Test performance of Optical Coherence Tomography Angiography in Detecting Retinal Diseases: A Systematic Review and Meta-analysis

Running Title: Optical Coherence Tomography Angiography Review

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Abstract

Objective: To investigate the diagnostic accuracy of optical coherence tomography angiography (OCTA) in detecting vascular characteristics of chorio-retinal disease.

Methods: Evidence acquisition: We searched Web of Science, Scopus and Medline by the citation of references and complemented these electronic searches by checking the list of references of included and review articles. Screening, selection, assessment and extraction was performed in parallel by two authors.

Results: Evidence synthesis: Systematic Review and exploratory meta-analysis. The ten studies that contributed to the meta-analysis enrolled 440 eyes and allowed constructing ten two-by-two tables. The tables reported on detection of choroidal neovascularisation (CNV) in eyes suffering from either age-related macular degeneration (4), central serous chorioretinopathy (2), myopia (2), foveo-macular vitelliform dystrophy (1) or a mixed cohort suffering from multiple retinal diseases (1). Of the ten studies, six used a cohort and four a case-control design. We found a pooled sensitivity of 0.90 (95% confidence intervals (CI); 0.82-0.95) and a pooled specificity of 0.97 (95% CI; 0.89-0.99). Corresponding positive and negative likelihood ratios were 32.3 (95% CI; 7.4-141.6) and 0.10 (95% CI; 0.06-0.20), respectively. No pooling was possible for retinal vascular parameters of diabetic retinopathy, polypoidal choroidal vasculopathy or detection of CNV activity.

Conclusions: The results of highly biased and heterogeneous studies assessing the diagnostic performance of OCTA highlight the need for further analyses of methodologically sound and sufficiently sized clinical evaluations.

Introduction

The recently introduced optical coherence tomography angiography (OCTA) technology has been proposed as a game changer for the detection and monitoring of various chorio-retinal diseases including age-related macular degeneration and diabetic retinopathy[1]. The OCTA assesses structural and functional information of the retinal and choroidal circulation in a non-invasive manner, thereby providing data that otherwise requires two additional tests; the invasive indocyanine green angiography (ICGA) and fluorescein angiography (FA). In addition, OCTA allows a depth-resolved assessment of vascular characteristics within individual plexus (superficial and deep capillary plexus, choriocapillaris) and retinal segments (inner and outer retina) in chorio-retinal pathologies.

Today, invasive technologies such as FA or ICGA are still considered the gold standard for the detection of vascular characteristics associated with chorio-retinal diseases[2-4], despite that repeated use is limited due to the risk of adverse events (i.e. allergic reactions), contraindications, and time- as well as cost-expenses[5-7]. These downsides triggered the desire of a quick, non-invasive test to replace invasive time- and labour-intensive imaging techniques.

Broad application of OCTA technology is not yet standard in daily medical routine for several reasons. The analysis of these images is time-consuming and sometimes even requires manual segmentation in some cases. Other disadvantages of OCTA include the limited field of view, the inability to depict leakage and sub-threshold blood flow and the occurrence of movement and shadowing artefacts. Since 2013 several groups have investigated the diagnostic properties of OCTA. However, the current body of evidence is highly fragmented, scattered and not easy to access due to inconsistent indexing in electronic databases. We are unaware of any systematic review presenting and summarising the diagnostic value of OCTA in assessing vascular characteristics in chorio-retinal diseases. In this paper, we therefore

conducted a comprehensive review investigating the evidence on the potential of OCTA in the diagnostic work-up of chorio-retinal diseases and the extent to which it could replace FA in clinical routine.

Methods

This systematic review was performed following the recommendations of the PRISMA statement[8].

Literature Search

We applied our search strategy without application of language restrictions on Web of Science (by citation of reference), Scopus (from inception until June 12th, 2017) and MEDLINE (PubMed interface). The applied search strategy is available on request.

Eligibility Criteria

Eligibility criteria were the availability of primary data allowing to calculate test performance characteristics. For an exploratory meta-analysis, we accepted FA as reference standard classifying absence or presence of choroidal neovascularisation (CNV).

Study Selection, Data Extraction, and Quality Assessment

We assessed the methodological quality of included publications as proposed by previously published principles[9]. Following recommendations of Whiting and colleagues, we did not use a summary score for ranking purposes[10]. For the quality assessment, we scrutinized methods of patient selection, data collection, descriptions of the OCTA and the reference test(s). We considered blinding to be present, if the person(s) classifying a vascular characteristic associated with a chorio-retinal disease (reference test) was unaware of the OCTA examination findings (index test) and vice versa. Two of the authors assessed papers and extracted data by a standardized form which is available on request. A senior epidemiologist was consulted when discrepancies occurred.

