Subfoveal choroidal thickness in ipsi- and contralateral eyes of patients with carotid stenosis before and after carotid endarterectomy: a prospective study

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Abstract

Purpose: To compare subfoveal choroidal thickness (SFCT) and associated clinical variables in patients with carotid stenosis (CS) before and six months after carotid endarterectomy (CEA).

Methods: The prospective non-randomized Helsinki Carotid Endarterectomy Study—Brain and Eye Sub-sTudy included seventy patients (81% male, mean age 69 years) and 40 control subjects (77% male, 68 years), from March 2015 to December 2018. Ophthalmological examination included SFCT measured with enhanced depth imaging-optical coherence tomography. CS was more severe (≥70% stenosis in 92%) ipsilateral to the CEA than contralaterally (<50% stenosis in 74%; p<0.001).

Results: At baseline, patients had thinner mean SFCT than control subjects in both eyes (ipsilateral, 222 vs. 257μm and contralateral, 217 vs 258 μm, p≤0.005). At follow-up, SFCT did not change in ipsi- and contralateral eyes compared to baseline in patients (p=0.68 and p=0.77), or in control subjects (p=0.59 and p=0.79). Patients with coronary artery disease had thinner mean SFCT vs those without it in ipsilateral eyes before CEA (200 vs 233 μm, p=0.027). In ipsilateral eyes of patients before CEA, thinner SFCT and ocular signs of CS, plaque and hypoperfusion related findings combined, were associated (p=0.036), and the best-corrected visual acuity, measured in logMAR, increased with increasing SFCT (r=–0.25; p=0.046).

Conclusions: SFCT is thinner in patients with CS without association between SFCT and the grade of CS. Unchanged SFCT after CEA suggests, that choroidal vessels in severe CS are unable to react to increased blood flow. Bilaterally thin SFCT could be considered as yet another sign of CS.

Introduction

The ophthalmic artery, the first branch of the internal carotid artery, is the main source of blood supply to the eye. Up to 70% of its blood flow goes to the choroid (Mrejen & Spaide 2013). Ophthalmic symptoms and

signs in patients with carotid stenosis (CS) may result from embolism to the ophthalmic artery and its branches from an ulcerated carotid plaque (Rubin 2006) or from hypoperfusion to the globe (Arthur et al. 2014; Hayreh 2015). Ocular signs such as Hollenhorst plaques and other posterior segment changes in the retina and optic nerve as well as anterior segment changes, may precede cerebral signs of CS. Clinicians should therefore be familiar also with these signs, in order to prevent a stroke (Lawrence & Oderich 2002; Biousse et al. 2018). Unlike these changes, the effect of reduced blood flow to the choroid caused by CS, is less well known, however.

Full-thickness choroidal imaging has been difficult, mainly because of blocking by the retinal pigment epithelium (RPE). Indocyanine green angiography and ultrasonography were conventional techniques to visualize the choroid. Discovery of enhanced-depth imaging spectral-domain optical coherence tomography (EDI-OCT) enabled more precise and detailed visualization of the choroid (Spaide et al. 2008), particularly choroidal thickness (CT). Repeatability in subfoveal choroidal thickness (SFCT) measurements using EDI-OCT has been validated, "a change of >32 μm in SFCT exceed interobserver variability" (Rahman et al. 2011) and better intra-observer repeatability compared to two observers has been shown (Cho et al. 2014). Measuring CT and choroidal volume (CV) based on Early Treatment of Diabetic Retinopathy Study (ETDRS) subfields has been introduced (Cheong et al. 2018). This method also requires manual measurement of CT, and is so far lacking normative data and assessment of repeatability. CT measurements have served in clarifying the pathogenesis of several ocular disorders such as age-related macular degeneration (AMD) and especially central serous chorioretinopathy, polypoidal choroidal vasculopathy, and other manifestations of the pachychoroid (Kim et al. 2011; Dansingani et al. 2016). The population-based Beijing Eye Study associated visual acuity with SFCT, indicating its functional role (Wei et al. 2013), and the Gutenberg Health Study found that CT was associated with cardiovascular risk factors (Schuster et al. 2019).

