A Next Generation High Resolution Adaptive Optics Fundus Imager

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ABSTRACT

The spatial resolution of retinal images is limited by the presence of static and time-varying aberrations present within the eye. An updated High Resolution Adaptive Optics Fundus Imager (HRAOFI) has been built based on the development from the first prototype unit. This entirely new unit was designed and fabricated to increase opto-mechanical integration and ease-of-use through a new user interface. Improved camera systems for the Shack-Hartmann sensor and for the scene image were implemented to enhance the image quality and the frequency of the Adaptive Optics (AO) control loop. An optimized illumination system that uses specific wavelength bands was applied to increase the specificity of the images. Sample images of clinical trials of retinas, taken with and without the system, are shown. Data on the performance of this system will be presented, demonstrating the ability to calculate near diffraction-limited images.

1. INTRODUCTION

Diagnosing retinal pathologies at earlier stages is at the heart of improving the resolution of fundus imaging systems, but because of inherent aberrations in the human eye that resolution is limited to approximately 20 to 30um. Adaptive Optics (AO) systems have been an essential tool to correct aberrations in astronomical telescopes and long range imaging for more than a decade, and the technology is now being applied to areas of industry and medicine. Experimental AO systems were built for imaging of the in vivo human retina and have shown very promising results. In a close partnership under the NATO Science for Peace program, Kestrel Corporation, ILIT of the Russian Academy of Science, and Moscow State University have built and tested the first prototype of a High Resolution Adaptive Optics Fundus Imager (HRAOFI) clinical device that can image the retina of human subjects close to the diffraction limit. Following the successful results of the first prototype a second instrument was built, this time under the auspices of the National Institute of Health (NIH). The new instrument addresses the shortcomings of the prototype and brings forward the existing enhancements. Emphasis was given to the physical integration of the instrument as well as the usability from the clinical usage point of view. We will be describing the changes that were made to improve the new instrument and the results of testing on human subjects. A plan for the deployment of the HRAOFI in a clinical environment at the Department of Ophthalmology of Iowa University is also presented along with the clinical relevance that supports the development of the technology for medical applications.

1. SYSTEM DESCRIPTION

The instrument is based on a commercial fundus imager (KFG2) that has been modified to accommodate the addition of a series of new subsystems. Those have been fully integrated to the fundus imager to create a self-contained instrument that operates much like a clinical unit. It is specifically designed to correct for the low-order aberration of large amplitudes. It was primarily built as an add-on to the original fundus imager; this concept should be applicable to a variety of commercial units. In this version the KFG2 was modified only to accommodate the space needed for the Shack-Hartmann sensor, no changes were made to its original optical configuration. The control system is based on a PC computer running under a Microsoft Windows environment and provides real-time images to the operator. The instrument is configured using the same basic architecture as described in the original prototype. The fundus imager

relays the retinal image to the input of the AO system and to the high-resolution camera. The pupil image wavefront is measured by a Shack-Hartmann sensor and a control signal is send to the bimorph deformable mirror for closed loop correction. The reference source is generated by a dithered 780nm laser source projected on the retina. The imaging illumination source is a continuous xenon short-arc lamp delivered by a fiber optic bundle. The light source has multiple filter and shutter capabilities and is fully programmable through the desktop.

2. UPGRADES FROM THE FIRST SYSTEM

2.1 Shack-Hartmann sensor

The response time of the AO control loop has been improved to approximately 4Hz. This is a significant improvement over the 0.6-0.8Hz of the previous system. This was achieved by replacing the video rate (30Hz) analog camera from the Shack-Hartmann sensor with a Dalsa digital CCD running at 77 frames per seconds. The lenslet array coupled to the CDD has a 0.3mm pitch and 3mm focal length. The deformable mirror software control loop and drive electronics were updated to improve the system's response time.

