Optical coherence tomography-based determination of ischaemia onset – the temporal dynamics of retinal thickness increase in acute central retinal artery occlusion

Daniel A. Wenzel, Robert Kromer, Syen Poli, Nils Alexander Steinhorst, Maria K. Casagrande, Martin S. Spitzer and Maximilian Schultheiss

1University Eye Hospital, Centre of Ophthalmology, University Hospital Tübingen, Tübingen, Germany
2Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3Department of Neurology & Stroke, University Medical Center Tübingen, Tübingen, Germany
4Hertie Institute for Clinical Brain Research, University Hospital Tübingen, Tübingen, Germany

ABSTRACT.
Purpose: Acute central retinal artery occlusion (CRAO) induces ischaemic retinal oedema. The purpose of this study was to define sensitivity and specificity of optical coherence tomography (OCT) based retinal thickness analysis in determining ischaemia onset in CRAO.
Methods: The relative retinal thickness increase (RRTI) in comparison with the fellow eye was analysed retrospectively in OCT scans of 66 patients diagnosed with CRAO between January 2010 and December 2019 within 48 hr of ischaemia onset. The natural course of RRTI and the sensitivity and specificity of OCT-based determination of ischaemia onset in identifying CRAO within 4.5 hr using the RRTI were evaluated.
Results: Relative retinal thickness increase (RRTI) in acute CRAO follows a hyperbolic curve with a steep incline within the early phase after which it reaches a plateau. Optical coherence tomography (OCT)-based retinal thickness analysis in CRAO allows to differentiate patients with ischaemia onset within the past 4.5 hr or thereafter with a sensitivity of 100% and a specificity of 94.3%.
Conclusion: Relative retinal thickness increase (RRTI) allows to identify CRAO patients that are eligible for a potentially beneficial reperfusion therapy within a therapeutic window of 4.5 hr with a high accuracy. Especially in patients with unknown ischaemia onset, this diagnostic tool could be of major importance in the future clinical management.

Key words: central retinal artery occlusion – ischaemia – optical coherence tomography – retinal ischaemia – retinal edema – stroke

Introduction
Acute central retinal artery occlusion (CRAO) causes massive monocular vision loss, for which so far insufficient evidence for any therapeutic option exists, and therefore, prognosis of visual recovery usually remains devastating (Kim et al. 2019). Especially with retinal ischaemia time exceeding 4–6.5 hr, all therapeutic options will most likely be ineffective due to the limited retinal ischaemia tolerance (Hayreh et al. 2004; Hattenbach et al. 2008; Schrag et al. 2015). However, evidence for superior outcomes after early intravenous thrombolysis within 4.5 hr after ischaemia onset has been growing recently (Schrag et al. 2015; Schultheiss et al. 2018). Although many patients with acute CRAO are aware of the onset time of vision loss, in numerous situations, it is difficult to determine whether ischaemia onset was within or beyond 4.5 hr prior to presentation, as for example about one third of CRAOs occur during nocturnal sleep (Schmidt, Schumacher & Feltgen 2009). Patients with unknown time of ischaemia onset may not qualify for thrombolytic treatment at all since risks usually outweigh unpredictable benefits. Unfortunately, there is no validated instrument or test, which allows an exact determination of ischaemia onset. As the central retinal artery provides the blood flow solely for the inner retinal layers (IRL; ganglion cell layer, inner plexiform cell layer, inner nuclear layer, outer plexiform layer), retinal thickness increase generally results from IRL oedema (Falkenberry et al. 2006; Schmidt, Kube & Feltgen 2006; Leung et al. 2007; Shinoda, Yamada & Matsumoto 2008; Chen, Hwang &
Chen 2011; Cornut et al. 2012; Furashova & Matthé 2017). Over time, in the chronic phase of CRAO, the oedema will eventually resolve and be followed by retinal atrophy of the IRL (Shinoda, Yamada & Matsumoto 2008; Ikeda & Kishi 2010; Chen, Hwang & Chen 2011; Cornut et al. 2012; Ahn et al. 2015). Nonetheless, the exact temporal dynamics of the natural course of retinal thickness changes in the acute phase of CRAO are not well described and, so far, remain inconclusive. Recently, we have shown that the retinal thickness increase shows a near-linear progression rate within the first 9 hr after ischaemia onset measured by optical coherence tomography (OCT) (Ochakovski et al. 2020). In this context, the objective of this study was to quantitatively assess the temporal changes in retinal thickness within the first 48 hr and to determine the ability of OCT-based retinal thickness analysis to specify the time of ischaemia onset in acute CRAO (< 8 hr) patients, which in the future may imply important consequences for possible reperfusion concepts, such as intravenous thrombolysis.

