VNIVERSITAT DE VALÈNCIA

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Memoria presentada por

Aikaterini Moulakaki

Para optar al grado de

DOCTOR en OPTOMETRÍA Y CIENCIAS DE LA VISIÓN

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Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of Learning.

El Catedrático de Universidad Robert Montés-Micó de la Universidad de Valencia CERTIFICA que la presente memoria ‘Crystalline lens response to different optical signals’, resume el trabajo de investigación realizado, bajo su dirección, por Dña. Aikaterini Moulakaki y constituye su Tesis para optar al Grado de Doctor en Optometría y Ciencias de la Visión.

Y para que así conste, y en cumplimiento de la legislación vigente, firma el presente certificado en Valencia, a Noviembre de dos mil dieciséis.

Fdo. Robert Montés-Micó

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Additionally, special thanks to Dr. Hema Radhakrishnan for having me at the University of Manchester for my secondment and helping me to successfully complete several experimental studies additional to this project.

Dedication

To my mother who left early from life.

Abstract

It is well known that the eye is capable of changing its power, in order to focus on objects that are placed on different distances. The change in focus of the human eye is established as accommodation and it is vital for the visual performance of the human eye, as accommodation has an essential contribution to it. Retinal image quality also influences the visual performance of the human eye, as well as the resolution of the images formed on the retina. The retinal image quality is described in terms of ocular aberrations.

The aim of this Thesis was to investigate the crystalline lens response to different optical signals. In order to achieve the aim of the study, the most widely accepted and powerful technologies of wavefront sensing, optical coherence tomography and adaptive optics were used to objectively appraise the accommodation mechanism of the human eye under different conditions.

In particular, initially it was assessed the accommodation response after short reading periods with two different handheld electronic devices, as well as the potential differences in accommodation response at various stimulus vergences, using a wavefront aberrometer. The acquired accommodation responses were not affected by the electronic devices employed due mainly to the young age and the level of the amplitude of accommodation of the subjects that were enrolled.

Then, a two-scaled study was conducted between different age groups to evaluate the changes that occur at the main structures that take part in the process of accommodation in the anterior segment of the eye (i.e. lens curvature and ciliary muscle area) using optical coherence tomography. It was identified that there are significant variations in the anterior segment structures that occur with the accommodation process. Whereas, with aging, the eye undergoes some significant anatomical changes that have an impact on the quality of vision and thus, of life.

Finally, using the adaptive optic system, it was investigated how the monochromatic higher-order aberrations influence on the accommodation response of the eye. More specifically, the accommodation response of the subjects' eye was measured under different conditions; with the

natural aberrations being present and with the odd and even higher-order aberrations being corrected. The odd and even higher-order aberrations were not helping the visual system to choose the right direction of accommodation, as with their partial correction the accommodation performance remained unaffected, in comparison to the condition of the total aberrations presence.

This Thesis has provided with valuable information about the accommodation mechanism and aging process of the eye that can be useful to improve the quality of vision and further of life of individuals with different age.

Resumen

El cristalino es una parte integral de la óptica del ojo humano. Junto con la córnea, el cristalino focaliza la luz que entra en el ojo sobre la retina. En sujetos jóvenes, el cristalino altera su forma aumentado el poder óptico del ojo con el fin de enfocar objetos cercanos, un proceso conocido como acomodación ocular. Esta capacidad del cristalino disminuye con la edad. La pérdida de la acomodación es también conocida como presbicia.

El cristalino se posiciona anatómicamente dentro del ojo gracias a las fibras de las zónulas que lo sostienen. Las fibras de las zónulas se organizan de manera radial alrededor del cuerpo ciliar hasta los anclajes en la parte periférica de la cápsula del cristalino. El cuerpo ciliar es un anillo, conectado con la esclera, consistente de músculos y tejidos que son adyacentes al iris. La superficie anterior del cristalino está rodeada por el humor acuoso formando el denominado segmento anterior del ojo, mientras que la superficie posterior del mismo está rodeada por el humor vítreo, el cual rellena el área entre el cristalino y la retina formando el denominado segmento posterior del ojo.

El cristalino está caracterizado por su elevado grado de transparencia. Esto es debido al posicionamiento adecuado de las fibras celulares que lo componen y su homogeneidad. El cristalino también contribuye a un mejor rendimiento óptico, ya que su índice de refracción es mayor en comparación con los del humor acuoso y vítreo.

La habilidad que posee un sujeto para acomodar disminuye con la edad de manera regular hasta su pérdida. La condición de incapacidad en la acomodación se conoce como presbicia. La progresión de la presbicia puede ser evaluada mediante la estimación de la amplitud de la acomodación. La amplitud de la acomodación se deteriora de manera lineal en un ojo que pasa de la juventud a la presbicia. El déficit de la amplitud de la acomodación resulta en una disminución de la potencia óptica del cristalino y en consecuencia en la habilidad de enfocar objetos cercanos sobre la retina.

Con el envejecimiento del ojo, el cristalino se ajusta a una serie de cambios que provocan la aparición de la presbicia. La principal causa de ésta es la rigidez de la sustancia que conforma el cristalino, la cual rápidamente disminuye la capacidad de variación de la forma del mismo cuando tiene que responder a un cambio determinado de la tensión zonular. Sin embargo, el grado de rigidez del cristalino es una de las causas de la presbicia, a las que hay que añadir además posibles cambios geométricos en el cristalino, en el cuerpo ciliar y en las fibras zonulares.

Otro parámetro que puede afectar negativamente a la acomodación del ojo es la reducción de la contracción del músculo ciliar con la edad. De todos modos, se ha concluido que el músculo ciliar tiene capacidad de contraerse a pesar de que la acomodación del cristalino se ha perdido completamente.

Las limitaciones en la visión que resultan de la presbicia pueden superarse con diversas soluciones. La solución óptica más ampliamente aceptada para la corrección de la presbicia es el uso de lentes oftálmicas para la visión de cerca o para la visión a diferentes distancias (progresivas). También es posible considerar la técnica de monovisión, que consiste en compensar un ojo para visión de lejos y el ojo contralateral para visión de cerca. Hasta la fecha no existe una solución disponible que proporcione una restauración real de la acomodación medida objetivamente de forma que sea comparable con la respuesta del ojo joven. A pesar de ello, se han propuesto numerosas soluciones con el fin de restaurar la acomodación.