2.2 Data Camera

The new data camera that was selected to acquire the high-resolution image is a KRC1 model from Elektron (St Petersburg, Russia). It uses a Kodak KAF-16801E of C1 cosmetic quality (highest) FPA sensor of 4096 x 4096 active elements. The pixel size of 9um is more closely matched to the nyquist modulation response of the optical system which is defined by the size of the pupil. The new sensor is also more sensitive with an absolute QE of 0.65 at 660nm and minimum of 0.3 from 400nm to 850nm. It connects to the computer via a USB2 interface.

2.3 Deformable mirror

A bimorph deformable mirror with new design parameters was specified and fabricated by ILIT to increase the correction dynamic range of low-order aberrations (figure 1). The new mirror was characterized at Kestrel's facility. This mirror provides a better correction for large focus and astigmatism variations. In the design of the mirrors for this application, two active piezoceramic plates, the first to correct for astigmatism and defocus and the second to compensate for defocus and high-order aberrations, were used. By stacking the electrodes in such a way we were able to obtain 35um of focus correction and 25um of astigmatism correction. The electrodes were created by evaporation depositing onto the second piezodisk.

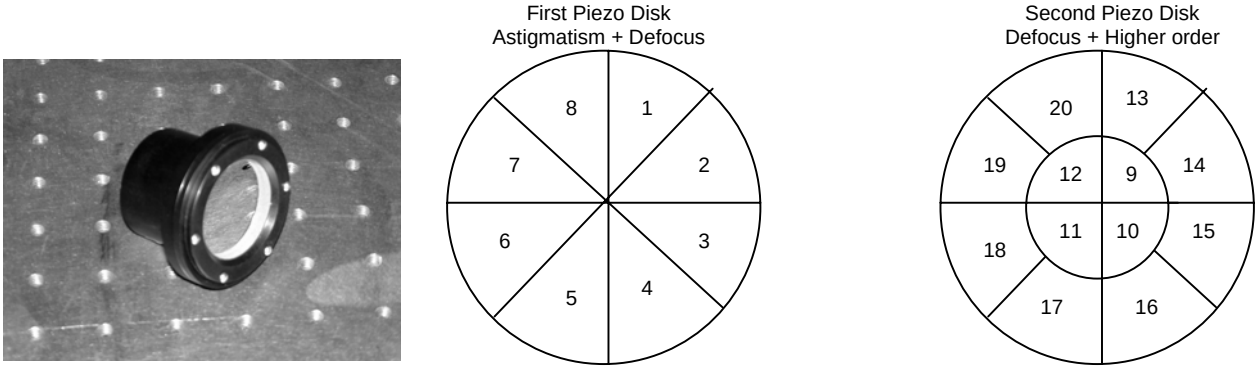

Figure 1. Deformable Mirror with piezodisk configuration

2.4 Image uniformity

Improvements in the optical design and layout have led to a better match of the field-of-view to the CCD sensor (figure 2). The magnification of the imaging was adjusted in such a way that the image would not overfill the sensor.

Uniformity of the image is improved due to less system vignetting by using fewer fold mirrors and making the remaining fold mirrors larger. More effort was also done on the optical coatings so that no central glare or ghosting is apparent in the new images.

