Int Ophthalmol (2019) 39:1523–1531
https://doi.org/10.1007/s10792-018-0973-4

ORIGINAL PAPER

Retinal ganglion cell complex and peripapillary retinal nerve fiber layer thicknesses following carotid endarterectomy

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Received: 12 February 2018 / Accepted: 16 June 2018 / Published online: 23 June 2018

Abstract

Purpose To examine changes in retinal ganglion cell complex (GCC) and peripapillary retinal nerve fiber layer (RNFL) thicknesses by optical coherence tomography (OCT) in contralateral and ipsilatateral eyes of carotid artery stenosis (CAS) patients before and after carotid endarterectomy (CEA).

Methods Forty-two consecutive patients diagnosed with CAS (70–99% stenosis rate) who underwent CEA were included in this prospective cross-sectional study. The indication for CEA was based on the Asymptomatic Carotid Atherosclerosis Study. Doppler ultrasonography and computed tomography angiography were performed to calculate CAS. All the subjects underwent an ophthalmological examination, including best corrected visual acuity (BCVA), intraocular pressure (IOP) measurements, biomicroscopy, fundoscopy, and OCT before and after the surgery.

Results The mean preoperative intraocular pressure was 15.2 ± 2.1 mmHg in the ipsilateral eye and 15.8 ± 2.7 in the contralateral eye. The mean postoperative intraocular pressure in the ipsilateral and contralateral eye was 18.6 ± 3.0 and 19.3 ± 3.8, respectively. The intraocular pressure was significantly higher in postoperative eyes ($p = 0.0001$). There was a statistically significant decrease in peripapillary RNFL thickness in superior quadrants postoperatively in ipsilateral eyes. The retinal GCC layer thickness was not significantly different before and after CEA in ipsilateral and contralateral eyes.

Conclusions Carotid endarterectomy results in thinning of the superior peripapillary RNFL thickness. To the best of our knowledge, this is the first study to examine peripapillary RNFL and GCC thicknesses before and after CEA.

Keywords Carotid endarterectomy · Ganglion cell complex · Retinal nerve fiber layer

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Introduction

The ophthalmic artery is the first intradural branch of the carotid artery. Thus, carotid artery blood flow plays an important role in ocular microcirculation [1]. Internal carotid artery (ICA) stenosis leads to chronic progressive hypoperfusion of the eye [2]. Previous studies reported that various ophthalmic manifestations, including decreased visual function, amaurosis fugax, rubeosis iridis, neovascular glaucoma, ischemic ocular pain, and optic disk edema or atrophy, were associated with reduced blood flow in the ophthalmic artery in carotid artery stenosis (CAS) patients [3, 4]. Ocular ischemia in CAS patients is thought to be due to direction of reverse blood flow from the ophthalmic artery to ipsilateral brain, known as the steal phenomenon [3]. However, in some patients with ICA disease, the eyes show no clinical symptoms of ocular ischemia [3]. The underlying reason for the lack of symptoms is unknown. Carotid endarterectomy (CEA) is a widely accepted, effective surgical treatment option for symptomatic and asymptomatic patients with high-grade CAS [2, 5, 6]. Numerous studies demonstrated improved retinal blood flow after CEA [7, 8]. However, information is lacking on changes in peripapillary retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thicknesses after CEA.

Spectral domain optical coherence tomography (SD-OCT) is a noninvasive, reproducible imaging method, which allows demonstration of macular and peripapillary regions in a short time, with high axial resolution [9, 10]. Thinning of peripapillary retinal nerve fiber and ganglion cell thicknesses, resulting in progressive injury of the optic nerve, is a well-known phenomenon in various diseases, such as glaucoma, optic neuritis, and non-arteritic ischemic optic neuropathy (NAION) [11–15].

There is a major risk of cerebral and ocular ischemic attacks in CAS patients, and CEA plays a vital role in preventing further cerebral and ocular ischemic events [5, 16]. Changes in RNFL and GCC layer thicknesses before and after CAS could provide valuable information to aid the management of CAS, determine the requirement for CEA, and assess the effect of CEA surgery. This study aimed to examine changes in retinal GCC layer and peripapillary RNFL thicknesses by OCT in contralateral and ipsilateral eyes of CAS patients before and after CEA.

