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REVIEW ARTICLE

USEFULNESS OF ADAPTIVE OPTICS IMAGING IN OPHTHALMOLOGY

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Abstract: The methods of imaging posterior segment of the eye are still improving. Conventional colour fundus imaging, fluorescein angiography (FA) and optical coherence tomography (OCT) have become routine in clinical practice to examine retinal diseases. This review presents the results of using adaptive optics (AO) to assess microvascular changes and cone parameters in retinal and systemic diseases.

In the future, adaptive optics technology might be used as a non-invasive method in clinical practice not only in retinal diseases but also in diabetology and hypertensiology.

Keywords: adaptive optics, retinal diseases, diabetes mellitus, hypertension, glaucoma, CSCR

Figures: 5 • **References:** 20 • **Full-text PDF:** http://www.pjambp.com • **Copyright** © 2020 Polish Aviation Medicine Society, ul. Krasińskiego 54/56, 01-755 Warsaw, license WIML • **Indexation:** Index Copernicus, Polish Ministry of Science and Higher Education

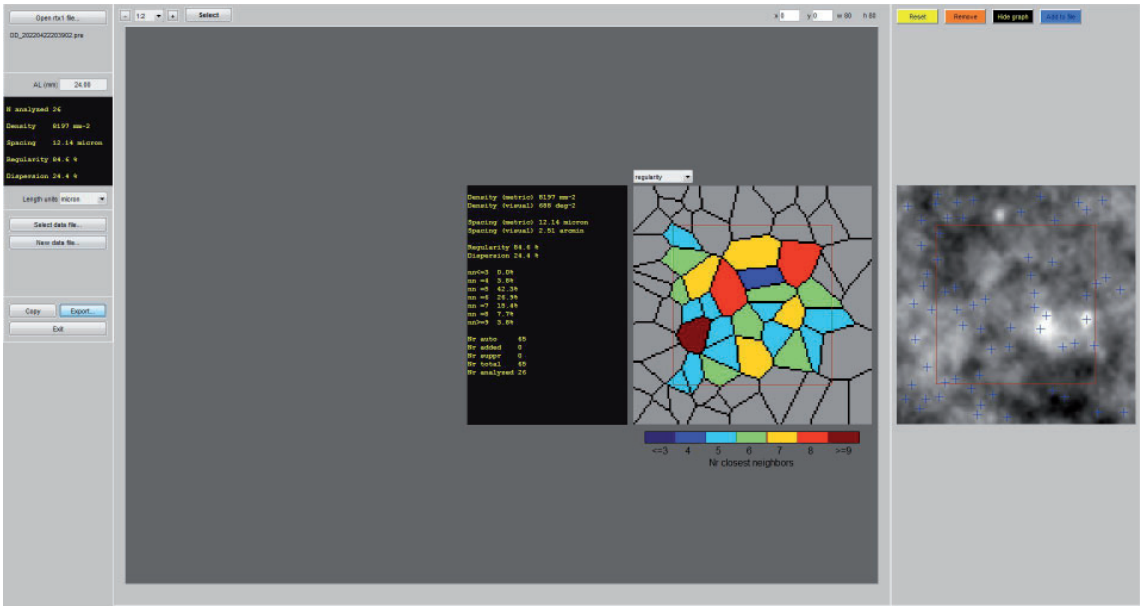

Fig. 1. Density of photoreceptors on rtx1. The colour scale shows the packing density in the central 4o x 4o.

INTRODUCTION

The methods of imaging posterior segment of the eye are still improving. Conventional colour fundus imaging, scanning laser ophthalmoscopy (SLO), fluorescein angiography (FA) and optical coherence tomography (OCT) have become routine clinical practice to examine retinal diseases (Figure 1, Figure 2).