Studies have shown that in eyes affected by CS, SFCT is thinner compared to fellow eyes (Kim et al. 2015; Wang et al. 2017; Wang et al. 2017; Akca Bayar et al. 2019) or control subjects (Sayin et al. 2015; Kang et al. 2019). Three studies have found either bilaterally thinner SFCT in CS (Lareyre et al. 2018), a thicker SFCT when CS was >70% (Akçay et al. 2016), or choroidal thinning before retinal changes (Wang et al. 2017). The last study suggested that SFCT may perform well in choosing the optimal schedule for carotid surgery. Changes in SFCT before and after carotid endarterectomy (CEA) has been the topic of four small

series (Lareyre et al. 2018; Rabina et al. 2018; Akca Bayar et al. 2019; Krytkowska et al. 2020), again with partly contradictory results and only one of these with control subjects (Akca Bayar et al. 2019).

In an effort to elucidate some existing controversies, we conducted a larger prospective study with healthy, age- and gender-matched control subjects. Our aim was: 1) to compare SFCT at baseline and six months after CEA and 2) to discover variables associated with SFCT by use of EDI-OCT.

Patients and Methods

Study design

This prospective non-randomized study is part of the Helsinki Carotid Endarterectomy Study - Brain and Eye Sub-sTudy (HeCES-BEST) conducted in the Helsinki University Hospital, Helsinki, Finland. HeCES-BEST involves ophthalmologists, neurologists, neuroradiologists, vascular surgeons and neuropsychologists to evaluate structural and functional changes in the brain and eye at baseline and six months after CEA. The ethics committee of the Hospital District of Helsinki and Uusimaa approved the study. Its design complies with the tenets of the Declaration of Helsinki. All participants gave their written informed consent.

Patients and controls

From March 2015 to December 2018, 71 patients and 41 control subjects were enrolled, all Caucasians. One patient and one control subject were excluded, the former because of inadequate co-operation in EDI-OCT and the latter was diagnosed with cancer. The inclusion criterion was CS 70% or more in the first evaluation leading to CEA. Six enrolled patients had an ipsilateral CS of <70% when assessed with CTA by an experienced study neuroradiologist. The exclusion criterion was recent (<6 months) cerebral infarction. Twelve patients (17%) had undergone CEA on the contralateral side a median of 0.6 (range, 0.2–17.2) years earlier. Healthy, unmedicated, age- and gender-matched control subjects, who underwent carotid ultrasonography to rule out CS, were enrolled from senior- and exercise clubs, and among hospital staff, relatives and friends.

Baseline and follow-up examinations

Both eyes of the 70 patients and 40 control subjects were examined at baseline. Twenty-nine patients (41%) underwent right sided and 41 (59%) patients left sided CEA. The right eye served as the control for the ipsilateral eye in 17 (42%) and the left eye as the control for the contralateral eye in 23 (58%) control subjects, the sides were randomly drawn. All patients except one were operated within two weeks of baseline examination; one patient needed further investigations for anemia and was operated 11 weeks after baseline examination. Patients were examined a median of 5.9 (range, 5.3–8.6) months after CEA. Seven (10%) of them were lost to follow-up: one had a postoperative cerebral infarction, two did not respond to invitation, and four withdrew from the study. Eight patients (12%) with bilateral CS underwent CEA of the contralateral side a median of 0.6 (range, 0.1–2.8) months after the first CEA, and the follow-up data from these patients were excluded from the analysis. All control subjects were examined twice with a comparative interval (median, 5.9; range, 4.8–6.9 months).

Clinical records and interview by a research assistant were used to collect patient data (Table 1). All participants had blood samples collected at the baseline, which are not presented in this manuscript, except that the diagnosis of dyslipidemia was based on low-density lipoprotein (LDL) level >3 mmol/L in our control subjects. Blood pressure was measured once in the sitting position from the brachial artery using an automatic sphygmomanometer (Omron, Omron Healthcare, Kyoto, Japan). Mean arterial pressure (MAP) was calculated with the formula: MAP = [Diastolic blood pressure (DBP)] + 0,412 x [Systolic blood pressure (SBP) – DBP] (Papaioannou et al. 2016). Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in meters). SBP was similar, whereas control subjects had higher DBP and MAP and lower BMI compared to patients (Table 1).