Methods

The present study was approved by the local ethics committee and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Forty-two patients who were diagnosed with CAS (70–99% stenosis rate) and underwent CEA surgery were included in this prospective cross-sectional study. The exclusion criteria were as follows: a history of any symptoms or signs of an ocular ischemic attack; a history of any ocular disease (glaucoma, diabetic retinopathy, maculopathy, age-related macular degeneration, ocular ischemic syndrome, epiretinal membranes, NAION or arteritic ischemic optic neuropathy, and optic neuritis) and any ocular surgery; a high refractive error ($\geq \pm$ 6D spherical $\geq \pm$ 3D cylindrical); disk abnormalities; a history of previous CEA or carotid artery stenting; total CAS; and bilateral CAS $>$ 50%.

All the subjects underwent an ophthalmological examination, including best corrected visual acuity (BCVA), intraocular pressure (IOP) measurements, biomicroscopy, fundoscopy, and OCT. Only patients with BCVA of 20/20 were included. Preoperative and postoperative single measurement of IOP was performed to the all patients in the daytime (at 14.00 pm) in upright posture with Goldmann applanation tonometry. In the study group, 21 patients had systemic hypertension and atherosclerosis, 11 had diabetes mellitus (without diabetic retinopathy), and 3 were current smokers or ex-smokers. The indication for CEA was based on the Asymptomatic Carotid Atherosclerosis Study [17]. Doppler ultrasonography and computed tomography angiography were performed to calculate CAS. All the patients underwent CEA under general anesthesia. The carotid artery was exposed by making a longitudinal incision along the anterior border of the sternocleidomastoid muscle. The common carotid artery, ICA, and external carotid artery were occluded with vascular clamps. The common carotid artery and ICA were longitudinally opened along the anterior vessel walls, and atheromatous plaques and nearby intima were carefully removed from the carotid bifurcation. The longitudinal incision was closed using a polytetrafluoroethylene patch. The vascular clamps were then removed, and the skin incision was closed.

An experienced investigator who was blinded to the study monitored the patients using SD-OCT (RS-3000 Lite, Nidek, Japan), according to macula map and disk map protocols. Macular thickness was examined in the following areas: the central 1 mm of the macula (fovea), 1–3 mm of the parafoveal macular area, and 3–6 mm of the perifoveal macular area. The GCC thickness [consisting of the RNFL, GCL, and inner plexiform layer (IPL)] was examined in the following areas: 1–3 mm of the parafoveal macular area and 3–6 mm of the perifoveal macular area. The RNFL thickness was examined in the following areas: superior, inferior, nasal, and temporal quadrants.

Statistical analysis

The Shapiro–Wilk test was conducted to assess the distribution of normality for continuous variables prior to the data analysis. For independent groups, the Student's *t* test was used for continuous variables with a normal distribution, whereas the Mann–Whitney *U* test was performed for continuous variables with a non-normal distribution. For dependent groups, a paired samples *t* test was used for continuous variables with a normal distribution, whereas Wilcoxon's signed-rank test was performed for continuous variables with a non-normal distribution. Descriptive statistics were expressed as mean and standard deviation for normally distributed variables and as median and first-quartile and third-quartile values for non-normally distributed variables. The significance level was determined as 0.05 in all statistical analyses. All statistical analyses were performed using IBM SPSS 20 (IBM Corp., Armonk, NY, USA).

Results

The study included 42 ipsilateral and 42 contralateral eyes of 42 patients (30 males and 12 females), with a mean age of 63.7 ± 5.58 years. The mean preoperative IOP was 15.2 ± 2.1 mmHg in the ipsilateral eye and 15.8 ± 2.7 in the contralateral eye. The mean postoperative IOP in the ipsilateral and contralateral eye was 18.6 ± 3.0 and 19.3 ± 3.8, respectively. The IOP was significantly higher in postoperative eyes ($p = 0.0001$) (Fig. 1). There was a statistically significant decrease in peripapillary RNFL thickness in superior quadrants postoperatively in ipsilateral eyes