The limitation of those methods are irregularities of the optics in the eyes causing "wave aberration". The use of adaptive optics (AO) technology corrects those aberrations and enables the visualization of cellular structures in human eye in vivo [11]. The technology of adaptive optics was first used by astronomer Horace Babcock in telescopes in 1953 [18]. The rtx1 (Imagine Eyes; France) is the first microscope using AO technology in ophthalmology. This non-invasive method allows visualization of single photoreceptor cell, lamina cribrosa, and blood vessels at the histological level [1]. The camera uses infrared illumination (wavelength of 850 nm). The field of single scan is 4° × 4° (1,2 mm x 1,2 mm square of retinal surface based on axial length of the eye) [17,20]. Further, it is possible to adjust the depth of the retinal region under examination. The manufacturer provided two computer programs for the analysis of the examination findings: AOdetect (for the analysis of photoreceptors) and AOdetectArtery (for the analysis of the structure of the retinal vessels) [18]. To conduct examination using AO technology, we need to provide some data such as the length of the eye and refractive error. AO also has some limits. It allows imaging of a small field of retina. The patient

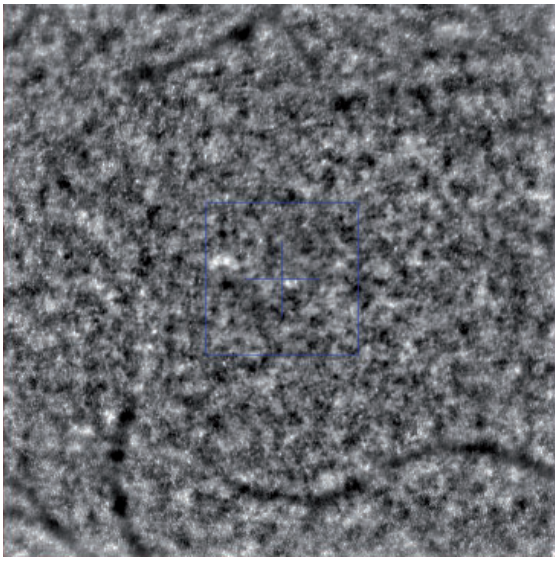

Fig. 2. Image of the macular photoreceptors obtained with AO camera.

pupil is required to be dilated above 4 millimetres. The results of international studies indicate that AO might be used in the future in clinical practice to diagnose and control patients with retinal diseases as well as microvascular abnormalities and glaucoma (Figure 3, Figure 4).

DIABETES MELLITUS

Diabetes is a chronic disease that affects many organs. The population of diabetic patients is estimated at 415 million [15]. Ocular complications include diabetic retinopathy, which is one