Grade of CS as analyzed with computed tomography angiography (CTA) according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method (Barnett et al. 1991), is described in Table 1. A 1.0 mm decrease in distal luminal diameter beyond a tight stenosis was used as the cut-off for a subtle near-occlusion (NO-s). The near-occlusion was classified as a full collapse (NO-fs) only if the luminal reduction exceeded 2.5 mm (Koskinen et al. 2017; Meershoek et al. 2018).

Ophthalmological examination

Baseline ophthalmological findings in patients and control subjects are shown in Table 2. Best-corrected visual acuity (BCVA) was measured in logMAR units using ETDRS charts. Intraocular pressure (IOP) was measured with a rebound tonometer (Icare® TA01i Tonometer, Icare Finland, Vantaa, Finland), the mean of three reliable measuring cycles was used. Bio-microscopy of the anterior and posterior segment was assessed with emphasis on findings related to impaired circulation (Lawrence & Oderich 2002; Mendrinos et al. 2010). After pupillary dilatation with tropicamide (Oftan Tropikamid® 5 mg/ml, Santen, Tampere, Finland), ultra-widefield images were obtained with Optos® 200 Tx (Optos, Dunfermline, United Kingdom) and 50° color and red-free fundus photographs centered on the macula and the nasal field, and 30° photographs centered on the disc were taken (FF450^{plus}, Carl Zeiss, Jena, Germany). Ocular signs of CS are dived into plaque- and hypoperfusion related findings (Table 3).

Optical coherence tomography

Spectral-domain EDI-OCT was performed using the Heidelberg Spectralis® (version 6.3.2.0; Heidelberg Engineering, Heidelberg, Germany). Caffeine intake and cigarette smoking was prohibited three hours before examination. Standardized scans were obtained using high resolution and automatic real-time function, with 16 frames and 49 sections in a 20° rectangle centered on the fovea. Manual calipers were used to measure SFCT at the center of the fovea following a standardized protocol (Boonarpha et al. 2015). In short, the calipers were placed at the outer edge of the hyperreflective RPE/Bruch's complex band and the choroid-sclera junction. SFCT was measured twice in different sessions. If the difference between the two measurements was <10 μm, the mean was calculated. If the difference was ≥10 μm, a third measurement was taken and the mean of the two nearest measurements with a difference of <10 μm was used. Measurements outside this limit were excluded from further comparison. The percentages of acceptable measurements in the ipsi- and contralateral eyes of the patients were 91% and 83% at baseline and 86% and 87% at follow-up, and in control subjects 88%, 88%, 83%, and 80%, respectively. The mean time of the day at the baseline EDI-OCT examination was 11:56 a.m. (± 1:28 hours) for patients and 11:48 a.m. (± 1:54 hours) for control subjects. The corresponding times at the follow-up were: 10:59 a.m. (± 1:31 hours) and 11:32 a.m. (± 1:56 hours), respectively. All examinations and measurements were performed by the same ophthalmologist (MA-K) masked to the operated side.

Statistical analysis

Descriptive statistics for continuous normally distributed variables are presented as means (standard deviations) and for non-normally distributed variables as medians (ranges), and for categorical variables as frequencies (percentages). To compare the variables between patient and control groups, two-sample *t*-test or Mann-Whitney *U*-test was used for continuous variables and chi-square or Fisher's exact for categorical variables. The differences in CS and ocular signs of CS between ipsi- and contralateral eyes were examined with McNemar-Bowker test. Mean SFCT values between ipsi- and contralateral eyes, and between pre- and postoperative visits were compared using linear mixed model with random intercept for a subject to account for the dependency between measurements on the same subject. Restricted maximum likelihood estimation was used in linear mixed model to get the unbiased estimates in the presence of missing data. Two-sample *t*-test was used to test the differences in mean SFCT between patients and controls. Associations of categorical characteristics with preoperative SFCT were analyzed using two-sample *t*-test or 1-way ANOVA with Tukey's adjustment for multiple comparisons. Correlations between continuous clinical characteristics and preoperative SFCT were calculated with Pearson or Spearman correlation coefficients. Statistical analyses were done using SPSS for Windows (version 26, IBM, Armonk, NY). Statistical significance was set at 0.05.