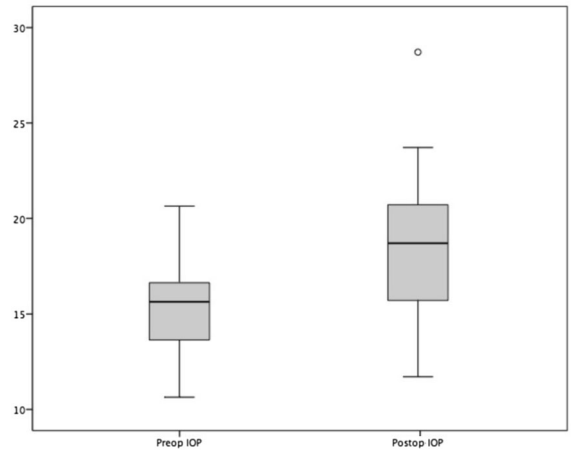

Fig. 1 Comparison of preoperative and postoperative IOP

(Tables 1, 2, Fig. 2). There was no statistically significant difference between preoperative and postoperative eyes in terms of foveal thickness (all p values > 0.05, Tables 3, 4). Parafoveal and perifoveal thicknesses were not significantly different before and after carotid surgery (all p values > 0.05, Tables 3, 4). The GCC thickness was not significantly different before and after CEA in ipsilateral and contralateral eyes (all p values > 0.05, Tables 5, 6).

Discussion

In this study, there was a statistically significant increase in IOP in both eyes 1 month after CAE. Peripapillary RNFL thickness in the superior quadrant was decreased in ipsilateral eyes postoperatively.

An autoregulation mechanism provides stable ocular blood flow to the retina, choroid, and optic disk [18]. However, in patients with CAS, dysfunction of this autoregulation mechanism leads to reduced blood flow, resulting in ischemia and hypoxia of astrocytes in the disk and mitochondria in retinal ganglion cell axons [18, 19]. This leads to apoptosis and autophagia of retinal ganglion cells [20]. Autoregulation of ocular blood flow is determined by ocular perfusion pressure. When the ocular perfusion pressure decreases below a threshold value, symptoms of ocular ischemic syndrome begin to appear [18]. Arterial hypertension reduces the ability of the eye to autoregulate blood flow when ocular perfusion pressure changes and exacerbates the ocular ischemic symptoms [21]

Table 1 Descriptive statistics and comparison results for preoperative–postoperative peripapillary retinal nerve fiber layer thickness

Parameters	Preoperative			Postoperative		
	Ipsilateral	Contralateral	*p* value	Ipsilateral	Contralateral	*p* value
pRNFL-S (μm)	121 (107–140)	114 (100–127)	0.26	110 (98–330)	122 (106–132)	0.19
pRNFL-N (μm)	86 (77–101)	81 (53–88)	0.11	80 (75–94)	75 (55–97)	0.62
pRNFL–I (μm)	119 (98–132)	130 (105–152)	0.14	121 (98–142)	125 (104–140)	0.74
pRNFL-T (μm)	70 (58–79)	67 (60–95)	0.64	64 (53–72)	63 (53–65)	0.61

Descriptive statistics are presented as median (25th–75th percentiles)

pRNLF peripapillary retinal nerve fiber layer, *S* superior, *N* nasal, *I* inferior, *T* temporal

Table 2 Descriptive statistics and comparison results for ipsilateral and contralateral peripapillary retinal nerve fiber layer thickness

Parameters	Ipsilateral			Contralateral		
	Preoperative	Postoperative	*p* value	Preoperative	Postoperative	*p* value
pRNFL-S (μm)	121 (107–140)	110 (98–330)	0.04	114 (100–127)	122 (106–132)	0.82
pRNFL-N (μm)	86 (77–101)	80 (75–94)	0.07	81 (53–88)	75 (55–97)	0.93
pRNFL–I (μm)	119 (98–132)	121 (98–142)	0.98	130 (105–152)	125 (104–140)	0.41
pRNFL-T (μm)	70 (58–79)	64 (53–72)	0.13	67 (60–95)	63 (53–65)	0.06

Descriptive statistics are presented as median (25th–75th percentiles)

pRNLF peripapillary retinal nerve fiber layer, *S* superior, *N* nasal, *I* inferior, *T* temporal

