ORIGINAL ARTICLE

Optical Coherence Angiographic Demonstration of Retinal Changes From Chronic Optic Neuropathies

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ABSTRACT

Glaucoma causes a decrease in peripapillary perfused capillary density on optical coherence tomography (OCT) angiography. However, other chronic optic neuropathies have not been explored with OCT angiography to see if these changes were specific to glaucoma. The authors evaluated OCT angiography in 10 patients who suffered various kinds of chronic optic neuropathies, including optic neuritis and ischaemic optic neuropathy, and found that all optic neuropathies showed a decrease in peripapillary vessel density on OCT angiography, regardless of the aetiology of the optic neuropathy. The peripapillary vessel loss on OCT angiography correlated well with the areas of retinal nerve fibre layer thinning seen on OCT.

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Introduction

Although fluorescein angiography has been used to image the retinal circulation for many years, it is unable to visualise the radial peripapillary capillaries or the deeper capillary network in the retina with enough detail in most patients to study capillary density in relation to nerve fibre layer loss and visual field topography.^{1,2} Diffuse fluorescence from the surface often obscures the filling of the fine radial peripapillary capillary network. An emerging new technology, optical coherence tomography (OCT) angiography, has the capability of evaluating the density of the radial peripapillary capillary network in much more detail than traditional fluorescein angiography.² OCT angiography is achieved by rapidly scanning the retinal tissue with sequential scans and evaluating the images for particle (blood cell) movement that can be used to construct microvascular density maps.^{2–5} Recent reports indicate that there is decreased optic disc perfusion and peripapillary capillary density on OCT angiography in patients with chronic glaucoma.^{4,6–9} This has led to speculation that reduced capillary density from OCT angiography in glaucoma eyes provides evidence for a primary role in the pathogenesis of glaucoma. However, as Schuman

pointed out in his commentary on OCT angiography, “recently acquired OCT angiography images still do not answer the question of which comes first: changes in ocular blood flow or optic nerve injury?”¹⁰

An evaluation of the peripapillary capillaries in other optic neuropathies can provide some insight into whether these findings are causative or secondary to optic nerve insult. This is because in other non-glaucomatous optic neuropathies, there may be a clear history of time course of onset and progression of damage upon which to compare structural, functional, and microvascular density changes. Second, there are many examples of optic neuropathy whose primary site of damage is not at the superficial peripapillary capillaries supplying the retinal nerve fibre layer; and in those cases, a subsequent decrease in capillary density would provide evidence for an effect of the retinal nerve fibre layer damage and not the cause. Using split-spectrum amplitude-decorrelation angiography algorithm, the perfused peripapillary vessel density can be quantified from OCT angiography-acquired images to create a flow density map. The purpose of this study was to evaluate for changes in the retinal peripapillary capillary network in response to a variety of causes of optic nerve damage.

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Methods

Study population

The study was approved by the Mayo Clinic Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. We reviewed the clinical and imaging data from 10 patients ≥ 21 years who suffered various kinds of chronic optic neuropathy and underwent OCT angiography from May 2015 through May 2016. This included one patient with arteritic anterior ischaemic optic neuropathy (AAION), three patients with non-arteritic anterior ischaemic optic neuropathy (NAION), three patients with optic neuritis, one patient with compressive optic neuropathy, one patient with traumatic optic neuropathy, and one patient with glaucoma.

All patients underwent a full neuro-ophthalmologic examination, which included best-corrected visual acuity (BVCA), automated Humphrey perimetry (24-2 SITA-standard) and/or kinetic Goldmann perimetry, and OCT imaging with spectral-domain OCT (Cirrus 4000 and Cirrus 5000 [Carl Zeiss Meditec, Dublin, CA, USA], Cirrus software version 6.0, and Optovue RTVue XR Avanti [Optovue Inc., Carl Zeiss Meditec, Dublin, CA, USA]).

Optical coherence tomography

OCT imaging was performed after pupillary dilation using spectral-domain OCT (Cirrus and Optovue RTVue). Signal strength < 7 for Cirrus and < 50 for Optovue were excluded from analysis.

For Cirrus OCT imaging, the peripapillary retinal nerve fibre layer thickness measurements were obtained using the optic disc cube 200×200 Cirrus protocol that covered the $6 \times 6\text{-mm}^2$ area centred on the optic disc. The macula measurements were obtained using the macular cube 200×200 Cirrus protocol centred on the fovea. The Cirrus ganglion cell layer algorithm was applied to the macular scans to provide the ganglion cell and inner plexiform thickness.

