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Retinal sensitivity above macular neovascularization under anti-VEGF therapy in exudative neovascular age-related macular degeneration

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Abstract

Purpose Growth of macular neovascularization (MNV) associated with development of complete retinal pigment epithelial and outer retina atrophy (cRORA) been observed in eyes neovascular age-related macular degeneration (nAMD) under effective anti-vascular endothelial growth factor (VEGF) therapy. We aimed to evaluate the influence of the presence of MNV on the sensitivity of the overlaying retina both in patients with or without cRORA and to generate hypotheses about their association.

Methods Pilot study on nAMD patients undergoing long-term anti-VEGF therapy that had also undergone microperimetry testing. Area of MNV and, if present, associated cRORA were identified on optical coherence tomography (OCT) volume scans and transposed onto en-face near-infrared images. Mesopic microperimetry performed at the same visit was then superimposed. Retinal sensitivity above the MNV and the surrounding retina were compared, excluding areas of cRORA.

Results Twenty-six eyes (19 f, 7 m; age 79.3 ± 5.7 y; fu 4.0 ± 1.8 y; 7.4 ± 2.5 inj./y) were classified into a no cRORA ($n = 11$) and a cRORA group ($n = 15$). In the no cRORA group, mean retinal sensitivity above the MNV did not differ from the surrounding retina (20.9 ± 2.8 vs. 22.0 ± 2.4, $p = 0.33$), while in the cRORA group, a lower sensitivity above the MNV in comparison to the surrounding retina was observed (16.2 ± 3.4 vs. 19.9 ± 2.0, $p = 0.001$).

Conclusion In the absence of cRORA, retinal sensitivity above the MNV did not differ significantly from that of the surrounding retina. These results could indicate a possible nutritional function of the MNV to the overlying retina in cases where no cRORA is present.

Keywords Exudative nAMD, anti-VEGF therapy, Macular atrophy (cRORA), Retinal function, Microperimetry

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Introduction

Intravitreal antiangiogenic therapy is the most effective treatment for exudative neovascular age-related macular degeneration (nAMD) at present [1]. After the initial loading doses, an improvement in best-corrected visual acuity (BCVA) in eyes with macular neovascularization (MNV) associated with a decrease in mean central foveal thickness on optical coherence tomography (OCT) is often observed. In the long-term, a stabilization of both function and fluid distribution can be achieved using different treatment strategies. These include pro re nata (PRN) treatment patterns such as the IVAN ("Inhibit VEGF in Age-Related Choroidal Neovascularization Trial"; for details see "methods") or CATT ("Comparison of Age-Related Macular Degeneration Treatments Trials") scheme as well as Treat-and-Extent (T&E) treatment algorithms [2–6].

As reported previously [7], we observed that even when effective anti-VEGF therapy successfully controls limits exudation, growth of the MNV during follow-up can be observed in many patients [8]. A similar growth was seen in type 1 MNV without accompanying exudation or adverse visual effects which was called "quiescent" MNV [9–11]. Some researchers propose that in cases where anti-VEGF therapy successfully limits exudation, the persistence or expansion of MNV might even serve as a nutrient source for the overlying retinal pigment epithelium (RPE) and retina [11, 12]. This would mean that MNV growth could help stabilize vision rather than contribute to its deterioration.

To analyze the influence of MNV on the function of the overlying retina, this study investigated retinal function above the MNV under long-term anti-VEGF therapy and compared it to retinal sensitivity outside the area of MNV using microperimetry. In light of several long-term studies [2–4, 6, 13–16] showing that macular atrophy (defined as complete RPE and outer retina atrophy (cRORA) according to the Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration (CAM) [17]) can develop and potentially affect retinal function, presence of cRORA was also assessed and function was analyzed separately for both, the group with and without cRORA.

Methods

Patients and imaging

In this pilot study to generate hypotheses, patients under successful long-term anti-VEGF therapy for nAMD were offered to undergo additional microperimetry and spectral domain (SD) OCT volume scans at the same visit at the Department of Ophthalmology, St. Franziskus Hospital Muenster, Germany, between 05/2021 and 05/2022. Only patients who agreed to the additional examination, had a minimum duration of prior anti-VEGF treatment of 2 years, and no sub- or intraretinal fluid at the time of imaging were included. Before the evaluation of retinal sensitivity, a quality analysis of the microperimetry was performed and eyes with malfixation or MNV larger than the examination field of the microperimetry were excluded. In cases of bilateral nAMD, the eye that first developed MNV and thus had longer follow-up was included in the analysis.

