Cellular level retinal imaging

Diagnostic and prognostic capabilities could be improved as a result of adaptive optics

By *OTEurope*
Reviewed by Mark Zacharria

Diagnosis of retinal diseases at an early stage is essential in the treatment and avoidance of serious visual damage. According to Dr Marco Lombardo, MD, PhD, researcher at IRCCS Fondazione G.B. Bietti, Rome, Italy, "Adaptive optics (AO) can provide very early stage diagnostic and prognostic information that can not be obtained with other retinal imaging techniques."

The rtx1 Adaptive Optics Retinal Camera (Figure 1) from Imagine Eyes (Orsay, France) is currently being used in several leading ophthalmic research centres as a Research Use Only device and is finding potential applications in the early diagnosis and monitoring of several different diseases. These capabilities can be attributed to the unique sensitivity of the device. Xavier Levecq, cofounder and CTO of Imagine Eyes said, "The rtx1 differentiates itself from current commercially available retinal imaging devices in that its imaging resolution of 250 line-pairs per millimetre (lppmm) reaches the cellular level." One of the key features of the instrument is a fully automated AO system that allows clinical researchers to view retinal cells and microstructures, such as cone photoreceptors, capillaries and nerve fibre bundles (Figures 2 and 3).

Figure 1: The rtx1 Adaptive Optics Retinal Camera.

Dr Lombardo added, "The rtx1 retinal camera has the potential of becoming a powerful instrument for the early diagnosis of diseases affecting the macular area. The ability to image the photoreceptor layer *in vivo* provides the opportunity to better understand the pathological processes leading to visual impairment and to non-invasively monitor normal retinal architecture. In the future, that may expand to include the progression of retinal diseases, and the efficacy of therapies at a cellular level."

Retinal function and disease diagnosis

Across the developed world, the major causes of vision loss can be attributed to age-related macular degeneration (AMD), diabetic retinopathy and glaucoma.[1] As each of these diseases cause damage to the microstructures of the retina, diagnosis usually occurs once damage has already happened. According to Dr Lombardo, "The opportunity to detect and monitor pathological variations in the photoreceptor layer at a very early stage of the disease can represent the basis for designing new diagnostic and treatment protocols to preserve the normal integrity and function of the retina." (Figure 4.)

For example, Dr Lombardo suggested that in cases of AMD it can be possible to view the granular contents in the early stages of drusen formation using AO imaging, allowing the verification of the cone mosaic aspect between drusen areas. In diabetic retinopathy, AO imaging can make it possible to verify the cone mosaic with faint intraretinal oedema, not seen in scanning laser ophthalmoscope (SLO) or

In short...

The rtx1 Adaptive Optics Retinal Camera (Imagine Eyes, Orsay, France) is a Research Use Only device that is currently being employed in several leading ophthalmic research centres in Europe, the US and Japan. It has been found in clinical research that compact AO imaging devices allow clinical researchers to examine diseases at the cellular level. In the future, AO medical devices may enable clinicians to detect diseases in the early stages, which will in turn prevent severe damage to visual function of patients. In addition to the early detection of diseases, this may provide the potential for use in monitoring the progression and evaluating the efficacy of treatments being used. In this article a number of potential clinical applications are revealed by doctors and the future of adaptive optics in retinal imaging is described.

optical coherence tomography (OCT) images.

Dr Kiyoko Nakashima, MD, PhD, Quinze-Vingts Hospital, National Ophthalmic Centre, Paris, France, has used the rtx1 in several research studies, including some on patients with macular dystrophy and retinitis pigmentosa who had reported symptoms that were inexplicable through current imaging techniques. She said, "In such cases, AO images often revealed microscopic retinal abnormalities that correlated better with subjective visual findings. In infrared reflectance AO images, the visibility of cones is dependent on the transparency and scattering of the retinal layers situated above the photoreceptors. Modifications in the structure of these layers are likely to affect both visual performance and AO findings."

Additionally, Dr Nakashima and colleagues had found a strong correlation between the patient's visual field response and the mapping of the cone photoreceptor visibility across the retina in glaucoma cases. "Therefore, AO images can be useful in understanding and predicting visual function," she added.