En particular, estas soluciones –las cuales son consideradas como una visión convencional del mecanismo de la acomodación– pueden dividirse en tres categorías: implante de lentes intraoculares (LIOs) acomodativas, reemplazo del contenido del cristalino y lensectomía con láser de femtosegundo. Aunque las LIOs acomodativas y el reemplazo del contenido del cristalino son métodos generalmente predecibles para el tratamiento de las cataratas, si alguno de ellos resultara fiable para la restauración de la acomodación entonces sería factible aplicarlos tanto para la eliminación de las cataratas como para la corrección de la presbicia.

Las soluciones para tratar la presbicia se basan en la consideración de que el sistema acomodativo se basa en el aumento de potencia de la parte ópticamente activa, alcanzando el cambio necesario en su geometría. Asegurar que el sistema modificado funcione correctamente requiere la comprensión de los mecanismos del sistema en relación a los cambios adicionales que son causados por la solución.

En las últimas décadas, se ha estudiado de manera exhaustiva la relación entre el desarrollo de la miopía y el grado de trabajo en cerca que un individuo realiza. Los individuos que pasan mucho tiempo realizando tareas cercanas, es decir, lectura, escritura, etc., tienden a desarrollar errores de refracción como miopía. Otro parámetro que conduce a la evolución de un ojo miope es el grado y la precisión del proceso de acomodación. Más específicamente, varios estudios han demostrado que los niños miopes presentan un mayor retraso acomodativo para objetos cercanos que los niños emétropes. Sin embargo, en todos estos estudios, se verificó que el aumento del retraso acomodativo no era perceptible en los adultos miopes tal y como era notorio en niños miopes. Esto se debe a la pausa del desarrollo de la miopía. Por lo tanto, el retraso acomodativo no se considera como la principal razón para el desarrollo de la miopía.

Sin embargo, hay teorías que se refieren a la relación entre el trabajo de cerca y el retraso acomodativo mostrando que el desarrollo del ojo miope es el resultado del desenfoque en la retina central. Todas las evidencias mencionadas apoyan la correlación entre el error refractivo miópico y el espesor del cuerpo ciliar, el trabajo en cerca y el retraso acomodativo.

Las aberraciones oculares permiten describir la calidad de las imágenes formadas en la retina. Dado que la acomodación se consigue mediante cambios en la forma y la posición del cristalino, se esperaría que las aberraciones del ojo cambiasen con la acomodación. Las aberraciones monocromáticas de bajo orden (1º y 2º orden) describen los errores de refracción simples: miopía, hipermetropía y astigmatismo. Mientras que las aberraciones monocromáticas de alto orden (3º, 4º, 5º, etc.) describen aberraciones tales como la aberración esférica o el coma. La aberración cromática es el resultado de la dependencia del índice de refracción con la longitud de onda. La aberración cromática se divide entre aberración cromática longitudinal y transversal.

Hasta la fecha se han desarrollado varios métodos para medir las aberraciones oculares. Es común utilizar estos métodos, que caracterizan el frente de onda, ya que permiten mapear los errores ópticos y el poder refractivo del ojo. Utilizando estos sofisticados instrumentos es factible medir con precisión y registrar todas las aberraciones ópticas del ojo. En particular, los principales métodos que se han desarrollado para medir las aberraciones oculares son el sistema de trazado de rayos, el de Tscherning y el de Shack-Hartmann. En todos estos métodos las aberraciones oculares se expresan y cuantifican en forma de aberración del frente de onda y se describen a partir de la clasificación de polinomios de Zernike.

La presente Tesis tiene como objetivo investigar la interacción entre la respuesta del cristalino y las aberraciones ópticas mediante la realización de diferentes estudios. Cada estudio conforma un capítulo separado que se refiere a continuación en este resumen.

Para empezar, el uso de ordenadores y dispositivos electrónicos digitales tanto para actividades profesionales como no profesionales se ha vuelto más frecuente en la sociedad moderna a nivel mundial. Los individuos de todas las edades muestran preferencia en el uso de dispositivos electrónicos portátiles (por ejemplo, teléfonos inteligentes, tabletas) para comunicaciones escritas (por ejemplo, mensajes de texto, correo electrónico, acceso a Internet). Esto resulta en la eventual sustitución de los materiales impresos ya que el uso de dispositivos electrónicos se ha convertido en parte integral de la vida cotidiana de los individuos.

Sin embargo, la pantalla relativamente pequeña y el tamaño de texto de tales dispositivos requieren distancias de trabajo cercanas que afectan a la acomodación necesaria por el cristalino. Esto es necesario para tener una visión clara y nítida en tales distancias. Por lo tanto, el uso prolongado de tales dispositivos en distancias de trabajo cercanas puede causar el desarrollo de síntomas dañinos como fatiga ocular, malestar ocular, ojo seco, diplopía y visión borrosa.

Por lo tanto, el objetivo del tercer capítulo de la presente Tesis fue evaluar la respuesta acomodativa después de cortos períodos de lectura utilizando una tableta y un teléfono inteligente, así como determinar las posibles diferencias en la respuesta acomodativa en diferentes vergencias de estímulo con un aberrómetro Hartmann-Shack. Para satisfacer las necesidades del estudio, dieciocho sujetos sanos (edad media: 28 ± 1,9 años, rango: 25 a 30 años) con astigmatismo inferior a 1 D, agudeza visual corregida 20/20 o mejor y hallazgos normales en examen oftálmico fueron incluidos en el estudio. Las respuestas acomodativas se midieron en tres condiciones diferentes: (i) relajado, (ii) después de leer 10 minutos en un iPad mini, y (iii) después de leer 10 minutos en un iPhone 4S. El material de lectura consistía en un texto con letras negras sobre un fondo blanco. El texto fue presentado en pantallas del iPad mini y del iPhone 4S con un tamaño de fuente que corresponde a 20/20 de agudeza visual.

Ambos dispositivos se colocaron a una distancia de 0,25 m de los ojos del sujeto. Los sujetos fueron instruidos a leer en silencio el texto durante 10 min. Después de completar cada condición, se obtuvieron tres medidas de respuesta acomodativa monocularmente a las vergencias de estímulo de 0,0, 1,0, 2,0, 3,0 y 4,0 D, empleando el aberrómetro irx3 Hartmann-Shack. Así, se registraron 15 mediciones de respuesta acomodativa con un total de 45 medidas para cada ojo. En cada una de las condiciones antes mencionadas, las medidas se recogieron en días diferentes al proporcionar aleatoriamente los dispositivos a los sujetos.

Para obtener los valores de la respuesta acomodativa, el coeficiente de Zernike de segundo orden (desenfoque) se convirtió a dioptrías. Se realizó un análisis estadístico para estimar la varianza sobre las diferentes vergencias de estímulo para las tres condiciones de acomodación. No se encontraron diferencias estadísticamente significativas ($p > 0,05$) entre las respuestas de acomodación en todas las condiciones.

