA, OA, TPCA, MPC
Stenosis/occlusion of internal or common jugular artery [36, 37]	CRA, OA, TPCA	CRA, OA, TPCA			CRA, TPCA
Atherosclerosis [38]	CRA, TPCA, MPC	CRA			
Glaucoma [31]	CRA, MPC, TPCA			OA, CRA, TPCA, MPC	CRA, MPC, TPCA
AMD ⁱ [28]	OA, CRA, MPC, TPCA		OA, CRA, MPC, TPCA		OA, CRA, MPC, TPCA

^aPeak systolic velocity, ^bEnd-diastolic velocity, ^cPulsatility index, ^dResistance index, ^eCentral retinal artery, ^fOphthalmic artery, ^gTemporal posterior ciliary artery, ^hMedial posterior ciliary artery, ⁱAge-related macular degeneration

and increase their rigidity. This remodelling ensures the stable velocity of flow in retrobulbar circulation, but at a reduced volume of blood flow. Changes in arteries occurring with advanced age are aimed at maintaining the effective ocular blood flow [1]. Only Baxter and Williamson [22] reported age-associated reduction of both PSV and EDV in the OA.

Harris et al. [20] demonstrated a correlation between circulation parameters in the OA and sex. Their estimates suggest that 30% of the decrease in ophthalmic arterial EDV is attributed to ageing in women and 12% of this decrease is caused by ageing in men. A significant change in EDV caused a significant increase in ophthalmic arterial RI in both sexes. The contribution of age to an increased RI was 50% in women and 26% in men [20]. The use of HRT was reported to reduce RI in the OA in postmenopausal women to a level not significantly different from that measured in young women, but significantly lower than the level in women in a comparable age group not using oestrogen supplementation. In the group of elderly women not taking HRT, the EDV values are significantly lower than those in younger and older women using HRT [18].

The central retinal artery (CRA)

Literature data related to the effect of ageing on the changes in blood flow parameters in the CRA are inconsistent. For example, a trend analysis [23] estimated a reduced blood flow velocity in the CRA at about 9.9% per 10 years [23], which corresponded with an age-related 4.9% increase in RI per 10 years.

In another study, Gillies et al. [24] compared retrobulbar blood flow parameters in two age groups. The mean age of the examined healthy volunteers was 25.2 years and 69.5 years, respectively. The researchers found the higher values of PSV in the older group, and attributed this to the gradual narrowing of the vascular lumen as the OA branches into the CRA. The study revealed a similar trend in both analysed groups. However, the technical difficulties with taking precise measurements in small calibre vessels could have biased the study [24]. Baxter and Williamson [22] reported an isolated increase of RI in the CRA and the central retinal vein (CRV) without significant changes in other blood flow parameters in these vessels.

Williamson et al. [25] analysed blood flow in retrobulbar arteries in a group of patients with cardiovascular disorders. They found an age-associated increase of RI in the CRA but no changes in flow velocities in the CRA and CRV. No similar increase of peripheral resistance in retinal vessels was detected. This may be related to the different histological structure of the retinal vascular wall, since they lack elastic elements that could maintain the proper blood flow velocity due to the increased rigidity and reduced diameter of the vessels.

No correlation between sex and the changes in blood flow parameters in the CRA was demonstrated [20]. In addition, the parameters of blood flow in the CRA did not change in postmenopausal women using HRT, which suggests that HRT does not improve retinal perfusion in the ischaemic disorders of the retina [18].

Short posterior ciliary arteries (SPCAs)

Age-related changes in blood flow parameters in SPCAs are more pronounced in women than in men. A reduced EDV and an elevated RI in PCAs were reported in women without a history of HRT. No changes in other parameters of blood flow in these arteries were found [20]. Similar observations were made by Harris-Yitzhak et al. in a group of postmenopausal women. Their study revealed reduced PSV and EDV but no change in RI values compared with a group of young women [18]. No correlation between the parameters of PCAs and age were found in men [20].

Gillies et al. [24], in a mixed-sex group of healthy volunteers, observed increased PSV values only in temporal PCAs (TPCA). On the contrary, Geenfield et al. [26] reported a reduced flow velocity in PCAs as well as an increased RI associated with age, but the differences between men and women were not significant. However, in this study group, higher DBP values measured in men could have had a possible interfering effect on the analysed parameters of blood flow [26].