Dr Nakashima's superior from the Quinze-Vingts Hospital, National Ophthalmic Centre, Professor Michel Paques, MD, PhD, has been using the research device in the fovea. This area is extremely small and important, so being able to image at the cellular level has aided his research immensely. "In our studies, AO fundus imaging documented the extent of photoreceptor damage better than any other imaging technique currently available. In an area so small and so important as the fovea, every cell counts and only AO has enabled such resolution," he said. "This device should be of great interest not only for the diagnosis of diseases affecting the fovea, but also to monitor them."

Prof. Paques and colleagues have already published cases of toxic damage to the fovea, the central part of the macula. He continued,

Figure 2: Imaging the retina at different depths. These images, acquired at 3°T × 2°S over a 4° × 4° field on a healthy 32-year old male subject, demonstrate how the rtx1 can image the retina at different depths [(a) cone photoreceptors, (b) capillaries].

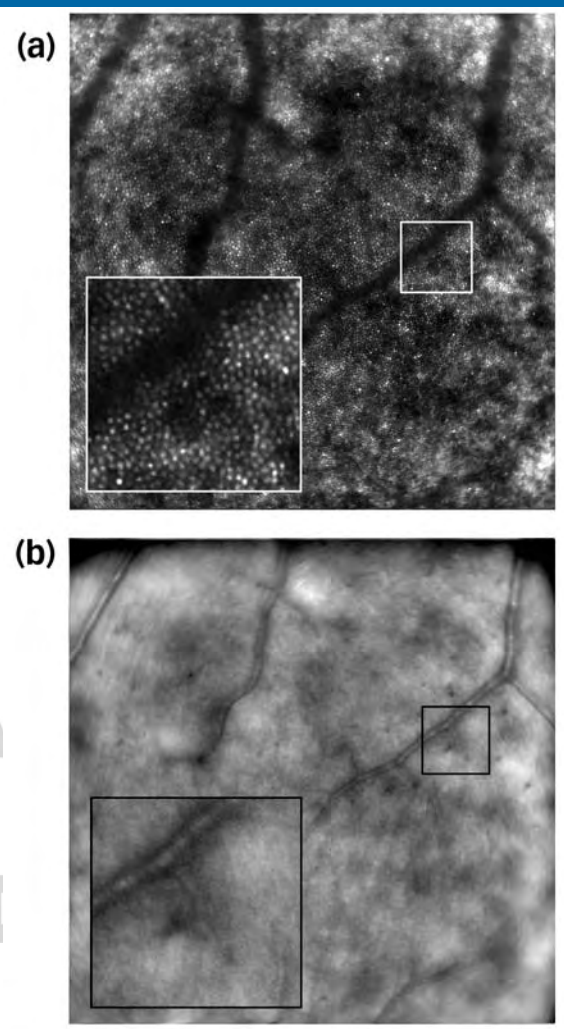
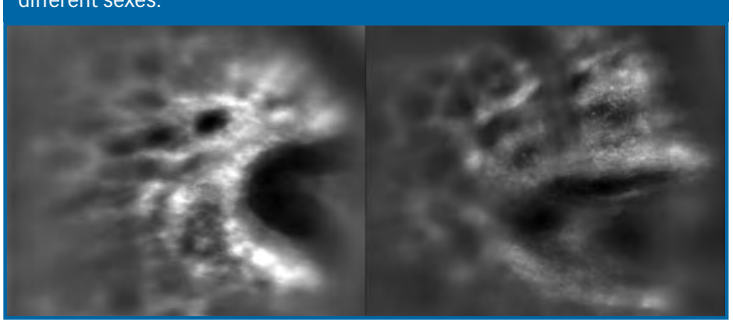


Figure 3: Imaging the lamina cribrosa. These images (left, a healthy 47-year old male, right, a healthy 24-year old female) of the lamina cribrosa demonstrate how imaging this microstructure with the rtx1 can reveal surprising similarities even in subjects from different age-groups and of different sexes.



"In these research cases OCT only showed faint damage to the photoreceptors, that could be (and actually was in most cases) missed by OCT, but was clearly shown by a 'single shot' AO image."

