

# *In vivo* measurements of macular and nerve fibre layer thickness in retinal arterial occlusion

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## Abstract

**Aim** To investigate the structure–function relationship in patients with retinal arterial occlusion by measuring the macular and the peripapillary retinal nerve fibre layer (RNFL) thickness and the visual sensitivity.

**Methods** This is an observational case series with three patients with central retinal arterial occlusion (CRAO) and two patients with branch retinal arterial occlusion (BRAO). The macular/peripapillary RNFL thickness and the visual field were measured with Stratus optical coherence tomography (OCT) and Humphrey visual field analyzer, respectively, at least 1 year after the diagnosis of CRAO or BRAO.

**Results** The macular thickness, in particular the inner retinal layer, and the peripapillary RNFL thickness were reduced in patients with retinal arterial occlusion. The decrease in the macular and the peripapillary RNFL thickness corresponded to the sites of retinal arterial occlusion with diffuse and segmental thinning found in CRAO and BRAO, respectively. Visual field defects were found in the corresponding locations of macular and RNFL thinning, and closely correlated with the degree of the structural damage.

**Conclusions** Structural damages in terms of reduction in the macular and peripapillary RNFL thickness were evident in patients with retinal arterial occlusion. A close structure–function correlation was found and a worse functional outcome is associated with a more extensive thinning of the macula and RNFL. OCT measurements of the macular/peripapillary RNFL thickness provide useful indicators to reflect the severity of the disease in retinal arterial occlusion and serve as a new

paradigm to study and monitor the disease longitudinally.

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**Keywords:** retinal arterial occlusion; optical coherence tomography; macular thickness; retinal nerve fibre layer thickness; structure–function relationship

## Introduction

Retinal arterial occlusion is an ocular emergency with potentially devastating visual outcome. Poor prognosis is associated with prolonged retinal ischaemia, which leads to irreversible injury to the retina. Information regarding the extent of retinal damage comes mainly from studies on animals.<sup>1–3</sup> Experimental studies in rhesus monkeys with transient central retinal artery occlusion (CRAO) produced by temporarily clamping the CRA at the site of entry into the optic nerve resulted in irreversible damage in the ganglion cell layer and the inner nuclear layer for an occlusion duration of 240 min.<sup>2</sup> Total or almost total optic nerve atrophy and nerve fibre damage were also evident.<sup>3</sup> Although structural damages can be examined in detail in experimental models, it is more difficult, if not impossible, to evaluate the corresponding functional change in animals. Clinical studies in humans with CRAO have focused primarily on functional outcomes.<sup>4</sup> Only a few human autopsy studies reporting the histopathologic findings in retinal arterial occlusion are available in the literature.<sup>5,6</sup>

Optical coherence tomography (OCT) is a non-invasive imaging technology that allows reliable and reproducible measurements of

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macular and retinal nerve fibre layer (RNFL) thickness.<sup>7</sup> The design is based upon the principle of low-coherence interferometry and measurement is determined by the time-of-flight delay from backscattering signals of the retina, analogous to ultrasound scan.<sup>8</sup> With the latest commercially available model, Stratus OCT, we measured the macular and the peripapillary RNFL thickness in five patients with central/branch retinal arterial occlusion (BRAO) and compared these with the corresponding functional deficits examined by automated visual field analyzer.

### Materials and methods

The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. Informed consent was obtained from five Chinese patients, diagnosed with CRAO/BRAO of at least 1 year duration, during the period from October 2002 to October 2004, after explanation of the purpose and nature of the investigations. Patients were recruited for measurements only if the other eye was normal. The diagnosis of CRAO/BRAO was based on (1) a history of sudden loss of vision or loss of superior/inferior half of the visual field in one eye, and (2) a cherry red spot, macular whitening, vascular attenuation, segmentation of blood column, and, in case of BRAO, the presence of emboli in one or more retinal arteries on fundal examination. The macular and the peripapillary RNFL thickness were measured with the fast/standard macular thickness and RNFL thickness (3.4) scanning protocols using the Stratus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA). Visual fields were examined with Humphrey field analyzer (Humphrey Field Analyzer II, Humphrey Instruments, Dublin, CA, USA).