For the Optovue OCT angiography imaging, the optic nerve and surrounding structures were

analysed by performing a $4.5 \times 4.5\text{-mm}$ scan centred on the optic nerve. Five consecutive volume scans were obtained in this region, each containing 216 A-scans. These images were registered, and the consecutive B-scans were used to calculate the decorrelation among the images to provide split-spectrum amplitude-decorrelation angiography (SSADA) images. This decorrelation between consecutive B-scan images was used to approximate blood flow. The radial peripapillary capillary network flow was visualised by analysing the SSADA images within the nerve fibre layer, and en face visualisation of the peripapillary capillary network was captured. The density of the perfused peripapillary vessels within the superficial $100\text{-}\mu\text{m}$ peripapillary retina was calculated using Optovue's automated software, AngioAnalytics (Version 2015.1.1.98), to create a flow density map. The vessel density was displayed as a percentage of the area occupied by the large blood vessels and retinal capillaries. The flow density map was analysed in the peripapillary region, which was defined as a $500\text{-}\mu\text{m}$ -wide elliptical annulus, extending from the optic disc boundary. The peripapillary area was separated into nasal, superonasal, superotemporal, temporal, superotemporal, inferotemporal, and temporal regions for analysis. The entire flow map was also divided into a 3×3 grid, and each of the nine areas was quantified.

Results

Chronic arteritic anterior ischaemic optic neuropathy (Case 1)

An 85-year-old male presented with AAION in the right eye. BCVA was light perception. Fundus examination revealed pallid disc oedema at initial presentation. At 1 month, the patient had no light perception. OCT showed mild retinal nerve fibre layer (RNFL) thinning and significant ganglion cell layer–inner plexiform layer complex (GCL-IPL) thinning. OCT angiography demonstrated a diffuse reduction in the peripapillary vessel density of 32.9% in the right eye compared with 57.6% in the unaffected left eye (Figure 1).

Figure 1. A 85-year-old male with prior arteritic anterior ischaemic optic neuropathy in the right eye. One month after arteritic anterior ischaemic optic neuropathy in the right eye, spectral-domain OCT shows mild diffuse thinning of the retinal nerve fibre layer (A, B, and F) in the right eye whereas the left eye is normal (F–H). There is diffuse severe thinning of the ganglion cell layer in the right eye (G). OCT angiography en face images centred on the optic discs show a diffuse reduction in the superficial peripapillary capillary density in the right eye (C) compared with a normal capillary density in the left eye (J). The vessel density is quantified and shown as flow density maps (D and K). The density of the superficial peripapillary vessels based on the boundaries shown in C and J and the grid shown in D and K are displayed (E and L). The average peripapillary vessel density in the right eye is 32.93% (red box, E) compared with 57.64% in the left eye (black box, L).

Chronic non-arteritic anterior ischaemic optic neuropathy (Case 2)

A 63-year-old male presented 3 months after suffering NAION in the right eye. BCVA was 20/20 with a dense inferior altitudinal defect on automated visual fields in the right eye. Fundus examination revealed superior pallor of the optic nerve. OCT angiography showed superotemporal papillary capillary loss that corresponded spatially to the RNFL thinning seen on OCT (Figure 2). The overall peripapillary vessel density was 46.1% in the right eye, with a localised area of thinning superotemporally of 38.4%.

Two more cases of chronic NAION with similar findings can be seen in Supplemental Figures 1 and 2.

Chiasmal compression (Case 3)

A 57-year-old female had a history of a junctional scotoma in the right eye from a sellar meningioma

that was resected 4 years prior. Prior to resection, BCVA was count fingers OD and 20/25 OS. After resection, BCVA improved to 20/20 in both eyes. Automated visual fields showed a residual bitemporal hemianopia with a superior and inferior arcuate defect in the right eye. Fundus examination revealed diffuse pallor OD and bowtie atrophy OS. OCT angiography showed predominantly superior and inferior peripapillary capillary dropout OD and temporal and nasal peripapillary capillary loss OS, which spatially corresponded to the peripapillary RNFL thinning seen on OCT (Figure 3).

Optic neuritis (Case 4)

A 30-year-old female had a prior history of optic neuritis in the right eye 12 years ago from underlying multiple sclerosis. BCVA at follow-up was 20/25. Automated visual fields showed a superior and inferior arcuate defect. OCT showed thinning

Figure 2. A 63-year-old male with prior non-arteritic anterior ischaemic optic neuropathy in the right eye. Visual field shows an inferior altitudinal defect in the right eye (A). Spectral-domain OCT shows superotemporal RNFL thinning in the right eye on the RNFL thickness and deviation maps (B), which is also apparent on the TSNIT plot that shows localised thinning of the superotemporal RNFL in the right eye compared with the left (red arrow, C). OCT angiography en face image centred on the right optic disc shows superotemporal papillary capillary loss (D) that corresponds spatially to the RNFL thinning seen on OCT. The vessel density is quantified and shown as a flow density map (E). The density of the superficial peripapillary vessels based on the boundaries shown in D and the grid shown in E are displayed (F). The superotemporal peripapillary vessel density is reduced at 38.39% (red box, F) compared with an average peripapillary vessel density of 46.09% (black box, F). There is also artifactual inferonasal peripapillary capillary loss from a loss of signal in this area from a posterior vitreous detachment (blue box, F).