Disease progression and treatment efficacy

Tracking disease progression within the retina over a specific timeframe will provide ophthalmologists with the tools to not only give their patients reliable prognostic information but will also enable them to monitor the efficacy of treatments being employed. Dr Nakashima explained the process that her team, with Dr Isabelle Audo, have used in analysing the progression of retinal diseases. "In recent studies, we superimposed AO images of the cone mosaic taken at different follow-up visits in the same pathological retinas and compared them cell-by-cell (Figure 5). In two visits separated by a couple of weeks, we were able to detect microscopic growth of pathological areas, over just a few photoreceptor cells, in cases of acute macular neuroretinopathy (AMNR)," she said.

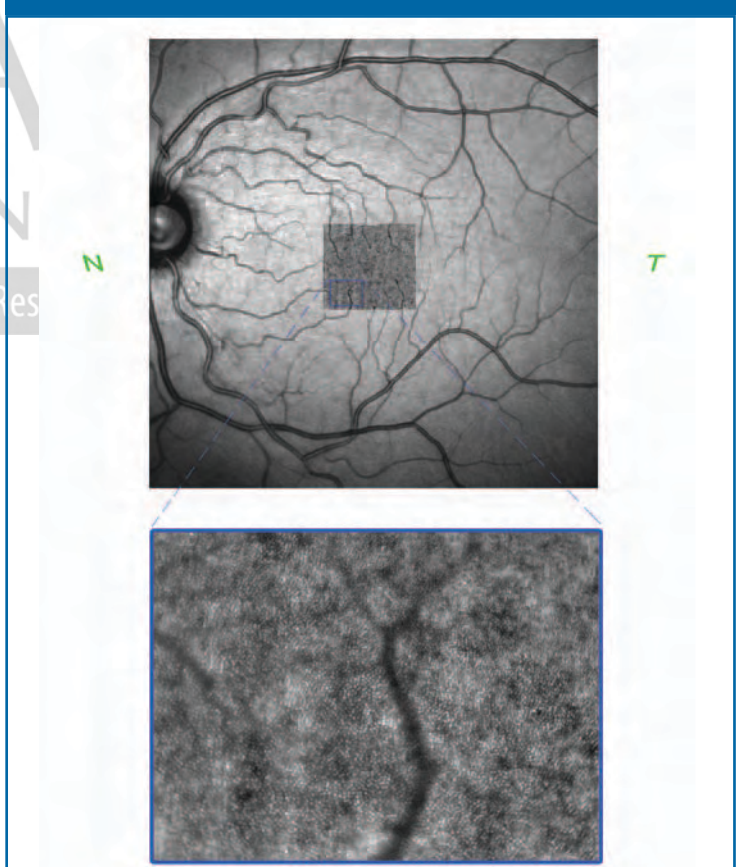
In a similar manner, it was possible for the team to observe the microscopic growth of drusen in age-related maculopathy patients. "The very high sensitivity of AO imaging shall help to drastically reduce the time needed to determine patients' prognosis for a number of diseases," she added.

Within the area of personalized medicine, Dr Nakashima revealed that AO imaging has the potential to help ophthalmologists move away from

Device specifications

- A compact, standalone, fully automated imaging system with a pupil alignment method very similar to commercially available OCT devices.
- Designed for clinical research environments.
- Qualified doctors or technicians familiar with current imaging techniques can operate the device.
- A 4° x 4° imaging field and internal fixation target that facilitate image acquisition over a wide field of the retina as well as imaging of the exact same location on the retina over time.
- Image depth and area can be specified as a result of the ability to focus on different layers in the retina combined with the high-quality live image.
- Acquisitions can easily be stitched together to form larger mosaics.
- An external fixation target for imaging at large foveal eccentricities. (In early investigations, images were acquired at up to 36°.)
- NIR light sources used for focusing and acquisition, making imaging sessions extremely comfortable in contrast to some fundus cameras that use bright flashes to illuminate the retina.