Además, se encontró un incremento moderado pero gradualmente creciente del coma para cada condición. Mientras que la aberración esférica disminuyó a medida que aumentaban las vergencias del estímulo. Estos resultados se compararon con la respuesta acomodativa ideal, demostrando que un cierto valor de retraso acomodativo estaba presente para todas las vergencias de estímulo.

Los resultados de este capítulo apoyan la hipótesis de que la diferencia entre las respuestas acomodativas ideal y real se atribuye principalmente a parámetros como la agudeza visual cercana, la profundidad de enfoque, el diámetro de la pupila y las aberraciones de frente de onda que están asociados con el proceso de acomodación. Las aberraciones del frente de onda también fueron dependientes del tamaño de la pupila seleccionado en el estudio, ientras que la respuesta acomodativa adquirida no dependía del dispositivo electrónico empleado en cada condición. Esto se asoció principalmente con la edad temprana y el nivel de amplitud de acomodación de los sujetos que participaron.

Además, como se ha mencionado antes, la acomodación del ojo humano es un proceso muy fluctuante y dinámico. La eficiencia de este proceso disminuye con la edad puesto que el cristalino pierde su elasticidad y la actividad del músculo ciliar se deteriora, dando lugar a la presbicia. Sin embargo, esta teoría puede no explicar completamente el desarrollo de la presbicia, ya que la respuesta del cristalino in vivo a la contracción del músculo ciliar sigue siendo objeto de investigación debido principalmente a las dificultades de visualización que se han enfrentado en las últimas décadas.

Además de la presbicia, existen otros tipos de disfunciones de la acomodación que son igualmente significativas para la presbicia y que influyen negativamente en la calidad de la vida diaria del individuo. La fuente de estas anomalías sigue siendo desconocida. Esto también se aplica en casos de inicio de miopía donde es evidente un mayor retraso en la acomodación sin que se identifique aún la fuente de tal anomalía en el proceso acomodativo. Por lo tanto, es esencial evaluar los cambios de las estructuras anatómicas en el segmento anterior del ojo en términos de longitudes axiales, curvatura del cristalino y área del músculo ciliar con la acomodación. El estudio del cuarto capítulo de la Tesis utiliza las capacidades de imagen del Visante® omni OCT para lograr este propósito.

Se incluyeron veinticinco ojos derechos de veinticinco adultos sanos de 20 a 45 años de edad (29,5 ± 6,7 años) y se midieron con el sistema Visiante® omni OCT. El error de refracción promedio fue de -0,77 ± 1,90 D. Los sujetos tenían también suficiente amplitud de acomodación (al menos 3,00 D) y agudeza visual corregida igual o superior a 20/20. El grosor central de la córnea (CCT), la profundidad de la cámara anterior (ACD), el grosor del cristalino central (CLT), la longitud del segmento anterior (ASL), la curvatura anterior del cristalino (ALC), la curvatura posterior del cristalino y el área del músculo ciliar fueron evaluados. Todas las medidas se tomaron para el estímulo presentado a 0,0 D en relación con el punto lejano del paciente y para los estímulos crecientes de -1,0 D, -2,0 D y -3,0 D de vergencia en relación con el estado acomodativo del ojo del sujeto. Todas las capturas se realizaron en el meridiano horizontal.

Se pidió a los pacientes que mantuvieran su fijación en el estímulo del instrumento antes de tomar la medida. Todas las medidas para cada paciente que tomó parte en el estudio se obtuvieron durante una sola sesión. El software utilizado de Visante® OCT dispone de un conjunto de diferentes tipos de exploración. Tres de ellos fueron utilizados en este estudio para evaluar los diferentes parámetros. Se comparó la variación de estos parámetros para los diferentes niveles de acomodación. En particular, con respecto a las medidas axiales centrales que se analizaron, no se encontró que las variaciones de la CCT fueran estadísticamente significativas (p> 0,05) entre ninguno de los estímulos acomodativos. La ACD mostró una reducción significativa (p <0,05) que fue mayor cuanto mayor era la vergencia del estímulo.

Al evaluar parámetros más internos del ojo, también se encontró un aumento significativo de CLT con la acomodación. La ASL también aumentó con acomodación (p <0,05) mostrando un movimiento hacia atrás del polo posterior. ALC y CMA se incrementaron significativamente (p <0,05) con la acomodación para todas las vergencias de estímulo presentadas. Se encontró que los cambios de la ALC eran significativos (p <0,05) entre los estímulos 0,0 D y -3,0 D, así como entre -1,0 D y -3,0.

Como es evidente a partir de los resultados del cuarto capítulo, hay variaciones significativas en las estructuras del segmento anterior que se producen con la acomodación. El estudio de estos cambios proporciona información adicional sobre el mecanismo de la acomodación que puede ser útil para los profesionales con el fin de lograr una mejor comprensión de este proceso y para ayudarles a tomar decisiones clínicas. Del mismo modo, el ojo humano está formado por estructuras complejas que hacen uso de diferentes mecanismos para lograr una función visual adecuada. Muchas de estas funciones se alteran a medida que el ojo envejece.

Una mejor comprensión de las alteraciones en la función acomodativa con el envejecimiento puede conducir a desarrollar nuevas soluciones ópticas y/o mejorar las existentes. Esto es particularmente importante ya que la reducción de la acomodación conduce a una disminución de la calidad de vida.

Para lograr esto, es crucial visualizar las estructuras de interés en el segmento anterior. Por lo tanto, el quinto capítulo de la Tesis tiene como objetivo evaluar las principales estructuras que participan en el proceso de acomodación en diferentes grupos de edad a través de OCT. Un total de 14 sujetos fueron incluidos en el estudio. Estos se dividieron en dos grupos: adultos jóvenes (20-25 años) y adultos (35-40 años). Todos los sujetos tenían suficiente amplitud de acomodación (al menos 3,00 D) y una agudeza visual corregida de al menos 20/20 en equivalente Snellen.

El equipo que se utilizó en el estudio para la visualización de las estructuras oculares fue el sistema Visante® omni OCT . Se evaluaron el espesor central del cristalino, el radio de curvatura anterior del cristalino y el área del músculo ciliar (CMA). Todas las mediciones se tomaron para el estímulo presentado a 0,0 D en relación con el punto remoto del paciente y para estímulos crecientes de -1,0 D, -2,0 D y -3,0 D de vergencia. Todas las capturas se realizaron en el meridiano horizontal.