Figure 3. A 57-year-old female with a history of a junctional scotoma in the right eye and temporal loss in the left eye from a sellar meningioma s/presection 4 years ago. Visual fields show a temporal defect with superior and inferior arcuate defects in the right eye (A) and a temporal defect respecting the vertical midline in the left eye (G). Spectral-domain OCT shows fairly diffuse RNFL thinning with relative nasal sparing in the right eye and predominantly nasal and temporal thinning in the left eye (B, F, H). OCT angiography en face images of the optic discs show fairly diffuse capillary loss with relative nasal sparing in the right eye (C) and predominantly nasal and temporal capillary loss in the left eye (I) that corresponds spatially to the RNFL thinning seen on OCT. The vessel density is quantified and shown as a flow density maps (D and J). The density of the superficial peripapillary vessels based on the boundaries shown in C and I and the grid shown in D and J are displayed (E and K).

Figure 4. A 30-year-old female with prior optic neuritis in the right eye. Visual field shows a superior and inferior arcuate defect in the right eye (A). Spectral-domain OCT of the right eye shows thinning in all quadrants except the temporal fibres (B), which is also apparent on the TSNIT plot where the temporal thickness is similar between the right affected and the left unaffected eye (black arrows, C). OCT angiography en face image centred on the right optic disc shows diffuse papillary capillary loss with sparing temporally (D) that corresponds spatially to the RNFL thinning seen on OCT. This relative loss is more apparent when the vessel density is quantified and shown as a flow density map (E). The density of the superficial peripapillary vessels based on the boundaries shown in D and the grid shown in E are displayed (F). The average peripapillary vessel density is 53.29% (red box, F), whereas the temporal peripapillary vessel density is 63.58% (black box, F).

of the RNFL in all quadrants except the temporal fibres. OCT angiography showed a very similar distribution of peripapillary capillary loss (Figure 4).

Two more cases of chronic optic neuritis with similar findings can be seen in Supplemental Figures 3 and 4.

revealed mild superotemporal pallor. Visual fields showed a mild inferior arcuate defect. OCT angiography demonstrated localised superonasal peripapillary capillary loss with a vessel density of 41.2% that corresponded to the RNFL thinning seen on OCT (Figure 5).

Glaucoma (Case 6)

A 61-year-old male with a history of primary open-angle glaucoma presented with a well-defined inferior nerve bundle defect and corresponding superior arcuate visual field defect. OCT angiography showed localised

Traumatic optic neuropathy (Case 5)

A 56-year-old male suffered a prior mild traumatic optic neuropathy in the left eye from a motor vehicle collision occurring 3 months prior to presentation. BCVA was 20/20. Fundus examination

Figure 5. A 56-year-old male with prior traumatic optic neuropathy in the left eye. Visual field shows an inferior arcuate defect in the left eye (A). Spectral-domain OCT shows localised superonasal RNFL thinning in the left eye on the RNFL thickness and deviation maps (B), which is also apparent on the TSNIT plot that shows localised thinning of the superonasal RNFL in the left eye compared with the right (red arrow, C). OCT angiography en face image centred on the left optic disc shows localised superonasal papillary capillary loss (D) that corresponds spatially to the RNFL thinning seen on OCT. The vessel density is quantified and shown as a flow density map (E). The density of the superficial peripapillary vessels based on the boundaries shown in D and the grid shown in E are displayed (F). The superonasal vessel density is 41.22% (red box, F) compared with an average peripapillary density of 53.92% (black box, F).

inferotemporal peripapillary capillary loss that corresponded to the RNFL thinning seen on OCT. The grid-based flow density map showed a vessel density of 39.7% in the inferotemporal box compared with 61.1% in the superotemporal box (Figure 6).

Conclusions

OCT angiography allows visualisation of the peripapillary capillary network, which is not visible on standard fluorescein angiography. This study demonstrates that all chronic optic neuropathies with retinal nerve fibre layer thinning and visual field defects have a decrease in the peripapillary capillary density on OCT angiography that corresponds to the RNFL thinning seen on standard OCT. This finding may not seem surprising for ischaemic optic neuropathies because ischaemia is presumed to be the aetiologic mechanism of the optic neuropathy. Decreased peripapillary capillary loss was also recently been demonstrated in a few cases of NAION by others.^{11,12} However, the location of ischaemia in anterior ischaemic optic neuropathy is thought to occur in the optic nerve head, with the circulation derived from the posterior ciliary arteries, and not in the superficial peripapillary retinal capillary plexus, which is derived from the branches of the central retinal artery. Other causes of optic neuropathy, such as optic neuritis and trauma, are not thought to have ischaemia as an underlying cause of the disease