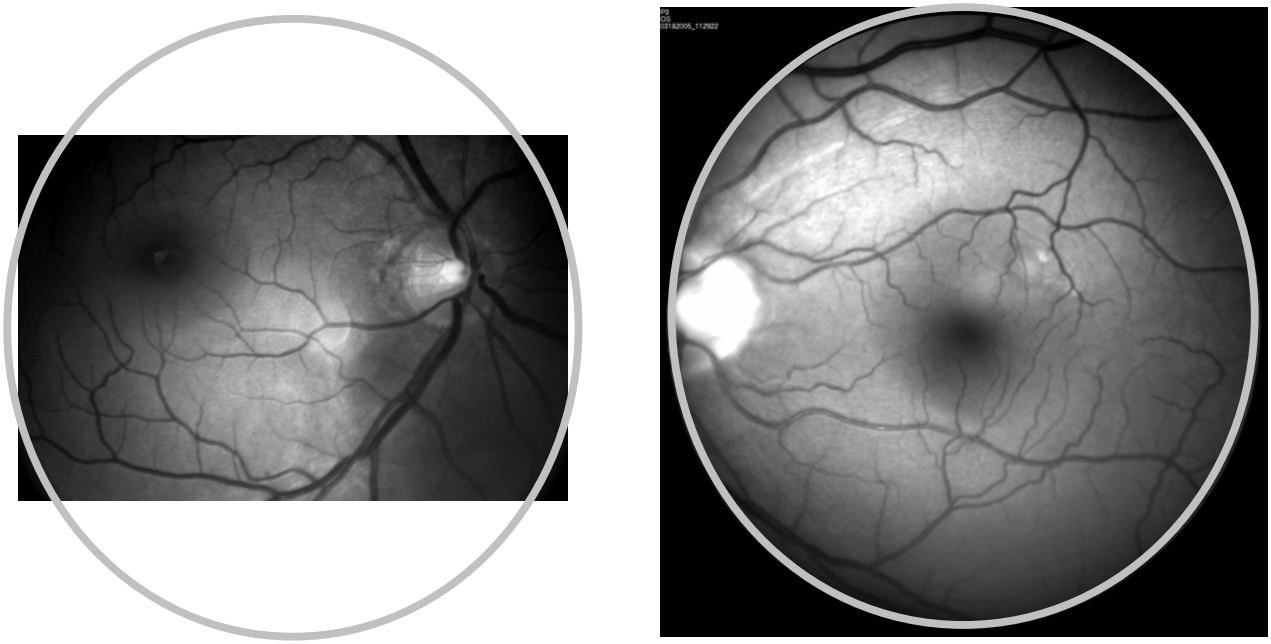

Figure 2. Image uniformity comparison between old (left) and new (right) system

2.5 Packaging and optical alignment

The first system was build as a direct add-on to a fundus imager, but the integration of too many components in a small package and the numerous turn mirrors required to fold the optical path in the enclosure made it difficult to align. The AO attachment had to by physically removed from the fundus imager and placed on a bench for alignment. A special fixture with a laser and a collimator had to be used. The bimorph mirror also had to be replaced with a reference flat to calibrate the Shack-Hartmann sensor. This process could take many hours and had to be conducted by experienced engineers. Once the instrument was reassembled it was very difficult to diagnose and troubleshoot.

A new concept was applied to the second system (figure 3). This unit became integrated by moving the Shack-Hartmann sensor optics and the dithered source laser components inside the fundus imager and folding the optical path of the data camera on top of the instrument. It provided more flexibility to the optical layout and provided the opportunity to introduce additional features such as an on-board laser for alignment. This makes the package more streamlined with easier access to the internal component(s). There is also the added benefit of having less weight hanging in the back of the instrument which makes it more stable and easier to align to a patient