All patients gave their written informed consent to anti-VEGF therapy and microperimetry evaluation. The study was approved by the local Institutional Ethics committee (2017-033-f-S) and adhered to the tenets of the Declaration of Helsinki for research involving human subjects. The data was anonymized and accessed for research purposes starting in 2023.

The diagnosis of nAMD was confirmed based on multimodal imaging acquired using Heidelberg Retina Angiograph 2 (HRA2) and Heidelberg Spectralis spectral domain-OCT (both Heidelberg Engineering, Heidelberg, Germany) including obligatory fundus fluorescein angiography (FFA). Patients were treated according to a PRN protocol as described in the IVAN study, with an initial loading dose of three injections followed by monthly control visits and retreatment with three consecutive monthly injections if "new activity", such as new fluid on OCT or new bleeding, was observed [18]. Treatment was performed with either bevacizumab, ranibizumab or aflibercept at the treating physician's discretion.

Microperimetry testing

Microperimetry testing using mesoptic MAIA microperimetry was performed 4 weeks after the last anti-VEGF injection in cases where no intra- or subretinal fluid was detectable to ensure this did not impact microperimetry findings. Pupils were dilated prior to the examination using 2.5% phenylephrine and 0.5% tropicamide to facilitate fundus tracking and patients underwent a short practice microperimetry test to accustom them to the procedure. Testing was performed with the preset 4 – 2 dB staircase strategy. The stimulus size was 0.43° (Goldmann III). The test grid consisted of 68 stimuli (achromatic stimuli, 400–800 nm) covering the central 18° of the retina [19].

Data annotation

Spectral-domain OCT imaging was performed on the day of microperimetry testing to assess anti-VEGF treatment effect. The area of MNV and, if present, cRORA were identified on OCT volume scans as previously described [8, 20]. In brief, areas of MNV and cRORA were identified based on OCT images and manually transposed onto en-face near-infrared reflectance images. MNV subtype was classified as type 1–3 based on multimodal imaging according to the latest Consensus Nomenclature for

reporting nAMD [21]. This annotated en-face image was then mapped onto the microperimetry grid by reducing the transparency of the en-face image and using landmarks, such as large vessels and the optic disc, to manually align both images. This transposition was performed using GIMP (version 2.10, www.gimp.org). All spots within the annotated MNV area and all those outside were added up separately and divided by the total number of spots to calculate the mean retinal sensitivity above the MNV and the surrounding retina as published previously [22]. To differentiate the influence of associated areas of cRORA, eyes were divided into two groups according to the presence of cRORA: the "cRORA" group and the "no cRORA" group. In addition to the absence or presence of cRORA we graded eyes with cRORA into subfoveal or extrafoveal extension and the mean retinal sensitivity in eyes with cRORA was calculated using the test points above the MNV outside the atrophic areas. Cases in which the whole area of microperimetry was covered by MNV were excluded from the analysis.

To assess other morphological criteria that could explain a difference between "cRORA" and "no cRORA" groups, central retinal thickness was measured by manually realigning the automated OCT thickness measurements provided by the Heidelberg Eye Explorer software (Heidelberg Engineering) in a way that only the neurosensory retina, and no MNV components were included in the measurements. The presence of sub- or intraretinal fluid within the central ETDRS subfield around the foveal centre point was manually assessed for each patient.

Table 1 Baseline characteristics of the whole cohort, and "crora" and "no cRORA" groups. P-values to compare between group differences were calculated using student's t-test. SD = standard deviation, cRORA = complete retinal pigment epithelial and outer retinal atrophy, logmar = logarithm of the minimum angle of resolution, mnv = macular neovascularization

	whole cohort	cRORA group	no cRORA group	*p*-value groups
no of eyes	26 (100%)	15 (58%)	11 (42%)	
age of onset (years ± SD)	75.4 ± 5.6	76.7 ± 5.5	73.5 ± 5.6	0.16
age at microperimetry (years ± SD)	79.3 ± 5.7	80.9 ± 4.6	77.0 ± 6.5	0.10
no of injections (mean ± SD)	28.0 ± 13.4	27.5 ± 13.0	28.7 ± 14.6	0.82
BCVA (logMar) (mean ± SD)	0.51 ± 0.31	0.63 ± 0.35	0.35 ± 0.16	0.01
MNV type (1–3)				0.61
type 1	9 (35%)	5 (33%)	4 (36%)	
type 2	14 (54%)	9 (60%)	5 (45%)	
type 3	3 (12%)	1 (7%)	2 (18%)	
central retinal thickness (µm) (mean ± SD)	242 ± 26	226 ± 21	267 ± 35	0.003