Figure 4: The left eye of a 25-year old female. In the top image, the SLO image with the superimposed AO images covering a 9° × 9° area. In the bottom image, the AO image focused at the photoreceptor layer showing the cone mosaic of the infero-nasal parafoveal region. Patches of cones with higher brightness across image are of general occurrence when imaging the photoreceptor layer. This is probably as a result of variations in reflectance of cones. (Image courtesy of Marco Lombardo, MD, PhD — IRCCS Fondazione G.B. Bietti, Rome, Italy.)



a one-size-fits-all therapeutic model to a more personalized approach to medicine. "Thanks to its ability to measure minute changes in the retina, AO can provide a very sensitive method of assessing the effectiveness of treatments just a few weeks or days after they are applied," she said. "In the future, it is likely that AO findings will support ophthalmologists in adjusting treatments and making therapeutic decisions. The need for such sensitive and precise diagnostic tools is increasing as a growing number of new treatment options become available to retinal ophthalmologists."

Ultimate goal

The future of AO retinal imaging, according to clinical research, seems to be in the early diagnosis of degenerative retinal diseases and monitoring treatment efficacy. Dr Nakashima said, "I foresee applications in detecting the early signs of diabetic retinopathy and several systemic diseases, including arteriosclerosis. In such diseases, early detection and treatment are essential to prevent the occurrence of serious damage."

Demonstrations of the rtx1 can be seen for the first time at this year's ARVO/ISIE and ARVO annual meetings. According to Mark Zacharria, director of global communications, Imagine Eyes, "We expect to meet a lot of enthusiastic ophthalmologists at these shows. It's one thing to see a still image of cones or vessels or a video sequence focused on one spot on the retina, it's quite another to see the rtx1's real-time visualization at that level while deciding what area to capture as a high-resolution fixed image."

Nicolas Chateau, PhD, cofounder and CEO of Imagine Eyes, concluded, "The device is currently being used in clinical investigations at leading research centres in the US, Europe and Japan whose staff regularly presents new findings at international ophthalmology conferences. We will work very closely with these early adopters clearly establish the diagnostic possibilities of the rtx1 with the goal of launching a medical diagnostic device in 2012 cleared and labelled according to CE and FDA rules."

Reference

1. M. Zacharria, B. Lamory and N. Chateau, *Nature Photonics*, 2011;**5**:24–26.

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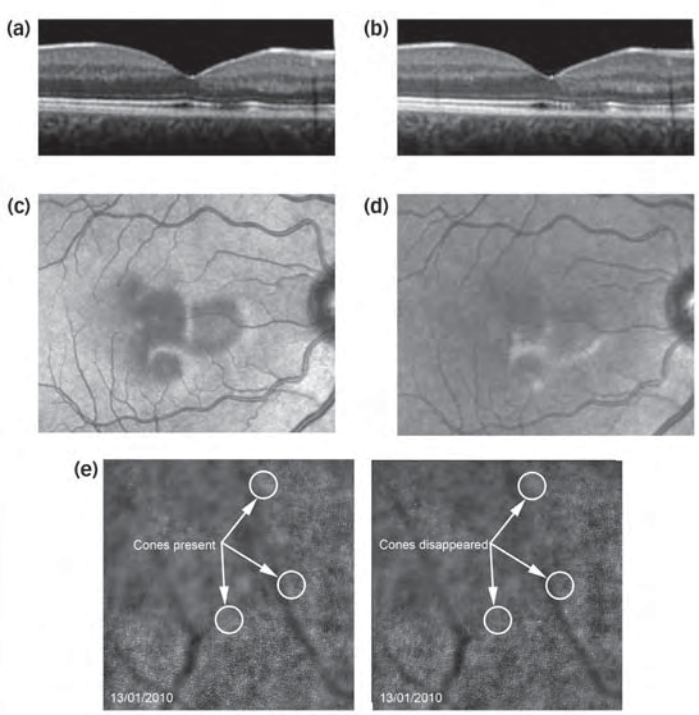
Figure 5: Tracking pathology progression cell-by-cell. In this case of acute macular neuroretinopathy, images taken one month apart show small changes, invisible to OCT or SLO, at the edge of the lesion where cones have disappeared. (Images courtesy of Dr Isabelle Audo and Dr Kiyoko Nakashima, Quinze-Vingts Hospital, National Ophthalmic Centre.)



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