Methods

Study design and patient selection

This study retrospectively analysed 66 patients diagnosed with CRAO, who had presented at two tertiary care facilities (University Eye Hospital Tübingen, Germany and Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, Germany) between January 2010 and December 2019. All patients with a reliable patient-reported time of symptom onset within the past 48 hr that also received an OCT scan of both eyes at their primary visit within 48 hr after ischaemia onset (time to OCT, TTO) were included in the further evaluation. Patients with reperfused CRAOs, a cilioretinal artery or retinal pathologies other than CRAO (reperfusion of the IRL, the AVRT, related macular degeneration, epiretinal gliosis etc.) were excluded prior to analysis. Sixty-six patients (mean age 71.5 ± 11.3 years) with acute CRAO, known time of symptom onset (<48 hr) and available OCT from their primary presentation (<48 hr) and no other pathologies than CRAO were included in further analysis (see patient data in Table 1). Median TTO was 14.0 ± 11.4 hr after symptom onset.

Retinal thickness increase

The retinal thickness in the unaffected non-ischaemic eyes did not differ significantly (p = 0.9913; see Table 1) between the patients that presented within 4.5 hr after ischaemia onset and patients with delayed presentation. On the affected eye, the retinal thickness differed significantly between patients presenting within or after 4.5 hr of symptom onset (p < 0.0001; see Table 1). Relative retinal thickness increase (RRTI) was measured between 1.1 and 46.0 hr after ischaemia onset. The median RRTI within the first 4.5 hr was 12.8 ± 7.2% (median ± SD) and 44.3 ± 20.9% in the group >4.5 hr.

Relative retinal thickness increase (RRTI) in CRAO followed a hyperbolic curve with a steep, near-linear progression within the first 4–5 hr and subsequent slope flattening reaching a plateau after 10–20 hr after ischaemia onset (see Fig. 1). During the first 10 hr, the RRTI was 3.83% per hour (95% confidence interval: 2.59–5.07% per hour).

Sensitivity and specificity

Prediction of the potential therapeutic window (<4.5 hr) using OCT-based retinal thickness analysis in CRAO patients can be evaluated with a multiple logistic regression analysis compromising age, gender, visual acuity and the RRTI as independent variables (compare Table 2).

The RRTI was the only significant predictor of the potential therapeutic window; hence, it was further explored using a receiver operating characteristic (ROC) curve analysis (compare Fig. 2). The area under the curve was 0.9782 for...
all patients (standard error = 0.0151; 95% confidence interval = 0.9487–1.000; p-value < 0.0001) and 0.9519 for patients with CRAO onset ≤12 hr (standard error = 0.0324; 95% confidence interval = 0.8884–1.000; p-value < 0.0001). Thus, a RRTI of 24.5% as a cut-off results in a sensitivity of 100.0% in both ROC curves and a specificity of 94.3% for all patients, respectively, 87.5% for patients within 12 hr after symptom onset whether CRAO onset was within or more than 4.5 hr before the OCT scan at primary presentation (Fig. 3). Representative OCT images from CRAO patients used to analyse RRTI at different times after ischaemia onset are presented below (see Fig. 4).

### Discussion

The present study visualizes the temporal changes in retinal thickness in acute CRAO over the initial 48 hr following ischaemia onset. As OCT enables the exact quantitative analysis of the retinal thickness, we showed that the RRTI is valuable in determining ischaemia onset of acute CRAO with unknown onset. Although it is well known that acute CRAO induces a retinal oedema, data dealing with the exact temporal dynamics of the retinal thickness increase, however, is scarce (Falkenberry et al. 2006; Shinoda, Yamada & Matsumoto 2008; Chen, Hwang & Chen 2011; Cornut et al. 2012). Our recent publication found near-linear retinal thickness increase as a function of time in the very acute phase (first 9 hr) of CRAO, which gave reason to us to investigate this possible biomarker’s behaviour over the first 48 hr after ischaemia onset in the present study (Ochakovski et al. 2020). We hypothesized that RRTI might be useful to be used as surrogate marker to determine whether a patient is within the therapeutic window of 4.5 hr – the period of time where a reperfusion therapy might be beneficial (Schrag et al. 2015; Schultheiss et al.
Table 2. Regression coefficients and significance levels. Positive values of the regression coefficient $b$ imply an Odds Ratio $> 1.0$, or being outside the potential therapeutic window, negative values imply an Odds Ratio $< 1.0$, or being within a potential therapeutic window (and of 0 would imply an Odds Ratio = 1, or no association).

| Predictor factor                               | Regression coefficient ($b$) | Significance level ($p$) | Odds ratio | Odds ratio |
|------------------------------------------------|-------------------------------|--------------------------|------------|------------|
| Intercept                                      | 2.094                         | 0.6149                   | 8.118      |            |
| Patient age                                    | 0.034                         | 0.5033                   | 1.035      |            |
| Gender                                         | 1.225                         | 0.4059                   | 3.403      |            |
| Visual acuity                                  | 0.045                         | 0.9731                   | 1.046      |            |
| Relative retinal thickness increase (RRTI)     | $-0.285$                      | $0.0014$                 | 0.7519     |            |

Bold indicates significance level.