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) as well as median and range. Statistical analysis for non-parametric parameter was performed using SAS (version 9.4, SAS Institute, Cary, North Carolina, USA) and R (version 4.3.0, https://www.r-project.org). *P*-values below 0.05 were regarded as statistically significant.

Results

In total, 33 eyes were included in this pilot study. During quality adjustment of data and images, 7 eyes had to be excluded, because the superimposed MNV covered the whole area of microperimetry. Therefore, in 26 eyes of 26 patients (19 female, 7 male) the OCT volume scans and microperimetry results were analyzed. Mean age at the time of microperimetry was 79.3 ± 5.7 years and mean follow-up was 4.0 ± 1.8 years. Mean total number of anti-VEGF injections was 28.0 ± 13.4 with a mean of 7.4 ± 2.5 injections/year. Initial MNV subtypes were classified as type 1 in 9 eyes (35%), type 2 in 1 eyes (54%), and type 3 n 3 eyes (12%).

Fifteen eyes (57.7%) showed cRORA at the time of microperimetry ("cRORA" group), while 11 eyes (42.3%) did not ("no cRORA" group). Groups differed significantly in the mean logarithm of the Minimum Angle of Resolution best-corrected visual acuity (logMAR BCVA), which was significantly worse in the "cRORA" group (0.63 ± 0.35) than in the "no cRORA" group (0.35 ± 0.16, $p = 0.01$). In the "cRORA" group, eyes with subfoveal extension of the atrophic lesion had worse BCVA compared to eyes with extrafoveal cRORA (1.02 ± 0.47 vs. 0.49 ± 0.13) even though this difference was not statistically significant ($p = 0.10$), most likely due to the small numbers of eyes in both groups. Central retinal thickness was significantly thinner in the "cRORA" group (226 ± 21 µm) than in the "no cRORA" group (267 ± 35 µm, $p = 0.003$). Presence of sub- or intraretinal residual fluid at the central ETDRS subfield appeared to be lower in the "cRORA" group than in the "no cRORA" group (20% (3/15) vs. 55% (6/11)), even though this difference was not statistically significant ($p = 0.09$). All other factors, such as age of onset of nAMD or number of injections, did not differ significantly between the groups (see Table 1).

In the "no cRORA" group, mean retinal sensitivity above the MNV did not differ from the surrounding retina (20.9 ± 2.8 vs. 22.0 ± 2.4, $p = 0.33$), while in the "cRORA" group, a lower sensitivity above the MNV was observed (16.2 ± 3.4 vs. 19.9 ± 2.0, $p = 0.001$, Fig. 1A, B). Mean retinal sensitivity above the MNV was also significantly lower in the "cRORA" group compared to the "no cRORA" group ($p < 0.001$), while mean retinal sensitivity of the surrounding retina was also slightly lower in the

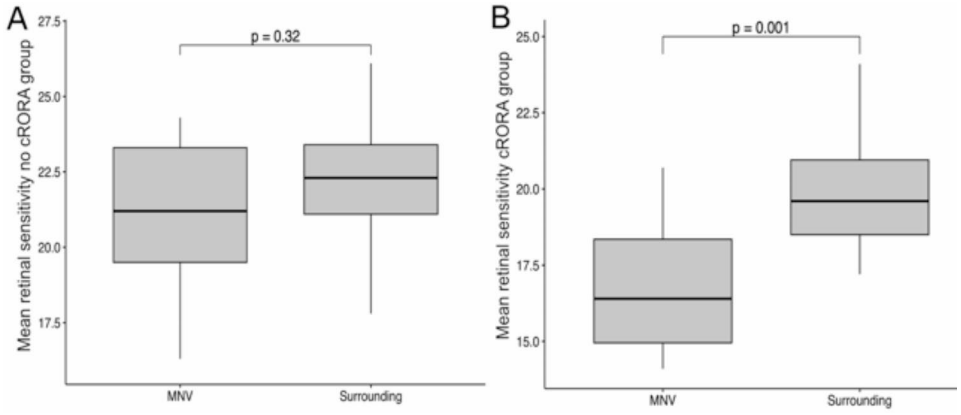

Fig. 1 Comparison of the mean retinal sensitivity above the macular neovascularisation and the surrounding retina for "cRORA" and "no cRORA" groups. No significant difference between mean retinal sensitivity was observed within the "no cRORA" group (**A**, $p = 0.32$), while in the "cRORA" group retinal sensitivity was significantly lower above the MNV than in the surrounding retina (**B**, $p = 0.001$)