Se pidió a los sujetos que mantuvieran su fijación sobre el estímulo de fijación del instrumento antes de capturarlos. Todas las medidas para cada paciente que tomó parte en el estudio se obtuvieron durante una sola sesión. El software utilizado de Visante® OCT dispone de un conjunto de diferentes tipos de exploración. Tres de ellos fueron utilizados en el estudio para evaluar los diferentes parámetros. Se comparó la variación de estos parámetros para los diferentes niveles de acomodación. Más específicamente, se encontró que el CLT era estadísticamente diferente (p <0,05) entre los grupos de edad, lo que indica un aumento significativo con la edad tanto en el estado no acomodado como en el estado acomodado de 3,0 D. Específicamente, se encontró que el espesor era mayor en el grupo con edades comprendidas entre 35 y 40 años de edad que en el de los sujetos más jóvenes. Sin embargo, al considerar el ALC no se encontraron diferencias estadísticamente significativas. En cuanto al CMA se observó el mismo resultado, sin diferencias significativas. Aunque no se encontraron diferencias significativas, se encontró que el radio del ALC era menor en el grupo de adultos, mientras que el CMA produjo valores ligeramente mayores para el grupo de adultos jóvenes.

Los resultados de este capítulo indican que, con el envejecimiento, el ojo experimenta cambios anatómicos que tienen un impacto en la calidad de la visión y en la calidad de vida. El estudio de estas variaciones proporciona a los profesionales información interesante sobre el proceso de envejecimiento del ojo que puede ser útil para proporcionar nuevos métodos destinados a retrasar la aparición de la presbicia.

Aparte del punto de vista fisiológico, una respuesta de acomodación adecuada es desencadenada por varias señales. Estas señales se caracterizan por parámetros subjetivos u objetivos que influyen en la calidad de la imagen retiniana. Se ha demostrado que el desenfoque es causado por una respuesta acomodativa incorrecta que se puede caracterizar por un signo positivo o negativo, en función de si el plano de imagen está delante o detrás de la retina. Adicionalmente, se ha podido demostrar que la aberración cromática longitudinal proporciona una señal direccional para la acomodación a tamaños de pupilas grandes a pesar de mayores niveles de aberraciones monocromáticas. Sin embargo, ha habido casos en los que la capacidad de acomodación no se perdió cuando las señales de la aberración cromática fueron eliminadas artificialmente. Esto indica la coexistencia de señales ópticas adicionales, que juegan un papel en la respuesta acomodativa.

Las aberraciones monocromáticas (excepto el desenfoque) también se consideran señales ópticas. Además, algunas aberraciones tienen una mayor contribución a la respuesta de acomodación que otras. Sin embargo, todavía se está investigando el papel exacto de las diferentes aberraciones en la respuesta acomodativa del ojo y si las aberraciones pares e impares contribuyen como signo señalado a la dirección de desenfoque o no. Así, el séptimo capítulo de la Tesis tiene como objetivo investigar el efecto potencial que las aberraciones monocromáticas impares y pares pueden tener sobre la respuesta acomodativa del ojo humano.

Ocho sujetos adultos jóvenes, que podrían acomodar en condiciones de luz monocromática, participaron en el estudio. Los sujetos se caracterizaron por astigmatismo inferior a 1 D, agudeza visual corregida 20/20 o mejor y hallazgos normales en un examen ocular. Se utilizó un sistema de óptica adaptativa para medir la respuesta acomodativa de los ojos de los sujetos bajo tres condiciones diferentes. En la primera condición estaban presentes las aberraciones naturales del sujeto, mientras que en las otras dos condiciones se corrigieron las aberraciones pares e impares del sujeto. Para lograr esto se empleóun software personalizado implementado sobre el sistema de óptica adaptativa. Este software controlaba adicionalmente el espejo deformable del sistema para corregir las aberraciones correspondientes a cada condición. En todas las condiciones las mediciones se realizaron monocularmente y se obtuvieron a partir del ojo dominante de cada sujeto.

Las medidas por tanto se obtuvieron bajo tres condiciones diferentes: (i) aberraciones naturales presentes, (ii) aberraciones de orden par corregidas y (iii) aberraciones de orden impar corregidas. En cada condición se adquirieron tres medidas para diferentes demandas acomodativas de 0,0 a 4,0 D, con un paso de 0,5 D. Así, se registraron 27 medidas de frente de onda por condición, con un total de 81 medidas para cada ojo. A los sujetos también se les permitió descansar entre los ensayos.

Para obtener los valores de la respuesta acomodativa, el coeficiente de Zernike de segundo orden (desenfoque) se convirtió a dioptrías. Luego, se visualizó la media de las tres medidas consecutivas para cada condición y demanda acomodativa considerada en el estudio. Los resultados mostraron diferencias estadísticamente no significativas (p = 0,26) entre las respuestas acomodativas bajo las tres condiciones. El retraso acomodativo fue mayor para las demandas acomodativas de 1.5D, 3.0D, 3.5D y 4.0D para la condición en la que se corrigieron las aberraciones pares, en comparación con la obtenida para las aberraciones naturales y corrección de las aberraciones de orden impar para las mismas demandas acomodativas.

Por lo tanto, este estudio demuestra que cuando se elimina la aberración cromática longitudinal como pista óptica para la acomodación, todos los sujetos que son capaces de acomodar bajo luz monocromática son capaces de acomodar adecuadamente a pesar de la eliminación de las aberraciones pares e impares de alto orden. Con este estudio, se sugiere que las aberraciones de orden par e impar no proporcionan ayuda para la acomodación ya que la respuesta acomodativa de todos los sujetos no se vio afectada por la corrección parcial de estas aberraciones.

Para concluir, todo lo anterior se describe con detalle en cada capítulo junto con el uso de gráficos para una mejor comprensión.