### Results

Table 1 presents the clinical information of three patients with CRAO and two with BRAO. Patients presented at varying time intervals from 4 h to 2 weeks from the onset of symptoms and all had initial visual acuity of 1/60 or worse. Case 1 had serial visual field and macular and peripapillary RNFL thickness measured over a year period (see below). The other four cases had OCT and visual field performed at least 1 year after initial diagnosis. In subjects with CRAO (patients 1, 2, and 3), diffuse reduction of macular and peripapillary RNFL thickness was found. Taking the non-diseased eye in each patient as normal reference, there were 18, 49, and 41% reduction of the average macular thickness and 18, 60, and 42% reduction of the average peripapillary RNFL thickness for patients 1, 2, and 3, respectively. Corresponding functional deficits in terms of loss in visual acuity and visual field correlated closely with the degree of structural damage. In contrast to diffuse thinning of the macular and peripapillary RNFL in CRAO, segmental decrease of macular and peripapillary RNFL thickness was found in patients with BRAO. Visual field defects were found in the corresponding sectors. Illustrative cases for CRAO and BRAO are shown in Figures 1 and 2.

### Case report

#### Case 1 (patient 1)

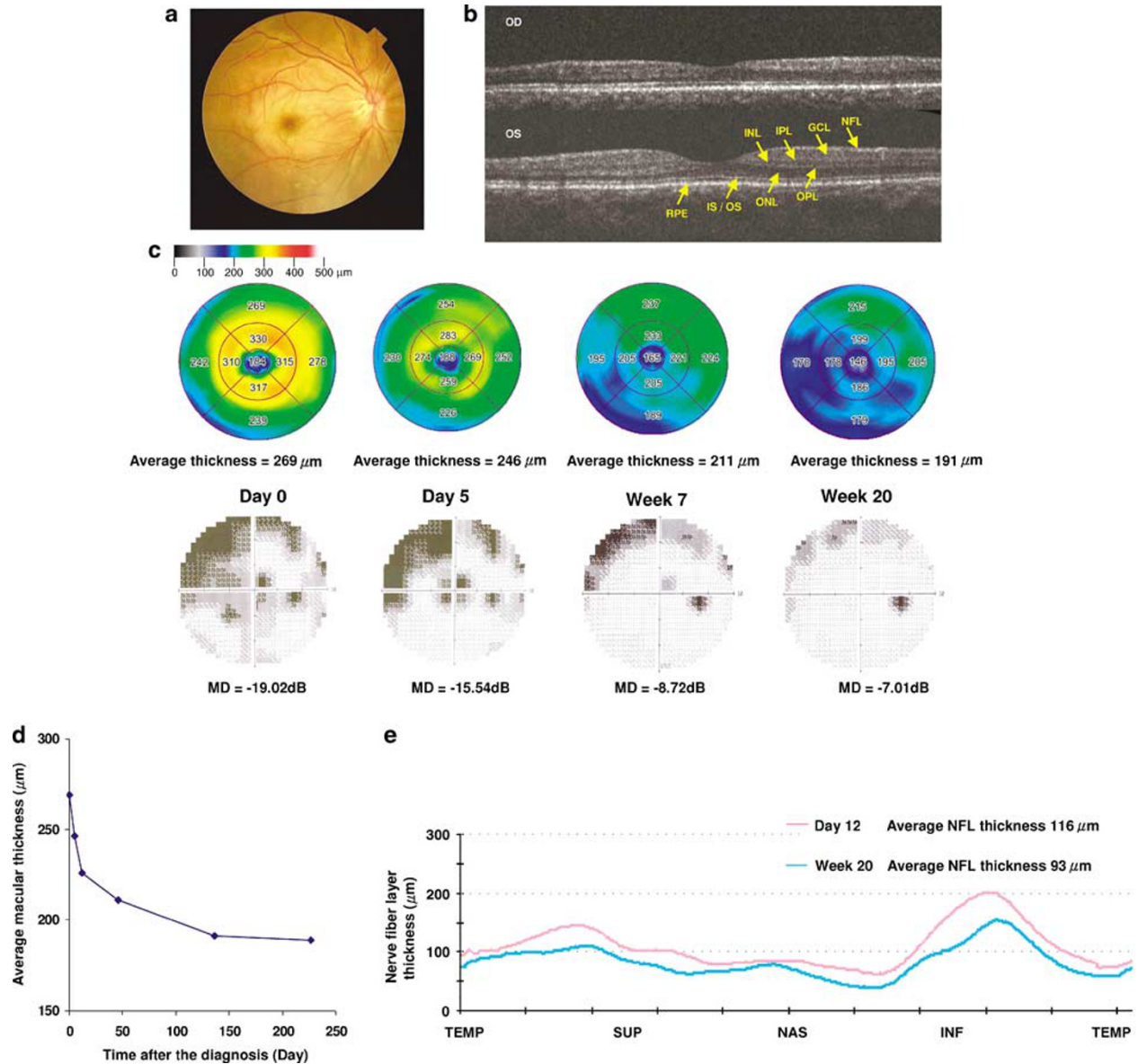
A 26-year-old lady was diagnosed with right CRAO 4 h after sudden loss of vision in the right eye. Immediate treatment including anterior chamber paracentesis, intravenous acetazolamide, and sublingual nitrate was given. The macula was oedematous (Figure 1a and c) and the average macular thickness and peripapillary RNFL