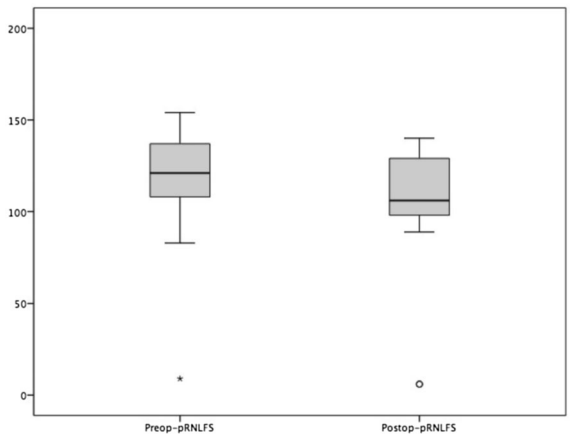

Fig. 2 Comparison of preoperative and postoperative peripapillary retinal nerve fiber layer thickness

Fluctuations in ocular perfusion pressure associated with atherosclerosis can have adverse effects on vessel diameters, thereby increasing the risk of ischemic injury [22]. Chronic hypertension adjusts the autoregulation mechanism to high levels and adapts the mechanism to higher blood pressures. This mechanism ensures that the patient is resistant to high but not low blood pressure [20]. In this study, most of the patients were hypertensive and accustomed to high blood pressure. The sudden decrease in ocular blood flow during surgery could contribute to ganglion cell death.

CEA is a well-known procedure to decrease the risk of strokes in CAS patients. However, the procedure is associated with a connatural risk of perioperative complications [23, 24]. For example, previous studies demonstrated that CEA increased cerebral and ocular blood flow [2, 25–28]. Research also reported that ciliary body ischemia caused normal or low IOP in CAS patients and that the blood supply of the ciliary body increased after CEA, leading to an increase in aqueous humor production and a subsequent rise in IOP [27, 29–31]. Kozobolis et al. [18] found no difference in IOP between eyes operated on and fellow eyes before surgery and IOP in postoperative month 6. In contrast, we found increased IOPs after CEA. However, the increase was slight (i.e., no greater than 3–4 mmHg). Thus, none of the patients required antiglaucomatous therapy and surgery. As the patients

Table 3 Descriptive statistics and comparison results for preoperative–postoperative foveal, parafoveal and perifoveal thickness

Parameters	Preoperative			Postoperative		
	Ipsilateral	Contralateral	*p* value	Ipsilateral	Contralateral	*p* value
Fovea (μm)	265 (249–288)	270 (251–294)	0.51	256 (245–282)	263 (249–291)	0.28
Para-S (μm)	332 (316–341)	336 (323–351)	0.32	319 (284–332)	331 (317–348)	0.06
Para-N (μm)	332 (326–340)	334 (324–341)	0.82	333 (320–340)	334 (322–348)	0.62
Para-I (μm)	328 (314–334)	327 (312–335)	0.84	321 (310–340)	328 (308–344)	0.84
Para-T (μm)	315 (306–327)	316 (306–323)	0.7	310 (298–328)	318 (307–332)	0.2
Peri-S (μm)	299 (284–303)	299 (286–303)	0.74	293 (278–303)	295 (282–311)	0.91
Peri-N (μm)	308 (292–319)	312 (299–318)	0.37	308 (291–317)	307 (296–318)	0.37
Peri-I (μm)	287 (265–302)	292 (274–300)	0.18	279 (266–299)	286 (274–297)	0.24
Peri-T (μm)	278 (269–290)	280 (269–294)	0.38	277 (266–295)	285 (274–302)	0.22

Descriptive statistics are presented as median (25th–75th percentiles)

Para parafoveal, *Peri* perifoveal, *S* Superior, *N* nasal, *T* temporal, *I* inferior

Table 4 Descriptive statistics and comparison results for ipsilateral–contralateral foveal, parafoveal and perifoveal thickness