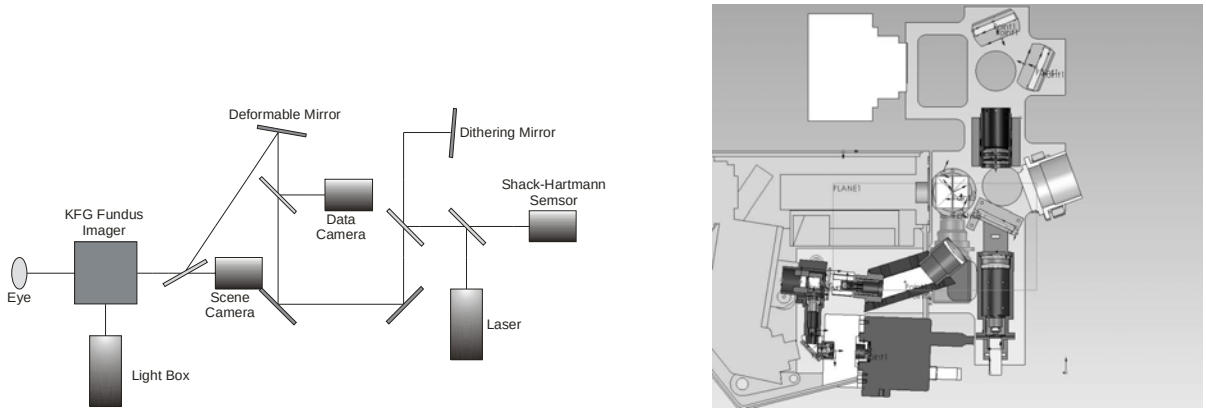

Figure 3. Optical layout changes

2.6 Operation and user interface

Because of the complexity of the first system it was difficult to operate with less than two people. The calibration and initial alignment verification, Shack-Hartmann interpretation, and deformable mirror control required an engineer experienced in AO systems, and the alignment of the patient to position the desired region of interest in the center of the field-of-view of the instrument required a skilled fundus photographer. Very few good quality retinal pictures were attained. Although this situation is not unusual in a research and development lab it quickly becomes difficult to manage in a clinical environment. The imaging sessions with patients have to be as concise and comfortable as possible. A significant portion of the target population is made up of senior citizens, many of them disabled, and the photographer must pay close attention to the patients and guide them through the imaging session. Since the imaging must be done by the photographer, who is the only one trained to interact with the patients, the engineers contribution had to be simplified and integrated in the system so the photographer could concentrate on the imaging session and not on the operation of the instrument.

The system now has an automated start-up sequence with diagnostics that survey the health of the major subsystems and generates reports to the user. An on-board laser and collimator generate a low-aberration reference beam of the proper size to calibrate the deformable mirror and the Shack-Hartmann sensor. The system is now calibrated from the desktop and becomes a simple procedural step. The user interface (figure 4) is stripped of advanced parameters, which allowed adjusting the different components, and is limited to basic commands to open and close the AO control loop and the standard exposure settings. The advanced parameters are integrated in an engineering user interface that is accessible only with proper permissions. The ergonomics are improved by the addition of a second monitor that displays only the acquired image which gives the operator a real-time view of the imaging quality.