**Table 1** Clinical features of five patients diagnosed to have central/branch retinal arterial occlusion

Patient	Age/sex	Diagnosis	Initial VA <sup>a</sup>	Final VA <sup>a</sup>	Duration of visual loss before the initial examination	Average macular thickness (μm) <sup>a</sup>		Average RNFL thickness (μm) <sup>a</sup>		Visual field MD (dB) <sup>a</sup>	
						OD	OS	OD	OS	OD	OS
1	27/F	Right CRAO	HM	6/15	5 h	191	234	95	116	-6.46	-3.18
2	76/F	Left CRAO	FC	FC	3 days	217	111	95	38	-0.11	-30.76
3	65/F	Left CRAO	FC	6/60	2 weeks	222	131	85	49	— <sup>b</sup>	—
4	62/M	Right inf. BRAO	FC	6/12	4 h	176	245	74	104	-6.41	-1.55
						superior 205 inferior 143					
5	61/M	Right inf. BRAO	1/60	6/10	10 days	183	238	76	98	-16.91	-3.55
						superior 220 inferior 122					

BRAO, branch retinal arterial occlusion; CRAO, central retinal arterial occlusion; F, female; M, male; OS, outer sement; RNFL, retinal nerve fibre layer. <sup>a</sup>Initial visual acuity was recorded at the first visit, whereas final visual acuity, average macular and peripapillary RNFL thickness, and visual field were recorded at the latest follow-up at least 1 year after the initial diagnosis.

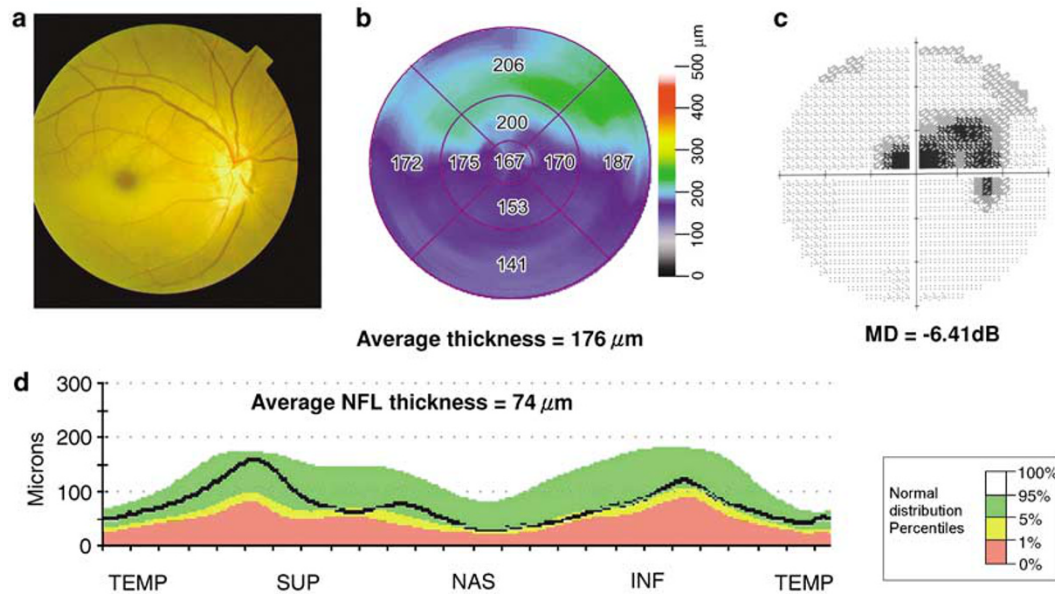
<sup>b</sup>Visual field could not be successfully performed in this patient because of poor reliability in repeated attempts.