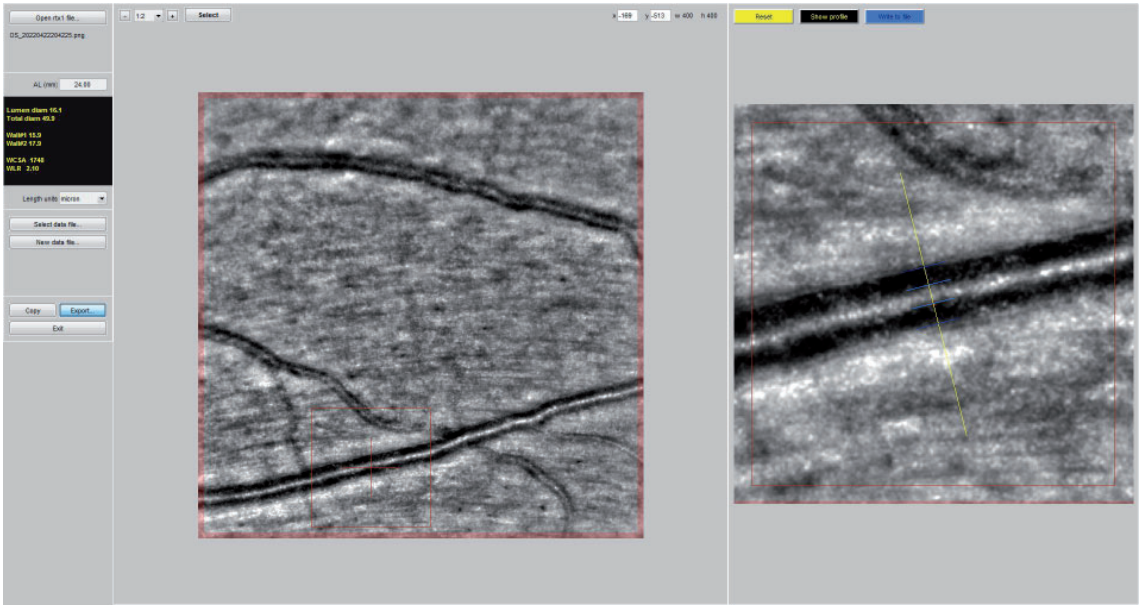

Fig. 3. Image of the retinal artery captured with rtx1 adaptive optics camera. Automatically calculated parameters: walls thickness, lumen diameter, total vessel diameter, cross-sectional area of vessel wall, and wall- to-lumen ratio.

of the leading causes of visual impairment worldwide. Chronic hyperglycemia leads to pathological changes of the microvascular structures and neurodegenerative changes in the retina. Clinical diagnosis of diabetic retinopathy relies on the detection of microangiopathy using ophthalmoscopic fundus examination and intravenous fluorescein angiography. The progression of ocular complications is associated with duration of the disease and the glucose levels. Currently, the diagnosis is made at relatively advanced stage. The studies revealed neuronal changes such as apoptosis of photoreceptors and retinal ganglion cells that precede microvascular abnormalities [20]. Lombardo et al. presented the results of their study of adaptive optics biomarkers for the assessment of the cone mosaic in 16 patients with type 1 diabetes mellitus [12]. They included eight patients with nonproliferative diabetic retinopathy and eight without changes on fundoscopy compared to a healthy group. The results show lower cone density and abnormalities in spatial arrangement of the parafoveal area in patients with type 1 diabetes mellitus, even in those without changes on fundoscopy. Similar results were reported by Zaleska-Żmijewska et al. [20], who assessed 36 subjects with diagnosed nonproliferative diabetic retinopathy using adaptive optics camera to measure cone parameters. Their analysis showed decreased cone regularity and density. Furthermore, Zaleska-Żmijewska et al. analyzed changes in retinal vessels structure. In their study, retinal vessels walls, lumen diameter (LD) and total vessel diameter (VD) were measured directly by AO.

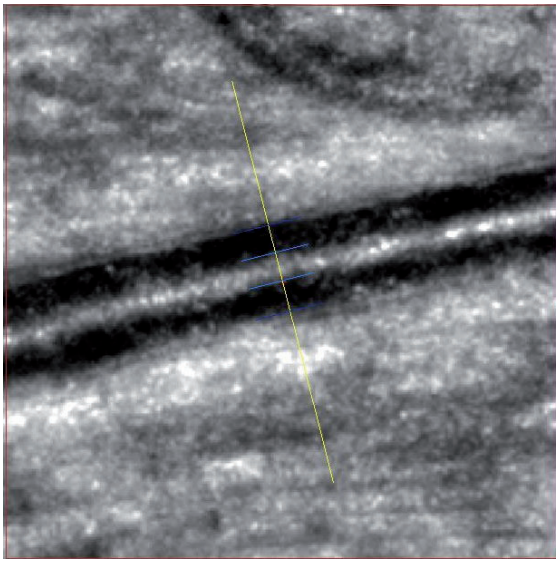

Fig. 4. Image of retinal artery.