In analogy to the ischaemic stroke, RRTI could be used in CRAO to identify patients within the 4.5-hr time window with a remarkably high diagnostic accuracy (100% sensitivity and 94.3% specificity). The RRTI differs a lot between each patient after the first 10 hr have passed (see Fig. 1). In ischaemic stroke, the existence of fast and slow progressors is well established (Rocha & Jovin 2017). According to the individual pathophysiology, the infarct growth of the ischaemic core into the penumbral area is modulated by collateral blood flow and therefore progresses at different speeds (Liebeskind 2005). The RRTI could resemble the ischaemic damage and vice versa a low RRTI could indicate retinal viability. Consequently, using RRTI as surrogate marker the therapeutic window for IVT could be tailored to each individual pathophysiology rather than to a standardized time window. If the therapeutic window is extended or the symptom onset is unknown, MRI should be performed prior to IVT to detect silent ischaemic lesions in order to prevent haemorrhagic transformation of infarcted brain tissue. Silent ischaemic lesions exist in 25–37% of CRAOs (Helenius et al. 2012; Lavin et al. 2018; Fallico et al. 2019).

The individual pathophysiology could also be the reason, why CRAOs show a very variable outcome. Schmidt et al. (2002) and Ahn et al. (2015) graded CRAO into three stages (incomplete, subtotal, total) according to visual acuity, clinical and fluorescein angiography findings (such as residual perfusion) and the amount of retinal thickening and found a significant correlation between the retinal thickness and final visual acuity (Schmidt, Schulte-Mönting & Schumacher 2002; Ahn et al. 2015). We are in complete agreement that a higher graded RAO induces higher RRTI and results in an inferior visual prognosis (Ahn et al. 2015). However, the current literature is ambiguous with conclusions on whether retinal thickness in acute CRAO can be used as a prognostic factor for the final visual acuity (Schmidt, Kube & Feltgen 2006; Shinoda, Yamada & Matsumoto 2008; Ikeda & Kishi 2010; Chen, Hwang & Chen 2011; Ahn et al. 2015; Chen et al. 2018). Due to the fact that studies report increasingly promising results for early IVT administration within 4.5 hr after ischaemia onset, it is important to identify these patients fast and with high certainty (Hattenbach et al. 2008; Schrag et al. 2015; Schlutheiss et al. 2018). Here, OCT-based retinal thickness analysis, with a sensitivity of 100% and a specificity of 94.3%, could become an important tool to test whether a patient is within the therapeutic window of 4.5 hr even when the symptom onset is unknown.

In ischaemic stroke patients with unknown symptom onset receive an MRI to evaluate whether those patients are within the 4.5-hr time window. A mismatch in visibility of an acute ischaemic lesion between diffusion-weighted imaging (DWI) MRI and fluid-attenuated inversion recovery (FLAIR) MRI is used to decide whether the patient is eligible for IVT. A multicentre observational study investigating the potential of this method to identify patients within a 4.5-hr time window after symptom onset yielded a sensitivity of 62%, specificity of 78%, a positive predictive value of 83% and a negative predictive value of 54% (Thomalla et al. 2011). These results were the basis for the multicentre, randomized placebo-controlled WAKE-UP trial, which showed that the patients treated with IVT according to the DWI-FLAIR mismatch had a significantly better functional outcome compared to the placebo group (Thomalla et al. 2018).
2016). Importantly, all of these studies fail to respect the temporal dimension of retinal thickness increase as OCT scans were performed mostly at different times ranging from 1 hr to up to 14 days after ischaemia onset, which may be one reason for contradictory conclusions (Schmidt, Kube & Feltgen 2006; Shinoda, Yamada & Matsumoto 2008; Ikeda & Kishi 2010; Chen, Hwang & Chen 2011; Ahn et al. 2015; Chen et al. 2016). Retinal oedema may still increase after the OCT scan was recorded depending on the timing of primary presentation. We consider that possibly the retinal thickness that has increased up to the time of OCT imaging correlates with permanent visual acuity deficits whereas the amount of RRTI that is needed to reach the plateau correlates to the penumbra, the nerve fibres that may benefit from a reperfusion therapy (McLeod & Beatty 2015). Future analyses need to consider the temporal changes in RRTI, especially within the first 10 hr. Nonetheless, the severity of CRAO is not of significant importance in the urgent situation, as treatment should be offered without further delay, independent of the CRAO stage. Also, the relevance of staging CRAOs into incomplete, subtotal and total may be less relevant in acute CRAO as our results show a clear correlation between symptom onset and RRTI with a remarkably high statistical accuracy within the first hours.