List of Figures

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List of Abbreviations

A: Accommodation

AC: Accommodation Convergence

ANCOVA: ANalysis of COVAriance

ANOVA: ANalysis Of VAriance

ACD: Anterior Chamber Depth

ALC: Anterior Lens Curvature

ASL: Anterior Segment Length

CCT: Central Corneal Thickness

CCD: Charge Coupled Device

CMA: Ciliary Muscle Area

CLT: Crystalline Lens Thickness

DoF: Depth of Field

DoF: Depth of Focus

HR: High Resolution

HSD: Honest Significant Difference

IR: InfraRed

IOL: IntraOcular Lens

LSD: Light Shaping Diffusor

LogMAR: Logarithmic Minimum Angle of Resolution

LCA: Longitudinal Chromatic Aberration

MRI: Magnetic Resonance Imaging

OCT: Optical Coherence Tomography

OPL: Optical Path Length

PSF: Point Spread Function

PSD: Position Sensitive Detector

PLC: Posterior Lens Curvature

rANOVA: repeated ANalysis Of VAriance

RRT: Retinal Ray Tracing

RMS: Root Mean Square

SD: Standard Deviation

UBM: Ultrasound BioMicroscopy

VDTO: Visual Display Terminal Operator

List of Symbols

A: Accommodation

AD: Accommodation Demand

AR: Accommodation Response

$\mathbf{C_n^m}$**:** Coefficient factor describes Zernike polynomials

$\mathbf{C_2^{-2}}$**:** Coefficient factor connected with oblique astigmatism

$\mathbf{C_2^0}$**:** Coefficient factor connected with defocus

$\mathbf{C_2^2}$**:** Coefficient factor connected with vertical astigmatism

$\mathbf{C_3^{-3}}$**:** Coefficient factor connected with vertical trefoil

$\mathbf{C_3^{-1}}$**:** Coefficient factor connected with vertical coma

$\mathbf{C_3^1}$**:** Coefficient factor connected with horizontal coma

$\mathbf{C_3^3}$**:** Coefficient factor connected with oblique trefoil

$\mathbf{C_4^0}$: Coefficient factor connected with spherical aberration

d: Distance

m: index describes the radial term of the aberration

n: index describes the angular term of the aberration

r: pupil radius

W: Wavefront

$\mathbf{Z_n^m}$: Zernike polynomial

ρ: radius

θ: angle

List of Units of Measurements

cd: candelas

D: Dioptres

m: metre

µm: micrometre

µW: micro Watt

mm: millimetre

msec: millisecond

min: minute

nm: nanometre

Table of Contents

CHAPTER 1

Introduction

1.1 Physiological background

The crystalline lens is an integral part of the optics of the human eye. Along with the cornea, the crystalline lens focuses the light that enters the eye on to the retina. In young individuals, the lens alters its shape increasing the optical power of the eye, in order to bring the objects in focus; a process known as accommodation of the eye. This capability of the lens eventually decreases as age passes until it is usually mislaid at the age of 50 years. The loss of accommodation is well known as presbyopia, of which its predominant causes remain contentious.

1.1.1 The crystalline lens

The position of the crystalline lens within the eye is illustrated on the Figure 1.1. The crystalline lens lies on the optical axis directly behind the iris. Its shape is approximately that of an ablate spheroid having a diameter of 9-10 mm and a thickness of 4-5 mm (along the axis of the eye) in an adult. The substance of the lens is displayed on the Figure 1.2. In particular, the lens is exteriorly covered by a capsule; an extracellular membrane of almost 10 μm thickness (albeit this differs according to the position of the lens and age of the eye), *(Fisher and Pettet, 1972, Barraquer et al., 2006a)*.

Figure 1.1: *Schematic layout of the structure of the eye globe (Adopted from (Damanakis, 1999)).*

The substance of the lens within the capsule is composed of specialized cells known as lens fibres, since their long thin form characterizes them. These cells are sorted as elderly concentric shells, with each cell being shifted from the anterior pole lens area (closest to the cornea) to the posterior pole lens area (closest to the retina). Nonetheless, during this run most of these cells are assigned with other cells of the same shell, generating a line pattern noted as sutures. These cell patterns become more complex, as proceeding exteriorly to the lens.

Figure 1.2: *The substance of the lens and the tissues encircling it (Adopted from (Damanakis, 1999)).*

New cell shells are developed at the exterior part of the lens substance throughout life. The new cell fibres are generated from the differentiation of the peripheral constituents of a layer comprised of cuboid epithelial cells, which lie on the anterior surface of the lens capsule. The cuboid epithelial cells are responsible for the evolution and preservation of the lens capsule. Since, the new cell fibres are developed to form a shell, they lose their cellular core remaining mainly inert. Based on the pattern of the shell growth, the age of the lens tissue is gradually increased from the outward (capsule) to inward (core) part of the lens. The elderly central part of the lens involves the core of the lens, whereas the rest part of the lens compounds its cortex. Between these two parts there is a sufficient delimitation, which is visible with the in vivo use of the slit-lamp photography *(Brown, 1973, Dubbelman et al., 2003b)*. This may be related with a barrier in the diffraction, which is detected in a similar position within the lens *(Sweeney and Truscott, 1998, Moffat and Pope, 2002)*.

The crystalline lens is being held at its position, due to the arrangement of the zonular fibres within the eye. The zonular fibres are radially organized, surrounding the ciliary body up to the attachment points of the peripheral part of the lens capsule. The ciliary body is a ring consisting of muscles and tissues that are adjacent to the iris and connected with the sclera (the white outer layer of the eyeball). The anterior surface of the lens is surrounded with the aqueous humour of the anterior chamber of the eye, while the posterior surface of the lens is surrounded with vitreous humour, which fills the area between the lens and retina of the posterior chamber of the eye.

The crystalline lens is characterized by its high degree of transparency. This is due to the properly placement of the lens cell fibres and their homogeneity. The crystalline lens, also, contributes to a better optical performance, as its refractive index is higher in comparison with those of the aqueous and vitreous humours. This results from the high protein content of the lens cell fibres (approximately 35% of their weight) *(Heys et al., 2004)*. The refractive index of the lens is not constant along its surface, but it eventually increases from 1.37 on its surface to 1.42 on its centre, reflecting the variety of the protein content within the lens *(Jones et al., 2005).*

1.1.2 The mechanism of accommodation

The crystalline lens is the component of the eye, which provides adjustable optical power in young eyes. This is achieved with the alteration of its shape, induced by the contraction of the ciliary muscle. Once the ciliary muscle is relaxed acquires a relatively large radius, which induces tension to the zonular fibres stretching the lens radially and outwardly. As a result the lens flattens and reduces its optical power, bringing distant objects in focus on to the retina. On the other hand, once the ciliary muscle is contracted moves radially and inwardly, reducing the tension to the zonular fibres and permitting to the lens to adapt a more spherical form. As a result the lens curvature increases, as well as its optical power, bringing close objects in focus on to the retina. The mechanism that activates the second configuration is established as accommodation, with the lens and eye to be characterized as accommodated, when viewing near objects. The reverse mechanism that activates the first configuration is established as disaccommodation, with the lens and eye to be characterized as disaccommodated (or unaccommodated), when viewing distant objects.

Both states of the lens are demonstrated on Figure 1.3. Furthermore, the gradient refractive index of the lens substance implies that the increase in lens power from disaccommodated to accommodated is not only dependent on the increase in curvature of both lens surfaces, but also it is dependent on the changes in curvature of the contours of the constant refractive index within the lens *(Garner and Smith, 1997)*, although this impact is difficult to be determined explicitly. Moreover, alterations in lens shape drive the onward movement of the anterior surface of the lens, at the same time that the posterior surface of the lens remains roughly constant. Overall, these variations are relatively small and contribute to a little modification of the power of the eye.