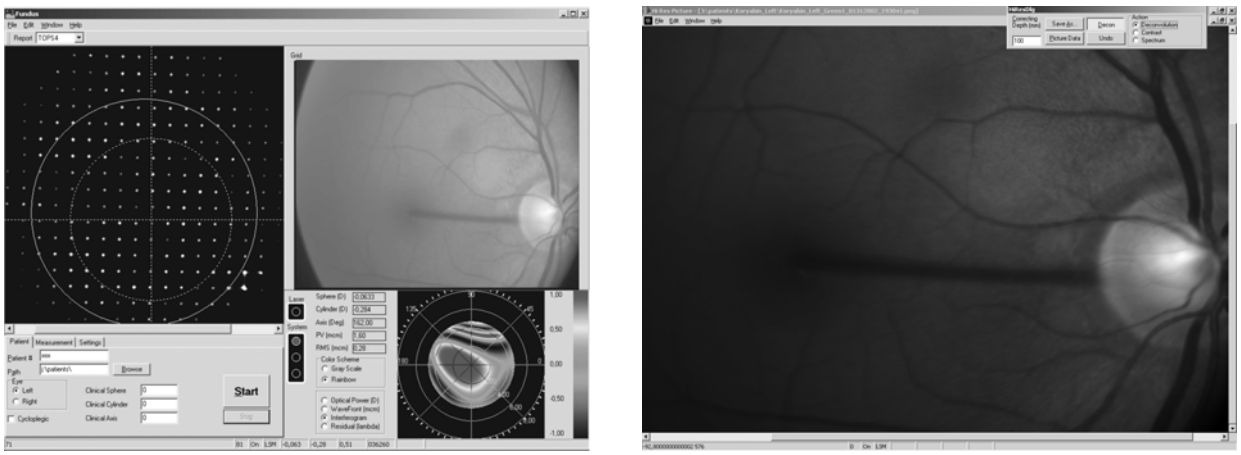

Figure 4. User Interface

3. COMPONENT AND SYSTEM TESTING

3.1 Bimorph mirror testing

The deformable bimorph mirror was characterized on a test bench prior to installation in the system and the results have been published in a previous paper (figure 5). Included here is a brief summary of the results. The deformable mirrors described have been tailored to a specific application, that of ophthalmic AO. In such applications the primary importance is that of available displacement, as the eye can possess severe aberrations that must be corrected by such mirrors. Unlike astronomical AO mirrors, the temporal performance can be much lower as the correction bandwidth is a few tens of Hertz as opposed to the hundreds, even thousands, of Hertz bandwidth required for astronomy. The performance penalty for such high-stroke devices is that they possess significant hysteresis, about 15% in these mirrors. While this is a problem for simple linear-control systems which assume a linear response between voltage and displacement, by careful calibration and more sophisticated control loop schemes this problem can be overcome.

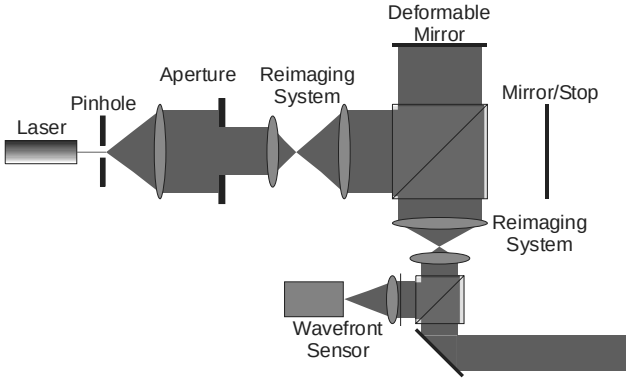

Figure 5. Deformable mirror test set-up

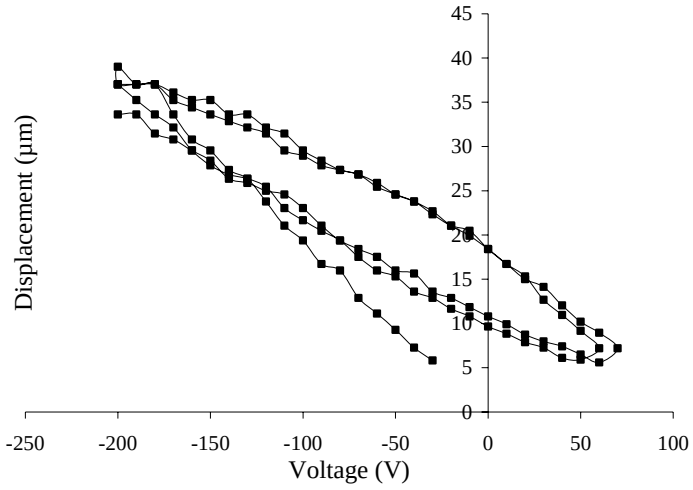

Figure 6. Defocus displacement calculated by measuring focal distance from the DM.

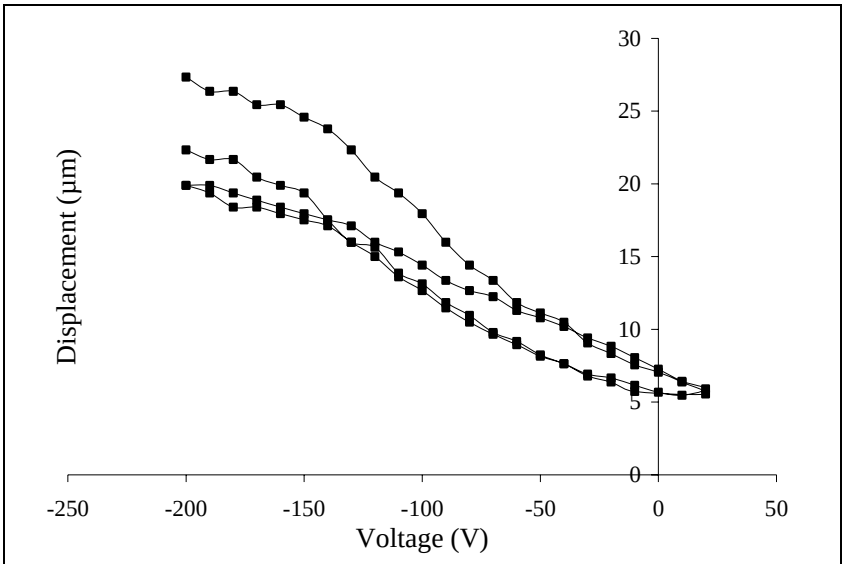

Figure 7. Astigmatism displacement calculated by measuring the focal distance from the DM.