Results

Subfoveal choroidal thickness

At baseline, the SFCT was within 5 μm of each other in both the ipsi- vs contralateral eyes of the patients (222 vs 217 μm, p=0.90, linear mixed model) and in control subjects (257 vs 258 μm, p=0.72, Fig.1). The SFCT was 36–41 μm thinner ipsi- and contralaterally in the patients compared to the control subjects (p=0.005 and p=0.004, two-sample *t*-test).

At the postoperative visit, SFCT did not change in ipsi- and contralateral eyes relative to their SFCT at baseline (p=0.68 and p=0.77, linear mixed model, Fig.1). It did not differ between the ipsi- vs contralateral

eyes, neither in the patients (225 vs 209 μm, p=0.13) nor in control subjects (261 vs 244, p = 0.62). The significant difference between the patients and control subjects in SFCT ipsi- and contralaterally was maintained at the postoperative visit (p=0.011 and p=0.007, two-sample *t*-test).

Grade of CS did not influence SFCT which remained unchanged postoperatively in ipsi- and contralateral eyes in patients with preoperative grade of CS >70% (225 vs 222 and 216 vs 212 μm, respectively; p=0.54 and 0.23, linear mixed model), including patients with NO, and also in contralateral eyes in patients with preoperative grade of CS <50% (218 vs 214 μm, p=0.32).

Effect of cardiovascular disease

At baseline, patients with coronary artery disease (CAD) vs those without CAD had a thinner SFCT in the ipsi- but no difference in the contralateral eyes (200 vs 224 and 202 vs 224 μm, p=0.027 and p=0.23, two-sample *t*-test, Table 4, Fig.2). At the postoperative visit, these values were not different in the ipsi- but were thinner in the contralateral eyes (210 vs 232 and 185 vs 219 μm, p=0.25 and p=0.050, respectively). Postoperatively, SFCT in ipsi- and contralateral eyes of patients with CAD and without CAD did not change relative to baseline (Fig.2).

Association between preoperative SFCT and clinical characteristics

We further analyzed which variables besides CAD associated with SFCT at baseline. An association was found between thinner SFCT and ocular signs of CS in the ipsilateral eyes (p=0.036, one-way ANOVA), but not in the contralateral eyes (p=0.30, two-sample *t*-test, Table 4). In line with this, we found an inverse correlation between SFCT and logMAR in the ipsilateral eyes (r = –0.25; p=0.046, Spearman rank correlation), but not in the contralateral eyes (r= –0.03; p=0.81), corresponding to increasing BCVA with increasing SFCT. No correlation was found in ipsilateral eyes between SFCT and spherical equivalent (r = 0.11; p = 0.39, Pearson correlation), age (r = –0.16; p = 0.20), BMI (r = 0.01; p = 0.95), SBP (r = – 0.14; p = 0.27) nor DBP (r = –0.10; p = 0.43). Furthermore, gender, smoking, DM, systemic hypertension,

dyslipidemia, amaurosis fugax, AMD, time of OCT measurement and grade of CS were unassociated with ipsi- or contralateral SFCT (Table 4).

The control subjects were analyzed similar to the patients, a correlation was found between SFCT and BMI ($r = -0.37$; $p=0.036$, Pearson correlation), but on one side only.

Discussion

To our knowledge, this seems to be the largest study thus far on SFCT in patients with CS before and after CEA. We showed thinner SFCT both before and after CEA in both eyes despite significant difference in the grade of CS ipsi- and contralaterally. In all evaluations, our patients had, in fact, thinner SFCT compared to control subjects. An association appeared also between SFCT and patients with CAD, as thinner SFCT was found preoperatively in ipsilateral eyes and postoperatively in the contralateral eyes. Furthermore, an association appeared between thinner SFCT and ocular signs of CS, and SFCT was correlated with BCVA, both findings in the ipsilateral eyes of our patients.