Besides the RRTI also the optical intensity ratio could also be utilized as a potential biomarker for retinal viability, visual outcome and to determine the CRAO onset (Chen et al. 2016). Also, this biomarker requires further investigations in future prospective trials.

Additionally, RRTI could be used to verify the patient’s statement concerning the time point of symptom onset (see Fig. 3). This is an important aspect, because sometimes, patients state the wrong time of symptom onset as monocular vision loss is perceived. Therefore, generally, a great difference between the reported and the actual CRAO onset is possible. Only if the patients report about a visual loss with both eyes open, the time of symptom onset is reliable. Consequently, the OCT can objectify the patient’s information of symptom onset, and if a great discrepancy exists (e.g. short time since symptom onset but massive retinal oedema), the patient needs to be questioned again to narrow down the time of symptom onset as far as possible.

Further, it needs to be emphasized that using the RRTI is a very straightforward tool, which is independent from the OCT device, whereas at the same time sidesteps problems of OCT-determined absolute RTI where refraction, axial length, age and gender and the OCT device itself may interfere as a possible bias. Generally, absolute RTI shows a broad interindividual range, making absolute RTI useless for the presented purpose. Concerning the acute management, it has to be stated that an OCT can be acquired very quickly within just a few minutes and therefore from our point of view should be performed on all patients with CRAO in the future. Performing focused OCT scans (macular scan) is quickly accomplishable without pupil dilation not only by ophthalmologists, but also by medical assistance personnel, emergency physicians as OCT devices are increasingly fully automated. Possibly, if systemic fibrinolysis proves beneficial, neurologists could as well be trained to speed up the management in patients with acute monocular vision loss.

As the data of this study were collected retrospectively, this is one of this study’s major limitation. Thus, the results of this publication are preliminary and will soon be further investigated in a prospective randomized designed study. Also, it should be considered that a potential selection bias could have influenced our results. Due to the nature of this study’s aim to investigate the correlation of two variables (time since ischaemia onset and RRTI), we were only able to analyse patients with known time of ischaemia onset to draw conclusions from RRTI and to validate OCT-based retinal thickness analysis for the presented purpose. Thus, patients with unknown ischaemia onset or missing OCT scans from primary presentation could not be respected in this study. However, we used data collected over 10 years at two tertiary care facilities, which to some extent should counteract this bias. This is the first study showing the temporal dynamics and a clear correlation between RRTI and ischaemia onset in acute CRAO up to 48 hr. Also, it needs to be mentioned that the concept of RRTI probably will not be
reliable when employed in patients who already are in a situation of monocular vision prior to the event of acute CRAO or feature a medical history with pre-existing retinal pathologies, such as age-related macular degeneration or epiretinal gliosis. Moreover, the fact that retinal thickness was measured manually may interfere with the objectiveness of our results, but automatic retinal thickness measurements by many OCT devices are not performed perpendicular to the retinal pigment epithelium resulting in inaccurate measurements. Especially in very myopic patients, this aspect is aggravated. Also, scans of retinas with CRAO show severe morphological changes (also CRAO) often causing errors in automatic segmentation by OCT software.

In order to entirely use the potential of OCT-based retinal thickness analysis and to implement the presented method into the clinical setting, a beneficial reperfusion therapy needs to be found. Future randomized controlled trials on the efficacy of early IVT (or any other reperfusion therapy) in CRAO should perform OCT imaging in the acute phase on all patients to ratify its clinical potential in determining ischaemia onset and deciding on IVT eligibility. Additionally, it needs to be evaluated whether RRTI may also be used as a negatively correlated biomarker for visual recovery potential (low RRTI, short ischaemia, better prognosis).

Currently, we are aware of one ongoing randomized placebo-controlled trial dealing with early IVT within 4.5 hr after symptom onset [THEIA study (NCT03197194), France] and a second one starting in October 2020 in Germany (REVISION study). If early IVT within 4.5 hr proves beneficial, OCT scans will not only be useful for the documentation of retinal damage – it could be the key instrument in the decision-making of IVT eligibility in patients with unknown ischaemia onset and therefore imply a potentially sight saving therapy.

Conclusion

In conclusion, this study introduces OCT-based retinal thickness analysis as a novel tool to determine ischaemia onset in CRAO patients, which serves to assess IVT eligibility, especially when ischaemia onset is unknown. Given that a future randomized controlled trial proves favourable outcomes for a reperfusion therapy, we hypothesize that this method could become a key instrument with a high accuracy (100% sensitivity, 94.3% specificity).

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Correspondence: Maximilian Schultheiss
Department of Ophthalmology
University Medical Center Hamburg-Eppendorf
Hamburg
Germany
Tel: +49 (0) 40 7410 - 52301
Fax: +49 (0) 40 7410 - 42301
Email: maximilianschultheiss@gmail.com