3.2 AO Frequency Response

As mentioned in section 2.1, improvements in the hardware and software have increased the frequency response of the closed-loop AO. This measurement is done by applying a defocus modulation at the input of the system. A mirror is mounted to the moving coil of a loud speaker and is controlled by a signal generator. The mirror is positioned at the focal plane of a lens to reproduce the imaging function of the eye (figure 8).

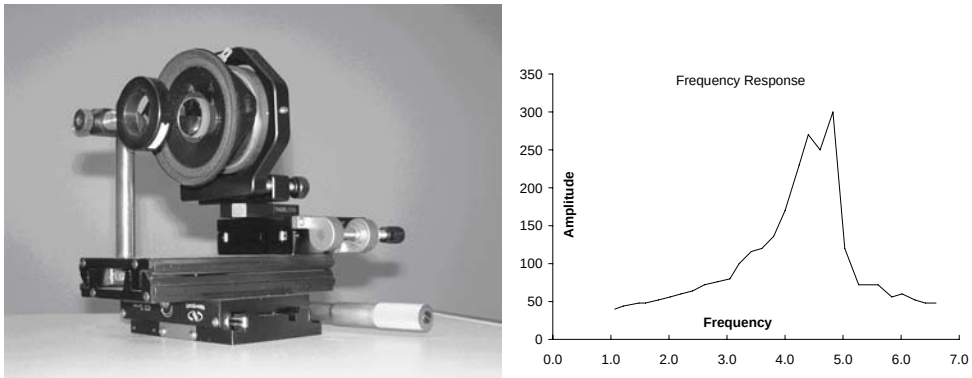

Figure 8. AO closed loop response

3.3 Imaging Resolution Test

The static system resolution was measured with a USAF 1951 target mounted in an artificial eye. Resolution was also measured through the field by displacing the target laterally in the focus plane of the artificial eye. Figure 9 shows that the resolution falls between group 6-4 and 6-5 which correspond to 90-100 cycles per millimeters.

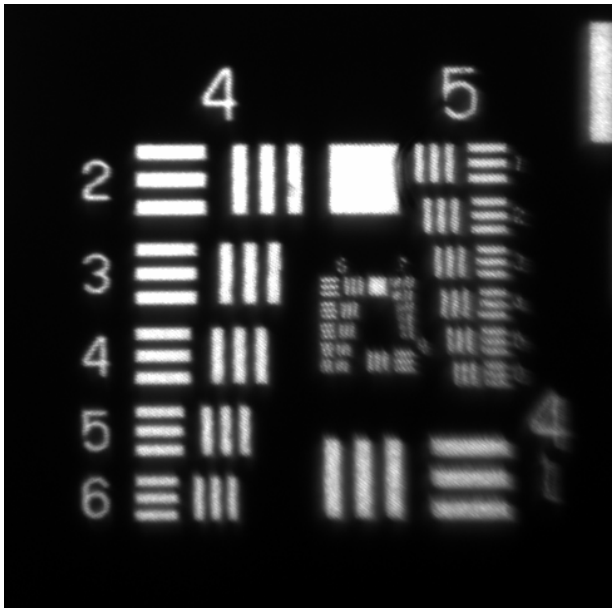

Figure 9. Resolution target image. The visible limit is between 6-4 and 6-5

4. HUMAN SUBJECTS TESTING

4.1 Clinical relevancy

The ability to correlate known histological changes in the retina which are occurring at the sub-clinical level with a robust visualization tool that would bring this information to an objective measureable level would be an immense advantage in ocular research. Super resolution imaging is positioned to be an innovative application which can translate histological events into the clinical relevancy of early detection. For example, if the fine vessels on the optic nerve head can be detected and monitored over time, a possible correlation of their appearances could be applied to the glaucomatous process and its root pathophysiology. Another potential use is the earlier detection of lesions or tissue changes which occur before microaneurysm formation in diabetic retinopathy. Microaneurysms are the earliest clinical lesion which can presently be visually detected in the clinical arena, however there are tissue changes occurring prior to the visualization of these lesions. A super resolution adaptive imager has the potential to find abnormalities that are pre-cursors to microaneurysm development. This could be a huge asset to clinical trials of pharmaceuticals for diabetic retinopathy.