We confirmed thinner SFCT in ipsi- and contralateral eyes in patients with CS (Fig. 1). In our study, mild CS on the contralateral side occurred in 74% of patients, who nevertheless had thinner SFCT, whether this indicates a compromised blood flow to the choroid even in mild CS is not yet known. As already mentioned, one study concluded, that when choosing the optimal time for surgery in CS, measuring SFCT could prove useful (Wang et al. 2017). Their conclusion is challenged by our finding of thin SFCT in mild CS. Our finding also challenges the theory that dilation of choroidal collaterals might cause choroidal thickening in early stages of CS (Yeung et al. 2020). On the other hand, we confirmed an absence of correlation between the grade of CS and SFCT (Sayin et al. 2015; Lareyre et al. 2018).

In concordance with recent findings (Sayin et al. 2015; Kang et al. 2019; Li et al. 2019) we found thinner SFCT in patients with CS compared to that of control subjects (Fig.1). The mean SFCT in large population-based studies has ranged from 252 to 255 μm (Wei et al. 2013; Schuster et al. 2019). This is in line with the mean SFCT in our control subjects, 244 to 261 μm. On the other hand, 33% of our control subjects had thin SFCT (<220 μm), and of these 74% had bilaterally thin SFCT, and 75% had thin SFCT at both visits. It seems, that bilaterally thin SFCT may exist also as a normal variation. However, age-matched control

subjects in our study, though without medications according to study protocol, had a higher DBP (single measurement) compared to that of the patients, and 80% were dyslipidemic (Table 1). The fact that only the patients used medications, such as antiplatelet and statin therapy, that enhance the circulation and endothelial function, might have influenced our results. If so, one could hypothesize that this would have narrowed the difference between the patients and control subjects which, however, was significant both before and after CEA. Our patients´ medication did not change during follow-up.

Thus far, four studies on SFCT after CEA have appeared (Lareyre et al. 2018; Rabina et al. 2018; Akca Bayar et al. 2019; Krytkowska et al. 2020). The Lareyre-group had 36 patients at baseline of whom 28 with follow-up results at 1 month and 19 at 3 months (Lareyre et al. 2018). After CEA, SFCT was increased at 1 and 3 months in the ipsilateral eyes (211 μm at baseline vs 226 μm at 3 months, $p<0.001$) and at 3 months in the contralateral eyes (215 μm vs 220 μm, $p=0.04$). Thinner SFCT compared to that of the normal population emerged in our study as well; their mean SFCT in ipsi- and contralateral eyes was comparable to that of our patients both pre- (211 vs 222 μm and 215 vs 217 μm) and postoperatively (226 vs 225 μm and 220 vs 213 μm). The Krytkowska-group measured mean CT and CV from 38 eyes of 19 patients in 9 ETDRS subfields at baseline, and at 2 days and 3 months after CEA. Compared to baseline, CT and CV had not changed at 2 days in either eye, whereas at 3 months the ipsilateral eye showed increase in total CT ($p=0.04$), including from 320 to 336 μm ($p=0.03$, without adjusting for multiple subfield comparisons) in the central subfield, and overall CV ($p=0.01$), including from 0.25 to 0.26 mm^3 ($p=0.06$, without adjusting for multiple subfield comparisons) in the central subfield. Unlike these two studies, we found no increase in SFCT postoperatively. It is possible that either the increase in SFCT after CEA is temporary, or the variability in SFCT measurements prevents detection of small changes. The Rabina-group´s study included 8 patients with a normal preoperative SFCT (268–277 μm) and no change 6 months after CEA (Rabina et al. 2018). The Akca Bayar-group study, using ETDRS subfields for evaluation of CT, included 43 patients with moderate (50-70%) or severe (>70%) CS at baseline, requiring stenting in 22 patients and CEA in 21 patients, and 40 control subjects (Akca Bayar et al. 2019). At baseline the subfoveal CT was thinner in moderate and severe CS as compared to controls (242 μm vs 249 μm vs 264 μm, $p=0.03$, without adjusting for multiple subfield comparisons), as well as in the other subfields. They concluded that only stenting in patients with moderate CS provided a recovery in CT, suggesting that higher grade of CS may lead to

permanent decrease in choroidal thickness. Our findings support this theory because our patients had no increase in SFCT after CEA.