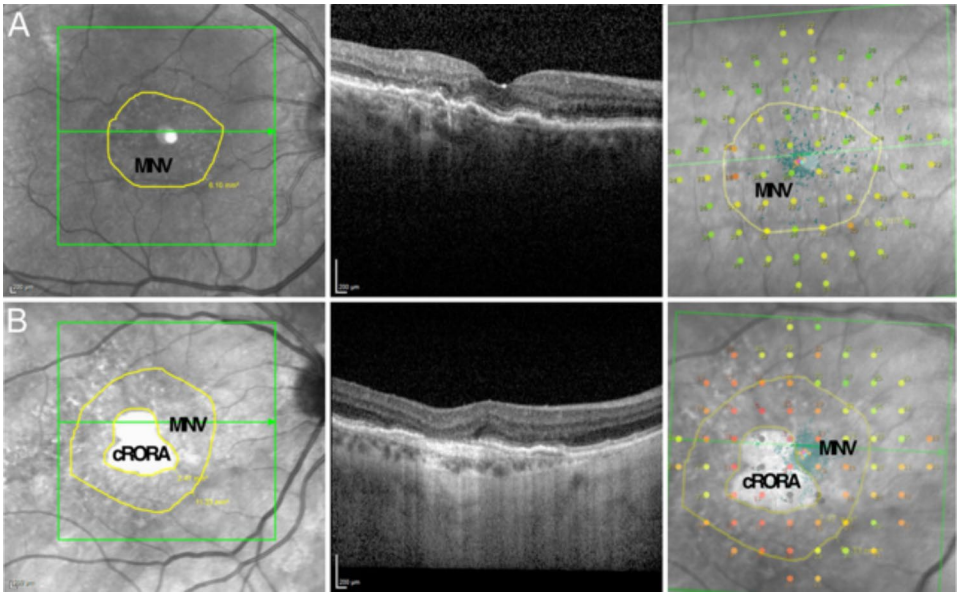

Fig. 2 Imaging examples of near-infrared reflectance images (NIR), optical coherence tomography (OCT), and transposed microperimetry images of patients included in this study. NIR with manually annotated areas of macular neovascularization (MNV) and complete retinal pigment epithelial and outer retina atrophy (cRORA) are shown left, structural OCT images in the center, and transposed microperimetry images on the right. **A**. Right eye showing MNV without cRORA (3 year follow-up with 33 injections). This shows a similar retinal sensitivity above the MNV (18–26 dB) and the surrounding retina (20–26 dB). **B**. Right eye showing MNV with cRORA (3 year follow-up with 22 injections). This shows reduced retinal sensitivity above the MNV (5–23 dB) adjacent to the area of cRORA, where 0 dB was observed. The surrounding retina showed a sensitivity of between 15–25 dB

"cRORA" group ($p = 0.03$). As shown by the example in Fig. 2, retinal sensitivity above the MNV was comparable with the retinal sensitivity of the surrounding in eyes without cRORA (Fig. 2A), while the mean retinal sensitivity was significantly reduced above the MNV in eyes with associated areas of cRORA (Fig. 2B).

Discussion

Our pilot study shows that retinal sensitivity above the MNV can be as good as at the surrounding, unaffected retina. Once cRORA develops, however, retinal sensitivity decreases significantly and is lower in the area of MNV than in the surrounding retina, even though areas of cRORA themselves were excluded from the analysis.

This is in accordance with previous microperimetry studies in nAMD that reported increased retinal sensitivity above MNV after the initial loading phase of anti-VEGF therapy, associated with a maximum of fluid reduction [23–26]. In this study, we used the same method to assess retinal function above MNV after a minimum of 2 years of intense anti-VEGF treatment to assess whether MNV may have long-term effects on retinal health. Our results show that even after a mean prior treatment duration of 4 years, retinal sensitivity above

the MNV was not significantly different from that of the surrounding retina. This supports the concept that MNV may have a somewhat nourishing effect (or at least no immediate detrimental effect) on retinal health and function, if no cRORA develops.