4.2 In-vivo imaging

Human subject testing was performed at the Moscow Eye Institute by a resident doctor. A total of fourteen (14) subjects were imaged with ages ranging from twenty-two (22) to seventy-four (74) years. The results were: three (3) subjects were normal; three (3) subjects have glaucoma; four (4) subjects have age-related macular degeneration (three (3) with the dry non-exudative type and one (1) with wet, or exudative type); and four (4) subjects have diabetic retinopathy of

varying stages, including background diabetic retinopathy and pre-proliferative diabetic retinopathy). The subjects' refractive data was also recorded.

4.3 Imaging protocol

The objective of the protocol is to collect pilot data from human subjects (controls and pathological) to determine the image quality that is attainable with the Super Resolution Fundus Imager from subjects with varying levels of retinal disease and anterior segment un-corrected vision. We collected images and performed the necessary deconvolution to maximize the image resolution.

One objective of these tests is to evaluate the effect of integration time on the image quality. Images were collected at three to four (3-4) different integration times from 20 ms to 80ms.

The "user friendliness" of the new device is evaluated subjectively. The evaluation criterion suggests that the SRFI must be operated by a skilled retinal photographer and not an engineer or scientist.

The control subjects, i.e. normals, were used to quantify the minimum integration time that can be used to collect images with sufficiently high well-filling and SNR. Each subject has a focus correction of +/- 2 to +/- 4 diopters of focus error and +/- 0.5 to +/1.0 of astigmatism.

Diagnosis	# of subjects	Diagnosis	# of subjects
Normals (non-age matched)	3	Glaucoma (visual loss)	3
Diabetes, preproliferative	2	Diabetes, non-proliferative	2
ARMD (wet, CNV)	2	ARMD (dry, drusen)	2

Table 1. Subjects diagnosis distribution

We are interested in obtaining images of the posterior pole (macular region) and the region of the optic nerve head. If there was a significant lesion in a region other than the macula or optic disc, we imaged that region as well. We tried to get a minimum of four images with the green filter for each of the two regions, and a minimum of two for each of the other two bands (red and blue).

We were primarily interested in imaging with a green filter (such as we are currently using at Kestrel). Fifty percent (50%) of the data will be with this filter. We tried to have twenty-five percent (25%) of the data imaged with a broadband red filter and twenty-five percent (25%) with a broadband blue filter.

We had 35mm color images, and/or digital photographs taken with a standard fundus camera. The individual's summary examination report was supplied. A photo of the pupil for each subject was recorded to document the pupil size during the photo session.

4.4 Results

Examples of these images are shown in figure 10. Comparing standard fundus imaging (figure 10, left) to the superresolution image of the inferior aspect of the optic nerve head of one of the glaucoma subjects, we notice the fine vessel architecture visible on the surface of the optic nerve in comparison to the information in the standard fundus imaging. Such vascular detail may be of clinical significance in the pathophysiology of glaucoma. In Figure 11, the comparison of the superresolution image in a diabetic with exudates and microaneurysms demonstrates the detail of these round lesions and also the detail of the fine vasculature near the macula. There are also some intriguing vascular shapes seen in this superresolution image which may give clues to further abnormal changes not seen with the standard fundus imaging. Suggestions of tissue changes which possibly could be detected with this device will be demonstrated in future rigorous clinical trials.