The wall-to-lumen ratio (WLR) and cross-sectional area of the vascular wall (WCSA) were calculated automatically. The results showed artery walls thickening, an increase in WLR and WSCA in correlation with the severity of diabetes. Similarly, Soliman et al. demonstrated a correlation between decreasing cone density in patients with DM II with different stages of retinopathy. They did not find correlation between cone density and the level of HbA1c or the duration of diabetes [16]. Zaleska-Żmijewska et al. presented the results of their study on patients with prediabetes [19]. The authors analyzed vessel structure and photoreceptors analysis in 12 patients with impaired

fasting glucose (IFG) and impaired glucose tolerance (IGT) compared to healthy subjects. The results showed arterial remodelling, characterized by increased wall-to-lumen ratio. The above results indicate that AO may be helpful in detecting diabetes complications before the onset of clinical symptoms. Therefore, it can be a useful tool for detecting early changes in patients at risk of developing diabetes (Figure 5).

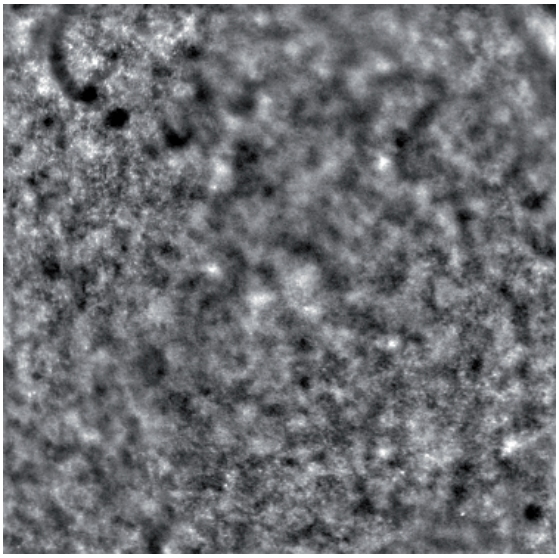

Fig. 5. Image of the macular photoreceptors of the right eye in patient with diabetic macular edema.

HYPERTENSION

It is commonly known that hypertension is an important risk factor for cardiovascular diseases. Currently, high blood pressure is responsible for more than 10 million deaths per year. The number of hypertensive patients is estimated to exceed 1.5 billion in 2025. Despite increasing awareness of hypertension and its complications, it can be asymptomatic, or it can cause non-specific symptoms. This is the reason why this condition is often diagnosed incidentally [3,4]. Ruchir A Mehta et al. presented the results of their study of retinal vessel changes in patients with arterial hypertension [13]. Chronic high blood pressure leads to vascular remodelling processes, accompanied by decreased lumen diameter and arteriolar wall thickening. The authors assessed retinal arteriolar morphometry with the rtx1 AO retinal camera using AOdetect Artery semiautomated software. They included 150 patients, 40 of whom were diagnosed with hypertension. The influence of arterial hypertension on the wall-to-lumen ratio (WLR) and wall cross-sectional area (WCSA) was examined. Ruchir A. Mehta et al. noticed statistically significant difference in WLR and WCSA between control and hypertensive groups ($P < 0.01$). On the other hand, only one retinal arteriole of one eye per patient was examined. For that reason, it is uncertain whether the changes in this arteriole are reflective of all other retinal vessels. The review of Dziedzic et al. presents the use of a combination of AO with OCT to evaluate retinal vascular changes [5]. The adaptive optics technique enables direct measurement of the retinal vessel wall (VW) and the lumen diameter (LD). In hypertensive groups, increased WLR caused by a decrease in LD and thickening of the arteriolar wall was described. Gallo et al. analysed retinal vessels of 1,500 patients recruited between June 2014 and December 2015 in the Cardiovascular Prevention Unit and another additional 276 subjects with hypertension recruited between November and December 2015 [6]. The aim of that study was to analyse WLR or LD cut-off values to discriminate control group from hypertensive patients using the rtx1TM Adaptive Optics Camera (ImagineEyes, Orsay, France). The authors reported that WLR was significantly higher in all hypertensive groups, compared with normotensives ($P < 0.0001$). The results of this study also showed narrower vessels in MAH patients (defined by elevated home / ambulatory AH despite normal office BP), indicating that retinal arteriolar remodelling in MAH and in non-controlled hypertensive subjects present the same features. According to the results of the above studies, the analysis of vascular changes using AO can detect subtle retinal microvascular modifications observed in the early remodelling process. It can be useful for early diagnosing, monitoring and for potential modification of antihypertensive therapy [13].