Parameters	Ipsilateral			Contralateral		
	Preoperative	Preoperative	*p* value	Preoperative	Postoperative	*p* value
Fovea (μm)	265 (249, 288)	256 (245–282)	0.64	270 (251, 294)	263 (249–291)	0.28
Para-S (μm)	332 (316–341)	319 (284–332)	0.07	336 (323–351)	331 (317–348)	0.27
Para-N (μm)	332 (326–340)	333 (320–340)	0.17	334 (324–341)	334 (322–348)	0.52
Para –I (μm)	328 (314–334)	321 (310–340)	0.47	327 (312–335)	328 (308–344)	0.86
Para-T (μm)	315 (306–327)	310 (298–328)	0.45	316 (306–323)	318 (307–332)	0.75
Peri-S (μm)	299 (284–303)	293 (278–303)	0.86	299 (286–303)	295 (282–311)	0.72
Peri-N (μm)	308 (292–319)	308 (291–317)	0.73	312 (299–318)	307 (296–318)	0.14
Peri-I (μm)	287(265–302)	279(266–299)	0.29	292(274–300)	286(274–297)	0.08
Peri-T (μm)	278 (269–290)	277 (266–295)	0.46	280 (269–294)	285 (274–302)	0.69

Descriptive statistics are presented as median (25th–75th percentiles)

Para parafoveal, *Peri* perifoveal, *S* Superior, *N* nasal, *T* temporal, *I* inferior

in the present study were assessed just 1 month after CEA, the increase in IOP could be attributed to the carotid surgery.

Numerous previous studies demonstrated thinning of the inner retina in chronic NAION patients [32–36]. Tesser et al. [37] reported the presence of infarcts in the superior quadrant in NAION patients. The loss of ganglion cells in NAION results in a reduction in macular and central retinal thicknesses. Other researchers showed that macular thinning in cases of chronic NAION was a good clinical determinant of visual dysfunction [33]. Kupersmith et al. [34] demonstrated decreased GCL and IPL thickness at month 1 in NAION patients but not RNFL thinning 1 month after NAION. In the present study, none of the patients had NAION or decreased visual acuity. Reperfusion was present in our patients.

During carotid surgery, hypoperfusion syndrome can occur because of clamping of the ICA [38]. Regional cerebral ischemia may also develop, depending on the capacity of compensatory mechanisms, such as collateral blood flow, oxygenation, and blood pressure [31, 38]. After removal of the carotid clamp and elimination of atherosclerotic plaques, ICA blood flow returns, with variable degrees of reperfusion. In

Table 5 Descriptive statistics and comparison results for preoperative–postoperative parafoveal and perifoveal GCC thickness

Parameters	Preoperative			Postoperative		
	Ipsilateral	Contralateral	*p* value	Ipsilateral	Contralateral	*p* value
Para-SN (μm)	111 (103–121)	115 (109–121)	0.51	107 (102–120)	112 (105–119)	0.63
Para-ST (μm)	105 (91–111)	110 (94–114)	0.24	97 (90–108)	111 (96–113)	0.06
Para-IN (μm)	114 (105–124)	106 (97–118)	0.46	113 (106–119)	114 (99–119)	0.69
Para-IT (μm)	107 (93–110)	104 (93–114)	0.93	101 (90–112)	108 (95–112)	0.64
Peri-SN (μm)	112 (104–117)	113 (106–117)	0.67	110 (101–116)	110 (106–117)	0.82
Peri-ST (μm)	88 (81–96)	91 (87–99)	0.75	86 (78–94)	91 (82–99)	0.39
Peri-IN (μm)	110 (98–117)	112 (104–114)	0.73	105 (96–116)	111 (99–114)	0.96
Peri-IT (μm)	84 (78–99)	92 (85–100)	0.32	83 (75–96)	91 (85–100)	0.06

Descriptive statistics are presented as median (25th–75th percentiles)

Para parafoveal, *Peri* perifoveal, *SN* superior nasal, *ST* superior temporal, *IN* inferior nasal, *IT* inferior temporal

Table 6 Descriptive statistics and comparison results for ipsilateral–contralateral parafoveal and perifoveal GCC thickness

Parameters	Ipsilateral			Contralateral		
	Preoperative	Postoperative	*p* value	Preoperative	Postoperative	*p* value
Para-SN (μm)	111 (103–121)	107 (102–120)	0.44	115 (109–121)	112 (105–119)	0.82
Para-ST (μm)	105 (91–111)	97 (90–108)	0.12	110 (94–114)	111 (96–113)	0.87
Para-IN (μm)	114 (105–124)	113 (106–119)	0.75	106 (97–118)	114 (99–119)	0.87
Para-IT (μm)	107(93–110)	101 (90–112)	0.87	104 (93–114)	108 (95–112)	0.87
Peri-SN (μm)	112 (104–117)	110 (101–116)	0.34	113 (106–117)	110 (106–117)	0.16
Peri-ST (μm)	88 (81–96)	86 (78–94)	0.14	91 (87–99)	91 (82–99)	0.61
Peri-IN (μm)	110 (98–117)	105 (96–116)	0.29	112 (104–114)	111 (99–114)	0.48
Peri-IT (μm)	84 (78–99)	83 (75–96)	0.21	92 (85–100)	91 (85–100)	0.45