Figure 1.3: *Schematic view of the mechanism of accommodation. In the disaccommodated state (left half), the light from a far object is focused on the retina. While, in the accommodated state (right left), the light from a near object is focused on the retina (Adopted from (Damanakis, 1999).*

The aforementioned description of the mechanism of accommodation is widely accepted universally, and it is the one that essentially suggested by von Helmholtz (1855) *(Helmholtz, 1855b)*. Nevertheless, so far, alternative mechanisms of accommodation have been proposed. For example, on 1970 Coleman recommended that the pressure of the vitreous humour to the posterior surface of the lens plays a vital role in identifying the accommodated and disaccommodated shapes of the crystalline lens *(Coleman, 1970)*. In the meantime, on 1992 Schachar disputed over the increased curvature of the accommodated lens. He supported that this effect is achieved by the increase of the zonular tension on to the equator of the lens *(Schachar, 1992)*. This suggestion comes on the contrary with von Helmholtz's approach. Still, after all most of the evidences, regarding the mechanism of accommodation, are in favour of von Helmholtz's theory. Thus, it is pointless to study in detail alternative assumptions. For example, on 1982 Fisher contested against Coleman's suggestion *(Fisher, 1982)*, while Wilson (1997) provided proofs across Schachar's mechanism *(Wilson, 1997)*.

1.1.3 Changes in the crystalline lens with age

The ability of the subjects to accommodate declines with age and regularly it is lost up to the age of 50 years. The condition of incapability in accommodating is well known as presbyopia. The progression of presbyopia can be evaluated by estimating the amplitude of accommodation, which is defined as the difference between the optical power of the fully accommodated and disaccommodated eye, and it is typically measured in diopters ($D=m^{-1}$). It has been identified that the amplitude of accommodation linearly deteriorates in an eye that passes from youth to presbyopia, as seen in Figure 1.4.

Figure 1.4: *Monocular amplitudes of accommodation as a function of age (Adopted from (Plainis et al., 2014)).*

The deficit of the amplitude of accommodation results to the decrease in the optical power of the lens, when it is fully accommodated. Consequently, the ability of focusing the closest object on to the retina relents with age. This is exclusively evident as the near point approaches the least possible working distance that an individual uses (i.e. for 4D of accommodation is required a focusing ability to objects placed at a distance of 250mm, as well as objects placed at a remote distance). Even though the eye is fully presbyopic, the Depth-of-Field (DoF) provided by the pupil favours clear vision over a moderate range of distances, which are also relied upon the lighting conditions. The depth of field influences on the subjective and objective measurements of accommodation. The subjective measurements of the accommodation of the eye are depended on the subject, that reports whether it is possible to focus on a given visual target or not. While, in the objective measurements of the accommodation of the eye, the optical power of the eye is estimated by using different accommodation stimuli. In addition, a great depth of field increases the range over which a subjective focus is achieved, at the same time that the objective optical power remains constant at the same range and point. Nonetheless, it has been identified that the residual objective accommodation in subjects older than the age of 50 years is mainly attributed to the Depth-of-Focus (DoF), although it has not been determined, when the accommodation of the eye can be measured objectively *(Hamasaki et al., 1956)*.

With the aging of the eye, the crystalline lens and its encircling tissues are adjusted to a series of changes that lead to the development of presbyopia. The most predominant cause of this is the actual stiffness of the substance of the lens, which rapidly decreases the degree of the alteration of the lens shape, when it responds to a given change of the zonular tension *(Fisher, 1971, Glasser and Campbell, 1998b, Glasser and C.W. Campbell, 1999)*. Nevertheless, the grade of the lens stiffness is still anticipated, as the different techniques deliver different results (compare for example Fisher, 1971 and Heys et al, 2004).

Moreover, the geometrical changes in the crystalline lens, zonular fibres and ciliary body are also potential factors of presbyopia progression. On 1973, Fisher suggested that the deterioration of the amplitude of accommodation is due to the increased stiffness of the lens substance, in correlation with the reduction of the stiffness of the lens capsule and the flattening of the lens *(Fisher, 1973)*. On 1986, Koretz and Handelman proposed that a decline in traction transmission from the zonular fibres to the lens substance is due to the increase of the lens thickness *(Koretz and Handelman, 1986)*. While, on 2005, Strenk et al presented that with aging there is an onward and inward movement of the ciliary body, results to less tension on the zonular fibres *(Strenk et al., 2005)*.

Another parameter that could negatively affect the accommodation of the eye is the reduction of the contraction of the ciliary muscle with age. Even though, several studies have been concluded on the fact that the ciliary muscle is able to move, even though when accommodation of the eye is lost (for example Pardue and Sivak) *(Pardue and Sivak, 2000)*.

Overall, the past fifty years it is more evident that the life limitations have changed, resulting to a constant transition into an aging society, worldwide *(UN, 2001)*. It has been anticipated that universally at least the 1/3 of the population will be over the age of 60 years up to 2050 in the developed countries *(UN, 2001)*. Therefore, presbyopic solutions have been increased on demand, but also a continuous increase in presbyopic solutions is evident, as the population aged 45 years and above continues to increase.

1.1.4 Restoration of accommodation

The limitations in vision resulting from presbyopia can be overcome with many solutions. The most widely accepted solution to correct presbyopia is either the use of progressive ophthalmic lenses to build up spectacles for near vision (i.e. reading spectacles) or the use of multifocal ophthalmic lenses to build up spectacles for far, intermediate and near vision. Using spectacles the required change in optical power of the eye is achieved, without facing any change to the eye itself. It is, also, possible to treat the eye in a way that a multifocal effect may be created; the use of the monovision technique according to which the one eye is trained for far vision while the fellow eye is trained for near vision *(Leyland and Zinicola, 2003, Dexl et al., 2011)*. However, the actual restore of the eye accommodation is being held when the optical power of the aged eye adjusts to the response of the neurological accommodation signal in such a way that it is comparable with that of the young eye. To date, there is no available solution, which provides actual restore to the objectively measured accommodation. Nonetheless, numerous solutions have been proposed to restore accommodation (for example a review provided by Glasser, 2008) *(Glasser, 2008)*.

In particular, a solution related to the scleral expansion surgery was inspired from the under dispute accommodation mechanism proposed by Schachar (see section 1.1.2). The sclera is being modified to increase the diameter of the ciliary muscle. This solution was intended to correct the decrease of the zonular tension, which is considered to be responsible for the appearance of myopia according to the mechanism of Schachar. Nevertheless, several studies indicated that this solution is not the appropriate to restore accommodation *(Mathews, 1999, Malecaze et al., 2001)*.