A study with 34 patients with CAD and 28 age-matched control subjects found significantly thinner SFCT in the former, concluding that “CT could serve as potential biomarker” of CAD (Ahmad et al. 2017), and the same suggestion appeared in a recent review (Yeung et al. 2020). Another study showed decreased choroidal vessel density and blood flow in OCT angiography, associated with higher grade of stenosis of coronary arteries (Wang et al. 2019). Our series included 22 patients with CAD, of whom 32% had had acute myocardial infarction, and 64% had undergone revascularization procedure. Our patients with CAD had thinner SFCT than did patients without CAD in ipsilateral eyes preoperatively and in contralateral eyes postoperatively (Fig. 2), whether thinner SFCT in CAD patients is the result of compromised blood flow in choroidal vessels, prone to change also on the unoperated side, remains to be determined. In the Gutenberg Health Study, cardiovascular risk factors such as sex, SBP, left ventricular mass index and dyslipidemia were associated with SFCT, mediated by aging (Schuster et al. 2019). Association of SFCT with higher BP, shown in other studies of DPB and higher mean blood pressure (Wei et al. 2013), as well as with arterial hypertension (Lareyre et al. 2018), was absent from our series. However, our patients were normotensive, albeit 84% had medication for arterial hypertension (Table 1). Neither did we find any association between SFCT and dyslipidemia, i.e. patients with medication for dyslipidemia. Controversy exists as to how diabetes affects CT (Laviers & Zambarakji 2014), we found no association there. Healthy individuals with higher BMI (>25) have thinner CT than do those with lower BMI (Yilmaz et al. 2015). Accordingly we found a negative correlation between BMI and SFCT in our healthy control subjects, but not in the patients with CS. Studies with EDI-OCT have confirmed age-related decline in SFCT of 16- 54μm per decade (Margolis & Spaide 2009; Ding et al. 2011; Wei et al. 2013). Probably due to the limited age range in our patients and control subjects, we found no correlation between age and SFCT (Table 1).

In our study, midperipheral hemorrhages were the most common findings in patients with ocular signs of CS (Table 3). These signs were associated with thinner SFCT in the ipsilateral eyes, despite that the grade of CS was not associated with SFCT (Table 4). To the best of our knowledge, this seems to be the first report on association between SFCT and signs of CS, which could suggest that thin SFCT might play a role in the pathogenesis of these changes. A functional role for SFCT has been suggested, because visual acuity has

been associated with SFCT (Wei et al. 2013). We also found better BCVA with increasing SFCT in the ipsilateral eye of our patients.

Diurnal variation in SFCT has occurred, ranging from 10 to 13 μm (Usui et al. 2012; Lee et al. 2014). We observed no association between SFCT and time of its measurement, the mean time being around noon. Diurnal variation should not, therefore, have influenced our results. In two studies, SFCT decreased by 8.7 and 15 μm for every diopter of myopic shift (Fujiwara et al. 2009; Wei et al. 2013). None of our participants had high myopia, their mean spherical equivalent was slightly on the hyperopic side with the ranges in ipsi- and contralateral eyes of patients and control subjects being similar (Table 2). Their spherical equivalent showed no correlation with SFCT.

All our study participants were Caucasians and mostly males, hence making our findings valid accordingly. Limitations in our study include lack of data on axial length, anterior chamber depth, and lens thickness, all of which may influence SFCT measurements (Wei et al. 2013). Another limitation concerns EDI-OCT measurement protocol, although we used high resolution and automatic real-time function, best quality in images would have required 100 averaged scans in each section. To our benefit, we evaluated SFCT in separate sessions and used only measurements within 10 μm to exclude images with indistinct choroid-sclera junction. Most of the studies on CT have not revealed their protocol in EDI-OCT imaging, however.

In conclusion, the bilaterally thin SFCT found in patients with CS, could be considered as yet another sign of CS, though bearing in mind that this finding may overlap with normal variation. Thin SFCT occured even in mild CS (<50%). An absence of recovery in SFCT after CEA supports the hypothesis that choroidal vessels may be unable to react to increased blood flow in patients with severe CS (>70%). Thin SFCT in patients with CAD, suggests that, in such patients, the systemic effect of atherosclerotic disease plays an additive role with local hemodynamic effect of CS. Furthermore, whether thin SFCT plays a role in the pathogenesis of ocular signs of CS, as demonstrated by midperipheral hemorrhages and other signs of ocular ischemic syndrome, is unknown. Future research is essential to confirm our findings.

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