Descriptive statistics are presented as median (25th–75th percentiles)

Para parafoveal, *Peri* perifoveal, *SN* superior nasal, *ST* superior temporal, *IN* inferior nasal, *IT* inferior temporal

cases of relative ischemia reperfusion, subclinical injury (reversible or irreversible) may occur [39–42].

Many previous studies reported that increased activation of the *N*-methyl-D-aspartate (NMDA) receptor was responsible for neuronal degeneration induced by ischemia reperfusion [43–45]. Retinal neurodegeneration (i.e., retinal ganglion cell apoptosis and thinning of the inner retina) occurred following intravitreal injections of high doses of NMDA [46, 47]. In experimental models of retinal neurodegeneration, decreased retinal blood flow exacerbated ischemic retinal injury [48, 49]. In addition, recent studies revealed that vascular endothelial growth factors (VEGFs) played an important role in retinal neuroprotection [50, 51]. Nishijima et al. reported that VEGF-A had neuroprotective effects in ischemia and that VEGF inhibition appeared to aggravate ischemia-induced neural damage [51, 52]. Research also demonstrated that VEGF and VEGFR-2 were upregulated in carotid stenosis and that circulating levels of VEGF and VEGFR-2 decreased after CEA [53]. Shvartsman et al. [54] reported that VEGF reduced axonal disruption and promoted axonal regeneration after acute ischemic injury.

Our findings pointed to reduced superior peripapillary RNFL thickness but relatively little loss in GCC thickness (macular RNFL, GCL, and IPL) after CEA. The observed pattern of injury may be explained by the protective effect of VEGF on axons relative to that of the ganglion cell body. As noted above, VEGF

plays a role in axonal protection. In the present study, ischemia reperfusion injury due to CEA may have reduced VEGF levels. The limited and relatively short period of ischemia may have caused localized superior peripapillary RNFL quadrant defects in ipsilateral eyes. We did not detect a significant difference between preoperative and postoperative RNFL thicknesses in contralateral eyes. The aforementioned may be explained by the regular blood flow of the contralateral carotid artery and absence of ischemia.

Zhang et al. [55] demonstrated that anti-VEGF treatment improved neurological function in patients with malignant tumors of the nervous system. Novitzky et al. [56] showed neuroprotective effect of bevacizumab after middle cerebral artery occlusion. These studies researched the situations where the VEGF levels are abnormally high. Anti-VEGF agents might have a neuroprotective effect in cases that the level of VEGF is high. We believe that the anti-VEGFs may have a negative effect on neuroprotection by reducing the levels of VEGF, which is already shown to decrease after CEA.

The outer retina is more resistant to ischemia than the inner retina [57]. This could be the reason that the disk was affected without any change in retina in our study. Previous histopathological studies have demonstrated that the peripheral superior sector of the optic nerve head demonstrates the greatest mean retinal ganglion cell axonal diameter. It was shown that axons of larger retinal ganglion cells might be more vulnerable to ischemic axonal injury. Because neurofilament phosphorylation requirement is greatest in this site of the optic nerve [58].

The limitations of our study are the relatively small number of patients and absence of long-term postoperative outcomes of the patients. In addition, we did not use laser speckle flowgraphy to measure ocular blood flow.

In summary, ischemia and reperfusion injury due to CEA results in thinning of the superior peripapillary RNFL. Patients may be prescribed anti-VEGF agents for various reasons. For axonal protection, patients should cease the use of such agents if possible in the early preoperative and postoperative periods of CEA. To the best of our knowledge, this is the first study to examine peripapillary RNFL and GCC thicknesses before and after CEA. Further long-term studies with large samples are needed to investigate whether these alterations are progressive and accompanied by GCC thinning in the following period.

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