Statistical analysis

Contingency tables consisted of true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) results. Sensitivity was calculated as TP / (TP + FN) and specificity was calculated as TN / (FP + TN). We used a unified model that was developed for the meta-analysis of diagnostic accuracy studies and plotted summary receiver operating characteristics (ROC) curves[11]. The indication of 95 percent prediction and confidence region on the ROC figure provided estimates of average sensitivity and specificity across included studies.

The minimum number of studies to perform a meta-analysis for a specific vascular characteristic was five. Consequently, a meta-analysis was not feasible for retinal vascular parameters of diabetic retinopathy (DR) (four studies), polypoidal choroidal vasculopathy (PCV) (one study) and detection of CNV activity (two studies).

We calculated likelihood ratios from the estimated pooled sensitivities and specificities and did not pool negative and positive likelihood ratios, following published recommendations[12].

We performed statistical analyses by using the Stata 14.2 statistical software package (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Study selection

After removing duplicates, electronic searches retrieved 1604 records that were screened by title and/or abstract. Subsequently, we excluded 1556 articles since they did not assess diagnostic accuracy of OCTA, contained no original data or did not investigate chorio-retinal diseases. Finally, forty-four articles were considered for inclusion and therefore read in full text. For the systematic review, 17 studies fulfilled the inclusion criteria. No further studies were included after screening the science citation index database or reference lists.
Out of the seventeen studies, ten qualified for the inclusion into the meta-analysis[13-22].
We outlined the study selection process in **Figure 1.**

Patients' characteristics

Systematic Review Seventeen studies that were included into the systematic review enrolled 996 eyes. The study population was heterogeneous regarding diagnosis, assessed chorio-retinal vascular characteristics and treatment status. Two studies evaluated chorio-retinal vascular characteristics associated with central serous chorioretinopathy (CSCR)[13, 16], seven with age-related macular degeneration (AMD) or PCV[14, 17, 18, 22-25], two with myopia[20, 21], one with foveomacular vitelliform dystrophy (FVD)[19] and one with a mixed cohort of patients[15]. Four studies investigated chorio-retinal vascular characteristics in DR, such as non-perfusion area, vessel density, micro-aneurysm and FAZ[4, 26-28].
Among studies investigating eyes with AMD and reporting the proportion of women, percentages ranged from 37.7 to 53.4 percent.

Meta-analysis Ten studies that were included into the exploratory meta-analysis enrolled 440 eyes. The study population was heterogeneous regarding diagnosis, assessed CNV type

and treatment status. Four studies evaluated CNV detection in AMD[14, 17, 18, 22], two in CSCR[13, 16], two in myopia[20, 21], one in FVD[19] and one in a mixed cohort of patients[15]. Three studies investigating CNV in AMD, myopia and CSCR reported on the proportion of CNV type (in total 77 eyes). Type I was found in 13 eyes (17%), type II in 45 eyes (58%) and a mixed type I and II pattern in 19 eyes (25%)[13, 18, 20]. In those five studies that described previous treatment of CNV, 151 eyes (82%) were treatment-naïve, 30 eyes were treated by anti-VEGF (16%) and 4 eyes (2%) had retinal laser treatment.

Among studies investigating CNV detection and reporting the percentage of women ranged from 28.0 to 85.0 (mean 49.5%).

We summarized patients' characteristics in **Table 1**.

Methodological characteristics

Systematic Review Of ten cohort studies, three studies were prospective, six retrospective cohorts and one study did not specify the type of design. Another seven studies (29%) used a case-control design. Within nine out of seventeen studies (53%), patients were included in a consecutive manner. Eight studies (47%) reported on the percentage of eyes that were excluded due to the provision of poor scanning quality and artefacts: the interquartile range was 9.8% to 20.6%, the total range reached from 2.7% to 33.3%[4, 16-18, 20, 21, 23, 25].

Meta-analysis One study (10%) investigated a prospectively recruited cohort with a consecutive patient enrolment and five cohort studies were conducted retrospectively. The remaining four studies (40%) had a case-control design. Overall, seven studies (70%) enrolled patients in a consecutive manner. Five studies reported on the percentage of eyes that were excluded due to the provision of poor scanning quality and artefacts: the interquartile range was 5.8% to 12.3%[16-18, 20, 21].

Methodological characteristics assessed by QUADAS-2 are summarized in **Table 2**[10]

Reference Tests and Index Test devices

Systematic Review For classification of chorio-retinal vascular characteristics, multimodal imaging (eight studies, 47%) and FA alone (six studies, 35%) were used most often. In all studies multimodal imaging included FA and/or ICGA while additional OCT or fundus photography were less frequently used.