**Figure 1** (a) Fundus photograph of patient 1 (CRAO) showing a cherry red spot and macular oedema. (b) OCT scan of right macula performed at week 20 demonstrates reduction in retinal thickness essentially at the inner retinal layer (upper panel). The left eye with normal macular thickness is shown in the lower panel for comparison. NFL, nerve fibre layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; OS/IS, outer/inner segments of photoreceptor; RPE, retinal pigmented epithelium. (c) Serial macular thickness maps and visual fields of the right eye recorded at day 0, day 5, week 7, and week 20. At day 0, the macular oedema was evident by the increased macular thickness in the OCT scan and a dense visual field defect. The oedema subsequently resolved at day 5. Despite continued improvement in visual sensitivity at weeks 7 and 20, increasing reduction of macular thickness is apparent in the OCT scans. The profile of the serial average macular thickness measurements plotted against time is shown in (d). (e) The retinal nerve fibre layer profile of the right eye measured with OCT at day 12 and week 20. Generalized reduction of RNFL thickness was noted and the average peripapillary RNFL thickness was reduced from 116 to 93  $\mu\text{m}$ .

thickness measured with OCT were 266 and 116  $\mu\text{m}$  for the right eye, and 233 and 114  $\mu\text{m}$  for the left eye, respectively. Visual field showed a right central and superior nasal defect (MD = -19.02 dB). The macular oedema subsequently resolved. The average macular

thickness returned to 246  $\mu\text{m}$  and visual acuity improved to 6/60 on day 5 (Figure 1c). The visual field defect also reduced (MD = -15.54 dB). Follow-up scans at weeks 7 and 20 demonstrated gradual thinning of the macula with average macular thickness of 211 and 191  $\mu\text{m}$ ,



**Figure 2** (a) Fundus photograph of patient 4 (Table 1) diagnosed with right inferior BRAO showing inferior macular oedema and a cherry red spot. OCT and visual field performed 2 years after the diagnosis demonstrate inferior macular thinning (b) and a superior paracentral scotoma (c). (d) Peripapillary RNFL thickness was reduced mainly over the inferior and nasal quadrants.

respectively (Figure 1c and d). Macular thinning was found essentially over the inner retinal layer (Figure 1b). Reduction of the average peripapillary RNFL thickness was also evident at week 20 (93 μm) (Figure 1e). Nevertheless, the visual sensitivity improved (MD = -7.01B) and the visual acuity returned to 6/15. All the structural and functional measurements remained at similar levels after 1 year.

*Case 2 (patient 4)*

A 62-year-old gentleman presented with sudden loss of superior visual field with visual acuity of finger count in the right eye. Fundal examination revealed inferior macular oedema and a cherry red spot. Anterior chamber paracentesis was performed and intravenous acetazolamide was given on presentation. Although the visual acuity subsequently returned to 6/12 after 2 months, a residual superior paracentral scotoma was still evident 2 years after the diagnosis. The average macular thickness was 176 μm with the average superior and inferior thickness measuring 205 and 143 μm, respectively. The average peripapillary RNFL thickness was also reduced (74 μm) with the inferior nerve fibre layer being most affected (Figure 2).