GLAUCOMA

Primary open-angle glaucoma (POAG) is a leading cause of irreversible vision loss worldwide. It is a chronic optic neuropathy characterized by progressive death of retinal ganglion cells and resulting changes in the optic nerve head. The pathogenesis of POAG is not well understood so far. It has been suggested that vascular pathologies may play an important role in the onset of and progression of POAG [2,8].

The purpose of the present report was to clarify the role of vascular risk factors in the pathogenesis of primary open-angle glaucoma. A detailed analysis of peripapillary arteriole was made using adaptive optics technology. Hugo et al. analysed results

from 31 patients with a bilateral POAG confirmed and in 29 healthy subjects. The authors reported that lumen diameter and total diameter were significantly lower in the glaucoma group than in the control one: 88.3 versus 102.3 (P=0.03) and 121.1 versus 134.4 (P=0.015). Thereby, they observed in POAG patients a reduction of the vascular calibre without modification of the vessel wall thickness, wall-to-lumen ratio and whole cross-sectional area. More research is needed to better understand the role of vascular risk factors in the pathogenesis and the development of glaucoma [8].

CSCR

Central serous chorioretinopathy is a disorder characterized by serious retinal detachment and/or retinal pigment epithelium detachment and associated with leakage of fluid through the RPE into the subretinal space. Gerardy et al. analysed cone density in the asymptomatic fellow eyes of patients with unilateral CSCR using adaptive optics [7]. The investigation showed a significant reduced density of foveal cones (at 2° of nasal and temporal eccentricity) between both groups (P = 0.001 and P = 0.027, respectively). Nakamura et al. presented their study findings related to photoreceptors and outer retinal layer thickness in patients with CSCR, using an adaptive optics fundus camera and spectral domain optical coherence tomography [14]. Based on a study of 12 patients with unilateral CSCR (12 eyes) and 30 healthy subjects (30 eyes), they observed that the cone densities of CSCR eyes decreased compared to those of the control eyes. The examination was performed both after resolution of subretinal fluid and at the 12-month follow-up, in the same location. Adaptive optics imaging showed a gradual increase in the number of macular cone densities during 12 months in patients with resolved CSCR. This observation was correlated with the thickness of outer retinal layer and visual acuity in a short term.

OTHER DISEASES

The current literature offers a few publications on examination findings using the rtx1 AO camera in other retinal diseases.

Inherited retinal diseases (IRDs) cause severe visual loss in over 2 million patients worldwide. Lin et al. [11] presented the results of their study on changes in the posterior segment of the eye in retinitis pigmentosa (RP). In this genetic disease patients suffer from night blindness, decreasing peripheral vision and reduction of central vision. The authors included 20 subjects with RP compared to a healthy group. The study revealed significantly lower cone density in patients with retinitis pigmentosa. The increased density correlated with the severity of the disease. Moreover, the authors of the available reports claim that the rtx1 revealed a significant reduction in cone density in IRD, even when photoreceptor abnormalities were barely visible in OCT images [9,10].

CONCLUSIONS

Based on the available published results, it may be concluded that adaptive optics technology is a non-invasive tool for evaluating the retinal vessel and photoreceptors. Research is currently underway to expand the use of OA in diagnostics, monitoring and treatment of systemic and ocular diseases. Retinal vasculature changes can help us analyze the condition of the systemic vascular system. Further studies are needed to confirm this assumption.

AUTHORS' DECLARATION:

Study Design: Magdalena Rerych, Katarzyna Paczwa, Radosław Różycki, Joanna Gołębiewska. **Data Collection:** Magdalena Rerych, Katarzyna Paczwa, Radosław Różycki, Joanna Gołębiewska. **Manuscript Preparation:** Magdalena Rerych, Katarzyna Paczwa, Radosław Różycki, Joanna Gołębiewska. The Authors declare that there is no conflict of interest.

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