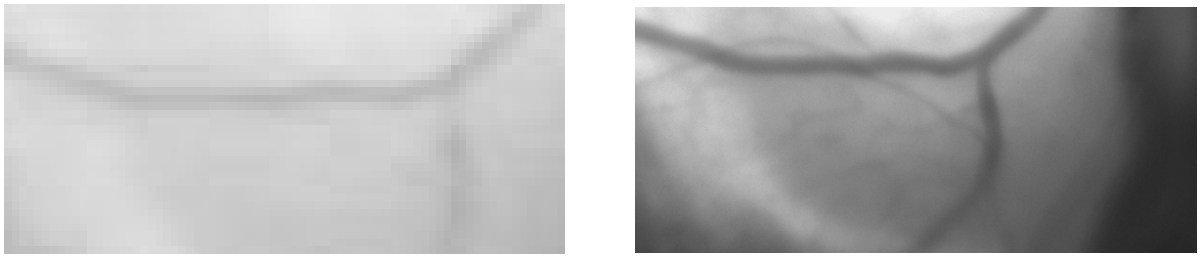

Figure 10. A fine vascular vessel in not visible on the regular fundus image (left)

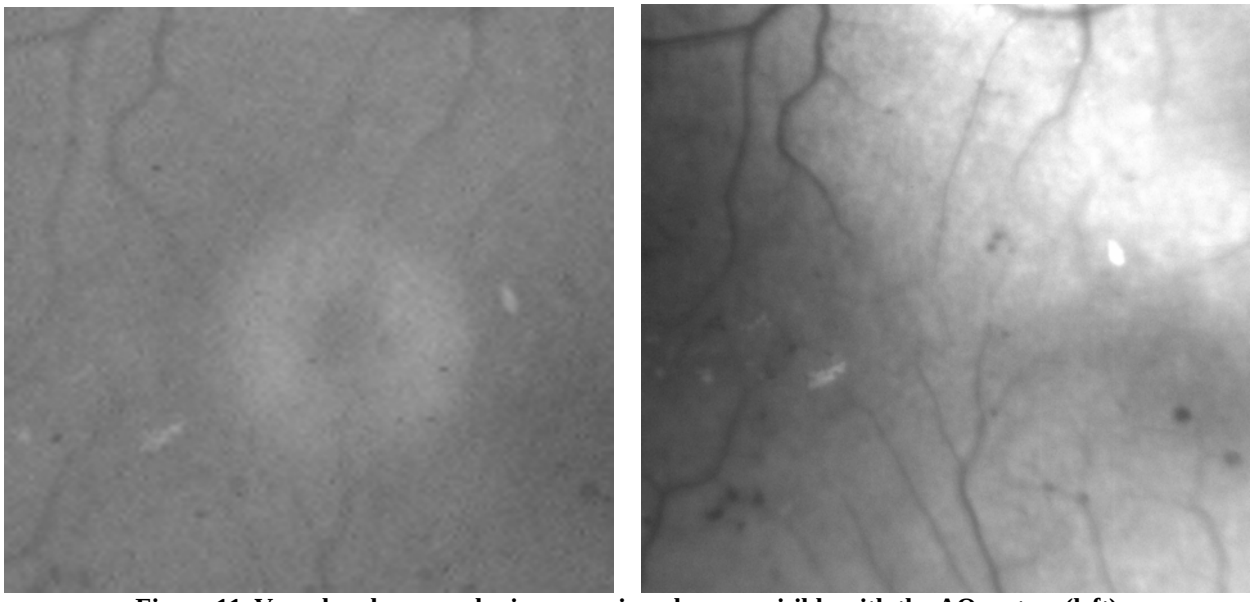

Figure 11. Vascular shapes and microaneurisms become visible with the AO system (left)

5. CONCLUSION AND FUTURE WORK

We have demonstrated a High Resolution Adaptive Optics Fundus Imager that is capable of dramatically increasing the resolution of retinal imaging in a clinical environment. Results show an increased ability to detect small retinal features that were not detectable with existing instrumentation. Kestrel Corporation is actively continuing its work in high resolution retinal imaging and will soon deploy its next generation system at Iowa University Ophthalmology Clinic to investigate the clinical relevancy of the system with Dr. Stephen Russell.