The remaining solutions –which are considered to be a conventional view of the accommodation mechanism- can be divided in three categories; implantation of accommodating IntraOcular Lens (IOL), lens refilling and femtosecond laser lentotomy.

The implantation of the accommodating IOL represents a further development of the up-to-date treatment of cataract. The typical cataract surgery includes the removal of the blurred structure of the crystalline lens, which is replaced with a thin artificial intraocular lens of particular dioptric power (non-accommodating IOL). The IOL normally is placed into the remaining lens capsule. Some from the existing IOLs are designed to provide a particular amount of accommodation, translating axially to the cornea in response to the ciliary muscle contraction and thus changing the dioptric power of the eye (i.e. the Crystalens from Bausch & Lomb and the 1CU lens from Human Optics). Nonetheless, the axial movement of these lenses, which is achieved in vivo, was found to be minor and non reliable. Objective measurements suggest that these IOLs do not provide enough accommodation *(Menapace et al., 2007)*. Nowadays, additional designs are addressed to provide substantial accommodation with relatively small movements that are provided by the ciliary muscle *(Hermans et al., 2008)*.

A very common complication of the accommodating IOLs is the change in the behaviour of the epithelial cells of the crystalline lens, which is followed by the removal of the crystalline lens substance *(Wormstone et al., 2009)*. The cells tend to proliferate over the entire capsule causing substantial light scattering, when they colonize to the posterior capsule (i.e. posterior capsule opacification). This is also considered as a drawback for the non-accommodating IOLs, however it can be treated by removing the problematic part of the capsule. The accommodating IOLs face a greater difficulty, as a potential additional removal of the material of the capsule after the IOL implantation, may lead to reversely influence on the mechanical conjunction between the ciliary muscle and the lens. In general, the accommodating IOLs face greater risk of posterior capsule opacification, as their mechanical requirements restrict them to adopt characteristics similar to those of the non-accommodating IOLs, which have been proved to reduce the risk of epithelial cells proliferation.

The lens refilling method also includes the replacement of the native lens substance. In this technique, instead of implanting a preformed device, a material such as the polymer is being used to sufficiently fulfil an emptied capsule *(Parel et al., 1986)*. The refilled lens is intended to be geometrically and mechanically the same with the new lens, as well as to be correspondingly unloaded to the response of the ciliary muscle contraction. One of the challenges noted with the lens refilling is the need to acquire the desired optical properties with a limited control available from the refilling process *(Koopmans et al., 2006)*. Along with this and the polymer leakage, these issues might be overwhelmed by inducing an IOL in the anterior surface of the refilled lens *(Nishi et al., 2008)*. This reduces the mechanical equality with the new lens, though. The lens refilling also faces issues with the posterior capsule opacification *(Nishi and Nishi, 1998)*.

Even though the accommodating IOLs and lens refilling are generally predictable methods for the treatment of cataract, if any of them will be proved reliable in restoring accommodation, then it will be feasible to apply them for both clearing the cataract lens and treating presbyopia.

The lens lentotomy leaves the native lens substance in its position, in comparison to the aforementioned methods. A pulsing femtosecond laser is being used to treat non-invasively the lens along with its conformity. The laser causes an ablation on the lens substance (~ 10 μm of diameter) on a little area at its focus. The repeated application of laser is used to create the pattern of an ablated tissue, which has been formed to increase the amplitude of accommodation *(Schumacher et al., 2009)*. The ablated areas cause light scattering inside the lens, whereat to maintain the visual clarity they do not have to interlope to the optical active area, which surrounds the axis of the lens.

The aforementioned solutions for treating presbyopia are based on the raw proportion of the accommodation apparatus to transmit power to the optically active part, in order to achieve the projected change in shape and optical power. Assuring that the modified system will work properly requires the understanding of the mechanisms of the native system in relation to the additional changes that are caused by the solution.

1.1.5 Refractive errors and accommodation mechanism

Myopia is one of the most important and outstanding topic for research, as it is characterized by rampant prevalence in each population and it significantly burdens the public health of each society. Myopia is a refractive condition according to which the axial length of the eye exceeds the focal point formed by the refractive components of the eye, namely cornea and crystalline lens. This condition is routinely managed either using spectacles or contact lenses. It has been demonstrated that the correction methods of myopia consume billion dollars every year in United States of America (USA) and Europe *(Vitale et al., 2006, Vitale et al., 2008)*. For example, the prevalence of myopia has been significantly raised the past years, affecting approximately the 1/3 of the population of Western Europe and USA, as well as the 1/5 of the population of Australia *(The Eye Diseases Prevalence Research, 2004)*. Nonetheless, up to date, the stimulation of the statistically compelling increase of myopia prevalence remains unknown, as the causality of myopia development.

So far, myopia is considered as a mismatch between the power of the refractive components of the eye and its length; the eye is either too powerful in the case of refractive myopia or too big in the case of axial myopia. However, studies have been demonstrated that the myopia occurrence is mostly attributed to a large axial length of the eye and not to a powerful refractive system of it *(van Alphen, 1961)*. On the contrary of myopia exists hyperopia, which is characterized by a reverse mismatch of that corresponds to the case of myopia within the eye. More specifically, in the case of hyperopia the refractive components of the eye focus on the light entering the eye behind the retina. This is due to the axial length of the eye, which is too short. Simultaneously with either myopia or hyperopia it is possible to co-exist the astigmatism, in which the refractive components of the eye focus on the light entering the eye both in front of and behind the retina. In general, the refractive states slightly vary between the two eyes of an individual. Based on the literature, the difference of at least 1 diopters (D) within the eyes of an individual is defined as anisometropia *(Linke et al., 2011, Hashemi et al., 2011)*.

Even though, the case of myopia is fully understandable when it appears, still there is debate regarding the mechanisms underlying the growth of a myopic eye *(Vitale et al., 2008)*. Therefore, if the stimulation of myopia and the ocular mechanism leading to the growth of a myopic eye are established, then new treatments will be developed to prevent and decelerate the myopia progression.