The present study also shows that microperimetry is suitable to analyze macular function spatially and quantitatively and may help to study functional decline in age-related macular degeneration in more detail [27, 28]. The influence of MNV and especially of intra- and subretinal as well as sub-RPE fluid on retinal sensitivity measured by microperimetry has been studied in several clinical studies [23–26]. These studies noticed decreased retinal sensitivity before treatment initiation and an initial increase in retinal sensitivity under anti-VEGF treatment due to fluid resolution. These studies did not, however, compare the functional response above the MNV under long-term anti-VEGF therapy. Given the continuous MNV growth observed even under effective anti-VEGF therapy [8], it becomes an important question whether decrease of retinal function in nAMD is a result of increased vascular permeability of the MNV or the presence of MNV itself. Our results may indicate that, if permeability can be controlled and no cRORA develops, the area above an MNV has a comparable retinal sensitivity to the area outside the MNV.

Only in the "cRORA" group did retinal sensitivity outside the atrophic area decrease in the area of MNV. Accordingly, the "cRORA" group showed a lower BCVA, which was even worse for patients with subfoveal cRORA. The lower retinal sensitivity above the MNV in this group can, however, not be explained by the presence of cRORA itself, since those areas were excluded from the analysis. It can also not be explained by a difference in sub- or intraretinal fluid, since there was no residual fluid in both groups and a lower central retinal thickness compared to the "no cRORA" group. This lower central retinal thickness was found to correlate with reduced BCVA in previous reports [29]. Interestingly, these results echoed the investigations of microperimetry studies in geographic atrophy. These also found a reduced retinal function in the area adjacent to cRORA, which was interpreted as photoreceptor damage preceding cell death [30, 31]. Accordingly, the lower retinal sensitivity in the cRORA group outside the atrophic area may be a sign of photoreceptor dysfunction in areas bordering cRORA. Therefore, in early stages before cRORA occurs, there is no clear reduction in sensitivity above the MNV. In the later stages, there is a clear reduction, and the transformation of the MNV results in atrophy in some parts of the overlying retina and in reduced sensitivity adjacent to these atrophic areas.

Our results may– if confirmed in larger studies - support the hypothesis that MNV development may be a positive biological repair mechanism to increase nutritional supply of the overlying photoreceptors. Only if atrophic areas develop does retinal sensitivity suffer and lead to a decline in function observed in long term follow-up studies in nAMD. The main goals of nAMD treatment should therefore be limitation of fluid exudation using sufficient anti-VEGF therapy and at the same time reduction of cRORA and fibrosis development. Whether this goal can be better achieved using longer lasting or bispecific agents or novel molecules designed to treat geographic atrophy needs to be assessed in future studies.

There are several limitations to our pilot study, whose aim it was to generate hypotheses for future, larger cohorts. Firstly, the number of eyes examined i is small, since microperimetry is a time-consuming examination and is hence not performed on a regular basis. Due to this small cohort size, some between group differences were not statistically significant, which they could have been in a larger cohort. Secondly, there were no microperimetry examinations before cRORA had developed and the conclusions on the adjacent retina in the "cRORA" group may be hypothetical. Also, the sensitivity of microperimetry measurements themself have to be defined in nAMD in more details to specify the functional differentiation of the overlying retina under long term transformation of the MNV and the outer retina. Therefore, the hypothetical considerations of this pilot study that the MNV itself without exudation may be nutritional for the overlying retina remain to be investigated in larger and prospective cohorts.

Author contributions

Laurenz Pauleikhoff: Data analysis and preparation of the manuscript. Martin Ziegler: Data acquisition. Isabel Bachmeier: preparation and review of the manuscript. Siqing Yu: preparation and review of the manuscript. Beatriz Garcia Armendariz: preparation and review of the manuscript. Daniel Pauleikhoff: Data acquisition, data analysis and preparation of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics committee of Westfalia/Germany (2017-033-f-S).

Consent to participate

Consent to participate and results to be published: informed consent to participate was obtained from all of the participants in the study (approved by the Institutional Ethics committee of Westfalia/Germany).

Competing interests

The authors declare no competing interests.

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