**Discussion**

The central retinal artery provides blood supply to the inner retinal layers. After passing through the lamina cribrosa, the major retinal arterial branches travel in the

nerve fibre layer and give rise to two main levels of capillary networks – the inner and the outer capillary plexus. The inner plexus is located at the level of the ganglion cell layer, whereas the outer plexus is found at the inner nuclear layer. It is, therefore, conceivable that ischaemic damage to these layers may be found when the retinal arterial circulation is compromised. Experimental studies on rhesus monkeys with CRAO produced by temporarily clamping the CRA at the site of entry into the optic nerve demonstrated reduction of retinal thickness in the nerve fibre layer, ganglion cell layer, inner plexiform layer, and the inner nuclear layer, with the degree of damage directly related to the duration of arterial occlusion.<sup>2</sup> Functional assessment with electroretinography (ERG) showed no permanent change of any ERG parameter in the animal model and there was no association of the ERG findings with the histologic measurements.<sup>2</sup> The relationship of structural loss to functional change in retinal arterial occlusion has not been investigated in clinical setting. To our knowledge, this is the first case series reporting the *in vivo* macular and peripapillary nerve fibre layer measurements and their association with functional changes in patients having CRAO or BRAO.

In the present study, reduction of macular and peripapillary RNFL thickness was found in patients with retinal arterial occlusion. A closer examination of the macular OCT scan showed that the thinning is essentially limited to the inner retinal layer (Figure 1b). The outer retinal layer, on the other hand, is relatively well

preserved. These findings are in agreement with histologic studies in the CRAO animal models.<sup>2,3</sup> Although serial monitoring of macular thickness is not possible in histologic studies, our data provide preliminary evidence demonstrating that the thinning/remodelling of the retinal tissue could persist for months. As illustrated in case 1, the average macular thickness gradually reduced after the ischaemic insult, reaching a minimum at the fourth month (Figure 1d). In addition, it was found that the extent of macular thinning is related to the location of occlusion. Diffuse macular thinning was found in CRAO, whereas segmental thinning, corresponding to the site of occlusion, was noted in BRAO (Figures 1c and 2b). There are up to seven layers of ganglion cell bodies in the macula, and as few as one cell layer in the peripheral retina. Damage in the ganglion cell layer in the macula would ultimately translate to loss in the nerve fibre layer. Similar to the pattern of macular thinning, loss of peripapillary RNFL was essentially found at the sector where the arterial branch was occluded (Figure 2d).

In terms of structure–function relationship, we found that the degree of macular and peripapillary RNFL thinning closely relates to the extent of visual field loss in the corresponding location. Although a worse functional outcome is in general associated with a more extensive reduction in macular/peripapillary RNFL thickness, the structure–function relationship is not exactly linear. As demonstrated in case 1, there was around 18% reduction in the macular and peripapillary RNFL thickness, and yet, the final functional loss was minimal. This could be explained by the concept of retinal redundancy in which a substantial number of retinal ganglion cells would have been lost before the development of visual field defect. In experimental glaucoma studies investigating the relationship between retinal ganglion cell number and visual sensitivity loss, it was found that the sensitivity loss was relatively constant for ganglion cell loss less than 30–50%.<sup>9</sup> Although a large visual field defect was found at presentation in this case, it improved on follow-up examination. Part of the initial functional deficit could be related to the development of macular oedema (Figure 1c), although irreversible functional loss could become evident if the structural damage is extensive, as exemplified in patients 2 and 3 (Table 1). Further investigation is warranted to study the role of retinal ganglion cells and their relationship with functional outcomes in retinal arterial occlusion.

It was proposed that the extent of retinal damage is directly related to the duration of ischaemic insults.<sup>2</sup> In

animal models, massive irreversible retinal and nerve fibre damages were observed in eyes with CRAO of more than 240 min duration.<sup>2,3</sup> In our series, although all the patients presented at time intervals longer than 240 min, some of them only suffered minimal structural and functional losses. This discrepancy could possibly be related to the fact that in the clinical setting, the actual duration of retinal arterial occlusion is often difficult to determine. In addition, individual susceptibility to the ischaemic insult and the amount of residual retinal circulation could also influence the final visual outcome.

The assessment and monitoring of patients with retinal arterial occlusion have traditionally been based on the functional investigations of visual acuity and visual field. We found that OCT could provide a fast and non-invasive approach to evaluate and monitor the structural changes of the disease, which are closely related to the functional outcomes. Analysis of the structure–function relationship may provide a new paradigm to understand retinal arterial occlusion.

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