Systemic diseases associated with cardiovascular disorders may contribute to an increase of RI in small peripheral vessels, including the retrobulbar ones [26].

Reference values for age-dependent retrobulbar circulation parameters measured by colour Doppler imaging

Age-dependent changes in retrobulbar circulation prompted Modrzejewska et al. [15] to establish the reference values for retrobulbar circulation in five adult age groups. The analysis was carried out on 162 healthy subjects without cardiovascular or ocular diseases. The influence of narrowing or occlusion in the carotid and vertebral arteries was ruled out in all subjects included in the study [15].

The analysis demonstrated a significant 25% reduction of PSV in the CRA between the subjects aged 20–31 years and 68–80 years. In addition, EDV and MV were lower in the CRA. A gradual age-dependent increase of RI in the CRA was also noted. A significant decrease of PSV and EDV, as well as an increase of RI were found in both PCAs. Of note is that the RI increased in the examined groups, but no significant changes in the parameters of arterial pressure or ocular perfusion pressure were identified. It seems that the choice of parameters for an analysis ensured that age was an independent risk factor for the observed changes in the retrobulbar circulation parameters. In the OA, the only age-dependent change was found for RI, while other parameters did not differ significantly between the analysed age groups. A gradual increase of RI in the OA was found in consecutive age groups, ranging from 0.66 in the subjects aged 20–31 years to 0.72 in the subjects aged 68–80 years [15].

More pronounced changes in retrobulbar circulation parameters may indicate that significant hemodynamic changes are detectable at first in smaller arteries than in larger vessels such as the OA. The prodromal symptoms of circulatory disorders may concern the areas supplied by these arteries. Therefore, the age of the examined subject has to be considered for the correct interpretation of retrobulbar circulation parameters [15].

Clinical implications

By analysing the values of the tested parameters in CDI, it is possible to recognise many ocular vascular diseases. Structural changes in the retinal vasculature have long been advocated to represent important

predictors of systemic vascular and cardiovascular diseases. Moreover, vascular dysregulation due to the induction of vasospasms inside the retinal and choroidal microvasculature, especially in older population, may play a role in the pathogenesis of glaucoma, AMD, or systemic hypertension. The vascular endotheliopathy, as a vasospastic propensity, is often associated with vasospastic syndrome, especially in woman, leading to retinal venous occlusion, ischaemic neuropathy, migraines and central serous chorioretinopathy. In this group of patients, both a low perfusion pressure and an increase in intraocular pressure as well as the phenomenon of reperfusion may cause changes in the optic nerve [27].

Ischaemia and hypoxia may be present inside the retinal and mainly in choroidal tissues and these factors trigger the development of subretinal neovascular membranes (CNV) in AMD or progressive myopia. Related to these results, the hemodynamic model of the pathogenesis of AMD was formed and suggested that AMD was caused by a progressive decrease in the compliance of the sclera and choroidal vessels, leading to an increase in the resistance (RI) of the choroidal blood flow in eyes with the exudative form of this disease [28]. Other authors suggested that ischaemia secondary to choriocapillaris atrophy might trigger neovascularisation [29]. The atrophic form of AMD results from the changes in the layer of the retinal pigment epithelium (RPE), photoreceptors and choriocapillaris. All vascular-atrophic changes cause a slow but severe decrease in visual acuity and lead to blindness.

Similar hemodynamic disturbances are seen in glaucoma, where a decrease in blood flow velocity and an increased resistance in small vessels (mainly the CRA but also the PCAs) lead to the impairment of retinal ganglion cells and the development of glaucoma [30]. Atherosclerotic lesions are not a risk factor for glaucoma damage; however, their presence increases the sensitivity to pressure changes in the eyeball and, in some cases, the so-called sclerotic glaucoma type [31].

Summary

Retrobulbar arteries supply blood to the eyeball and orbit. Disorders of blood flow within these anatomical structures may lead to the development of ocular

diseases with the risk of visual impairment of vascular aetiology, such as thromboembolic lesions within the vessels of the retina and optic disc, glaucoma, or age-related macular degeneration. Remodelling of the arterial wall, abnormal secretion of vasoactive substances, and the relationship between hormonal activity and mechanisms regulating retrobulbar circulation influence changes in flow parameters in these arteries. The age of the subject should always be taken into account when interpreting the parameters of retrobulbar blood flow measured by colour Doppler imaging.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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