In twelve studies (71%), the AngioVue software was used on the RTVue XR Avanti spectral domain (SD)-OCT device (Optovue, Fremont, CA) to perform OCTA between 2014 and 2015. Other studies performed OCTA on Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), on AngioPlex CIRRUS HD-OCT model 5000 (Carl Zeiss Meditec, Inc., Dublin, USA) or on DRI OCT Triton (Topcon) prototypes. Twelve studies allowed additional manual adaptation of the segmentation boundaries, if necessary[4, 13-15, 17-19, 21, 23-25, 28].

Meta-analysis For classification of chorio-retinal vascular characteristics, multimodal imaging (five studies, 50%) and FA alone (five studies, 50%) were used.

In eight studies (80%), the AngioVue software was used on the RTVue XR Avanti SD-OCT device (Optovue, Fremont, CA) between 2014 and 2015 to perform OCTA. The six studies that described inner and outer boundaries of outer retinal segmentation, reported heterogeneous settings. The inner boundaries were either set on the outer aspect of the inner nuclear layer (INL), at the outer aspect of the outer plexiform layer (OPL) or at the exact level of the OPL. The outer boundaries were either set anterior to or at the exact level of the Bruch's membrane (BM). Within three studies, slabs of the choriocapillaris were also evaluated for CNV detection. Seven studies allowed additional manual adaptation of the segmentation boundaries, if necessary[13-15, 17-19, 21].

Table 3 shows the reference tests that were used for classification.

Test performance

Ten studies reporting on CNV detection by retinal specialist assessing OCTA images allowed calculating test performance parameters. Sensitivity ranged from 0.50 to 1.00 and specificity ranged from 0.68 to 1.00. Within the five studies that reported on CNV detection in AMD sensitivity ranged from 0.50 to 1.00 and specificity ranged from 0.68 to 1.00. The sensitivity of two studies reporting on the assessment of the FAZ within DR patients ranged from 0.68 to 0.91 and specificity ranged from 0.67 to 0.76. We provide detailed results in **Table 3.** Hierarchical summary ROC curves of studies assessing CNV detection are depicted in **Figure 2a** across chorio-retinal diseases and in **Figure 2b** for AMD.

Results from the HSROC-Analysis

In general, the pooled sensitivity of studies that assessed CNV detection was 0.90 (95% confidence intervals (CI); 0.82 to 0.95) and the pooled specificity was 0.97 (95% CI; 0.89 to 0.99). The corresponding positive and negative likelihood ratios were 32.3 (95% CI; 7.4 to 141.6) and 0.1 (95% CI; 0.06 to 0.20), respectively.

The pooled sensitivity of studies assessing CNV detection in AMD was 0.88 (95%CI; 0.71 to 0.96) and specificity was 0.96 (95%CI; 0.74 to 1.00). The corresponding positive and negative likelihood ratios were 22.7 (95%CI; 2.73 to 188.2) and 0.12 (95%CI; 0.04 to 0.34).

Discussion

Main findings

An exploratory meta-analysis of CNV detection in OCTA scans, assessed in a small patient sample provided promising results for both, sensitivity and specificity. However, four studies used a diagnostic case-control design which is appropriate for "proof of concept" evaluations, but has been claimed to exaggerate index test performance[9]. To perform a meta-analysis for vascular characteristics associated with DR, data were too scarce.

Results in the light of existing literature

Over the past years, research on OCTA has grown exponentially, but to the best of our knowledge, this is the first quantitative and comprehensive assessment of studies investigating the diagnostic value of OCTA. However, there are several narrative reviews on clinical applications and technological characteristics of OCTA available[29-34].

This systematic review shows promising results of OCTA but it remains unclear to what degree the reported diagnostic accuracies of the heterogeneous and highly biased studies can be transferred into clinical practice. In a personal communication with one of the authors we learned that some OCTA studies involved many hours of post hoc manual segmentation work which is not applicable in daily medical routine. Also, it is unknown, how uniformly and accurately manual segmentation was performed within the studies included into this systematic review.

Recently, Hwang and colleagues stated that OCTA could be a promising candidate for monitoring the microvascular status in DR[28]. On the other hand, detection of microaneurysms was shown to be significantly lower compared to FA. The study by Salz and colleagues corroborated these findings[35]. Interestingly, several authors stated that the OCTA was superior to FA in the assessment of FAZ. However, the sensitivity of automatic FAZ

delineation varied substantially among included studies depending on the investigated plexus and measurement approach[26, 27, 35]. Also, estimates for diagnostic accuracy of OCTA to detect CNV in diseases that are typically associated with type 2 CNV membranes, such as i.e. myopia, were not higher.