process, and these cases also showed similar loss of the peripapillary vessel density on OCT angiography in our series. As in anterior ischaemic optic neuropathy, the location of the primary damage is not thought to occur in the superficial retinal nerve fibre layer or its circulation derived from the central retinal artery but from damage further posterior in the intraorbital or intracranial portion of the optic nerve. This is an important finding because prior papers have shown that glaucoma causes a decrease in the peripapillary capillary density, which has led some to wonder whether the decreased blood flow seen on OCT angiography may be capturing the underlying pathogenesis behind glaucoma.¹⁰ However, our finding that all optic neuropathies show a decrease in peripapillary vessel density after a period of time that spatially corresponds to RNFL loss suggests that the decrease in peripapillary retinal capillary flow density is secondary to optic nerve injury and subsequent retinal nerve fibre layer loss with associated decrease in capillary flow rather than the primary cause.

Wang and colleagues also found decreased optic nerve blood flow on OCT angiography in patients with prior optic neuritis,⁵ and Ghasemi et al. found decreased visibility of the peripapillary capillaries in one case of autoimmune optic neuritis, four cases of NAION, one case of dominant optic atrophy, and four cases of Leber's hereditary optic neuropathy.¹¹ Mase et al. found that the radial peripapillary capillary density is

Figure 6. A 61-year-old male with glaucoma in the right eye. Visual field shows a superior arcuate defect in the right eye (A). Spectral-domain OCT shows inferior > superior RNFL thinning in the right eye (B), with the inferotemporal thinning especially apparent on the TSNIT plot (red arrow, C). OCT angiography en face image centred on the right optic disc shows localised inferotemporal papillary capillary loss (D) that corresponds spatially to the RNFL thinning seen on OCT. The vessel density is quantified and shown as a flow density map (E). The density of the superficial peripapillary vessels based on the boundaries shown in D and the grid shown in E are displayed (F). The inferotemporal vessel loss is more apparent on the grid density map, which shows an inferotemporal density of 39.71% (red box, F) compared with an average peripapillary density of 55.53% (black box, F).

proportional to the RNFL thickness in the superficial peripapillary retina of normal eyes, supporting the notion that the radial peripapillary capillaries are the vascular network responsible for supplying the RNFL.¹³ This suggests that chronic optic neuropathy leads to a reduction in nerve fibres in the optic nerve, which, in turn, reduces metabolic need and presumably results in reduced or absent capillary blood flow through a neurovascular coupling mechanism. These findings do not rule out an ischaemic mechanism underlying glaucoma but do suggest that the changes seen on OCT angiography in the peripapillary capillary network are unlikely capturing this process.

OCT angiography of the peripapillary capillary network may be important in monitoring chronic diseases. It provides another structural element to follow and could end up being a sensitive and/or confirmatory specific measurement for glaucoma progression and other chronic optic neuropathies that correspond to retinal nerve fibre layer loss. The degree of loss of the peripapillary capillary network relative to RNFL loss may also provide a means for differentiating various chronic optic neuropathies. For instance, there may be more profound loss of the peripapillary capillaries in AAION or NAION compared with optic neuritis for a given amount of RNFL loss. In addition, acute injuries can be explored to see if the relationship between capillary flow density and thickness of the RNFL differs among different types of optic nerve damage and time after insult.

Limitations of this study include the retrospective nature of the case review and relatively small number of patients studied. Disc oedema from acute anterior ischaemic optic neuropathy obscures the analysis of the peripapillary capillaries and, therefore, this study focused on chronic optic neuropathies. Despite these limitations, OCT angiography appears to show a spatial correspondence between capillary flow density and pattern of RNFL loss. Further work needs to be done to determine how early the peripapillary capillary flow density is reduced following an optic nerve insult. This will likely be best determined with serial OCT angiography images in patients following acute retrobulbar optic neuritis or traumatic optic neuropathy because the optic disc oedema

from acute anterior ischaemic optic neuropathy can obscure analysis of the peripapillary capillary network. It is also important to recognise that, in its current state, OCT angiography provides a binary image depiction of capillary flow; areas with capillary density have some flow, and areas without capillaries imaged have no flow. As quantitative means evolve to reveal the degree of flow, there may be more important information on the relationship of capillary blood flow on a continuous scale to the functional and structural status of the retinal axons.

In this study, a variety of optic neuropathies with permanent visual field defects and RNFL loss showed a loss of the peripapillary capillary network, which spatially corresponded to locations of RNFL thinning seen on standard OCT. This provides evidence that reductions in peripapillary capillary flow density captured on OCT angiography in many optic neuropathies, including glaucoma, are secondary to optic nerve (and RNFL) damage, rather than the primary cause of the optic neuropathy.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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