Strength and limitations

This systematic review applied state of the art methodology[11]. Due to the limited number of studies (and studies per clinical subgroup) separate meta-analyses were not feasible for all clinical strata. For the same reason, we also refrained from exploring heterogeneity statistically. We discovered substantial heterogeneity by clinical (diagnosis, assessed CNV type or proportion of treatment-naïve cases) and methodological variation (the quality of reporting and the used study design) between included studies. Arguably, bias was introduced into our results by mixing effects found in cohorts and case-control studies[9]. Most certainly, heterogeneity was also introduced by variations in hard- and software (i.e. variations in segmentation boundaries, occurrence rates of artefacts and in approaches to automated analyses of chorio-retinal vascular parameters) that was used to perform OCTA. Another source of substantial bias must have been introduced by the fact that the investigators were presented with conventional cross-sectional OCT scans alongside *en face* OCTA images. Particularly in the case of CNV detection, conventional cross-sectional OCT scans would have been highly suggestive of CNV. Since studies included into this systematic review were not designed to provide conclusive and clinically useful results, they did not conduct a priori sample-size calculations which would be required in diagnostic accuracy studies[36].

We excluded several papers comparing OCTA imaging with established reference tests due to the lack of data allowing the construction of two-by-two tables. In this respect, it may be justified to repeat these analyses when additional data are available. Finally, in view that four

out of ten studies included in the meta-analysis used a diagnostic case-control design, we believe that the pooled results must be interpreted very cautiously.

Implications for practice

To date, OCTA has not yet found its place in clinical practice. The degree to which OCTA will be established and ultimately change practice in the future may be decided by its ability to provide robust information on quantifiable and reliable vascular parameters that are comparable across the devices and software. Automated and standardized segmentation that is highly accurate even in patients suffering from chorio-retinal diseases will be needed to use OCTA in the clinical routine. In this context, it will also be vital to seek consensus on viable terminology of OCTA associated vascular parameters and segmentation boundaries across different devices and software. Further, standardised protocols allowing a rapid image acquisition in busy clinics, even in patients with poor fixation are needed. Even though the proportion of OCTA images providing sufficient scanning quality for grading reported in this systematic review was comparable to FA, this is not yet consistent with real-life clinical experience.

For its application in the management of patients with DR, future scanning protocols with higher speed will hopefully allow high quality depiction of the retinal periphery.

For the application of OCTA in CNV detection, it will be crucial to balance the trade-off between high scanning sensitivity and motion artefacts. High sensitivity will be required for detection of CNV in treatment-naïve patients in which CNV are often not yet properly arterialized and therefore show unorganised and hardly detectable blood flow. This also applies to patients with large pigment epithelial detachments.

Implication for further research

Only recently, the OCTA technology has entered clinical ophthalmological practice. This may be one reason for the limited body of evidence assessing the diagnostic usefulness of OCTA. In clinical routine, OCTA is most commonly used in combination with other imaging techniques. As a result, studies are warranted that will investigate these combined approaches and thereby provide more practical data than single-modality outcomes. Studies included into this systematic review, had insufficient reporting quality. We call for reasonably sized prospective studies providing information as proposed by the STARD statement. Future studies will also need to study possible sources of heterogeneity such as varying conventions for segmentation and terminology. OCTA may be a useful case to apply machine learning algorithms to detect those parameters with as strong association with chorio-retinal diseases. However, these studies too, will require large samples of validly collected data allowing a sound derivation and validation of these algorithms.

In view that the high number of artefacts in OCTA images lead to a substantial amount of exclusions within per protocol analysed studies, it will be essential for future studies to define a strategy how to deal with them in the analysis (i.e. sensitivity analysis) and present this procedure in the publication.

Conclusion

Findings from preliminary and heterogeneous studies provide promising characteristics of test performance for OCTA assessing vascular parameters associated with chorio-retinal diseases. OCTA may therefore be a viable alternative in patients suffering from chorio-retinal vascular disease and allergic reactions to fluorescein. However, it will still need to be established to what extent these results transfer to daily medical routine.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Titles and legends to figures

Table 1 Study characteristics, patient population.

Table 2 Methodological characteristics assessed by QUADAS-2.

Table 3 Test performance characteristics.

Figure 1 Study flowchart.

Figure 2a Hierarchical summary ROC curve of studies assessing CNV detection by OCTA.

Figure 2b Hierarchical summary ROC curve of studies assessing CNV detection by OCTA within AMD patients.