Several studies have been proved that the myopic eye globe is more ovate than the emmetropic eye globe *(Mutti et al., 2000, Atchison et al., 2004, Logan et al., 2004)*. This relative axial elongation of the eye corresponds to a greater refractive error of the ovate eyes. Numerous researchers have been proposed different theories on how the aforementioned axial elongation occurs to the most ovate eyes. In particular, the researchers of the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study suggested that the ovate nature of a myopic eye might results of an internal source, which restricts the development of the equatorial region within the eye globe *(Mutti et al., 2000)*. The crystalline lens has been excluded from this theory, as during the conduction of in vitro experiments was identified that the lens has the capability to stretch *(Manns et al., 2007)*. Nonetheless, this does not apply for the ciliary muscle, which seems to constitute a potential source of such internal restriction *(Mutti et al., 2012)*. Additionally, Atchinson et al introduced external restrictions of the orbital wall that prevails over the ovate nature of the development of the myopic eye *(Atchison et al., 2004)*. Though, this theory was rejected by the researchers of the CLEERE Study Group when they found that myopia occurrence preceded of the rapid myopia development, axial elongation and peripheral hyperopia. The researchers justified that the accelerating pace of the myopic eye development might not occur if a constant external source (i.e. orbital wall) was restricting the equatorial evolution *(Mutti et al., 2007)*. Logan et al proposed that the axial and transverse dimensions in the development of the myopic eye might be regulated independently from each other *(Logan et al., 2004)*. Though, the CLEERE Study Group supported that is under question whether the ciliary muscle constitutes an internal source that restricts such development *(Mutti et al., 2000)*.

Functionally, the ciliary muscle is responsible for the changes that occur to the shape of the crystalline lens during the accommodation process of the eye. Through this process is possible, the forward change of the position of the image from the retina, so that the closer objects to come into focus *(Beers and Van Der Heijde, 1994, von Helmholtz, 1867)*. Furthermore, due to the behaviour of the ciliary muscle is possible the development of the eye to an axial direction. Thus, the eye is getting more ovate and myopic. For these reasons, it has been anticipated *(Gwiazda et al., 1993, Gwiazda et al., 1995, Gwiazda et al., 1999)* that there is a direct effect of the eye accommodation to its development; a correlation that will be deeply discussed later on this section.

Throughout the accommodation process, the fibres are reorganized resulting to a further inward and anterior movement of the internal part of the ciliary muscle *(Rohen, 1979)*. Although, it has been identified that the ciliary muscle maintain the previously described ability throughout life, a similar anterior/inward position to accommodation posture has been described for the aging eye *(Strenk et al., 2006, Tamm et al., 1992)*. Despite this, the aforementioned reorganization contributes to over exceed the reduction of the refractive index of the crystalline lens, which loses its ability to accommodate with age. The changes that are associated with age have been described on section 1.1.3.

To our knowledge, still remains unclear why an eye can be evolved further than its focal point, formed by its refractive components. To clarify this, several risk factors should be taken into account. For example, genetics plays a crucial role to the development of refractive errors, as it has been established that children of myopic parents have an increased probability of becoming myopic *(Mutti et al., 2002)*. Additionally, several researchers admit that the environment is considered as an important risk factor for the development of myopia. The extrapolation of the established visual stimulus that is required for emmetropization *(Wildsoet, 1997, Mutti et al., 2005)* became the origin of the most widely accepted theory, concerning to the development of a myopic eye. This theory states that a hyperopic defocus signal on the retina urges the eye to elongate, in order to meet this defocus. However, the origin and position of such defocus signal has been widely discussed over the past decades. While, it is well emphasized the role of the near work *(Angle and Wissmann, 1980, Richler and Bear, 1980, Zylbermann et al., 1993, Zadnik et al., 1994)* and accommodation lag to the development of myopia *(Gwiazda et al., 1993, Gwiazda et al., 1995, Gwiazda et al., 1999)*.

Over the last decades, it has been comprehensively studied the relationship between the myopia development and the degree of near work that an individual uses. More specifically, on 1980 Argle and Wissnam *(Angle and Wissmann, 1980)* employed data from a survey conducted from 1966 to 1970. In this survey children from 12 to 17 years old participated, so that the researchers to support the well-known ‘use-abuse’ theory for the development of myopia. This theory refers to the increase of myopia prevalence in educated populations, as it is obvious that a great part of near work is employed by educated individuals. The initial theory indicated that individuals who spend plenty of time for near tasks (i.e. reading, writing, etc.) develop refractive errors (i.e. myopia). Additionally, on 1980 Richler and Bear found a correlation between refractive errors and near work (hours per day) in a population namely Newfandlanders of age more than 5 years old *(Richler and Bear, 1980)*. In particular, the researchers demonstrated that the refractive error increased as the hours of doing near work increased per day. In a study composed of 870 teenagers, Zylbernam et al (1933) found that a subset of 193 Orthodox Jewish male students yielded significantly greater degree and prevalence of myopia in comparison to the rest sample *(Zylbermann et al., 1993)*. The researchers assumed that this was due to an experiment, which was characterized by sustain near vision and repeatedly changes in accommodation. Moreover, Zadnik et al (1994) *(Zadnik et al., 1994)* and the Orinda Longitudinal Study of Myopia (OLSM) Group established that children with myopic parents had larger eyes even before the occurrence of myopia, in relation to the children with non-myopic parents.

Except from the previously described correlation between the myopia and near work, another parameter leading to the evolution of a myopic eye is the degree and accuracy of the accommodation process. Studies conducted to animal models exhibited that if a negative lens is placed in front of a young animal's eye, the eye evolves to balance the presumed hyperopic defocus. When the lens is removed from the front part of the eye, then the refractive error of the eye imitates that of the initial defocus derived from the use of the lens. A similar effect is also evident for the myopic defocus, which is induced from positive lenses, albeit this was more noticeable to chicken than primates *(Schaeffel et al., 1988, Smith and Hung, 1999)*. The same applies in the case of anisometropia. In particular, a study conducted to the eyes of monkeys implied that if a negative and positive lens is placed separately in front of the eyes of the same animal model, then it is evident the development of anisometropia.

Although, these experiments cannot be performed to humans, in terms of ethics, studies of the accommodation lag have provided knowledge regarding the role of the defocus in the evolution of myopic eyes to humans. Gwiazda and colleagues have shown that the myopic children yield a greater accommodation lag for closer targets than that of the emmetropic children. The authors predicted that the accommodation lag generates a hyperopic defocus, almost the same with that obtained from the animal lens compensation experiments, which can stimulate the evolution of the myopic eye *(Gwiazda et al., 1993, Gwiazda et al., 1995)*. They, also, demonstrated that the myopic children have great accommodative convergence/accommodation (AC/A) ratios, which may be the explanation of the increased accommodation lag. A child with high AC/A ratio is able to recline its accommodation, in order to reduce the accommodative convergence and maintain the binocular vision, which induces accommodation lag *(Gwiazda et al., 1999)*. Additionally, Gwiazda and colleagues justified whether the accommodation abnormalities preceded of the development of myopia, demonstrating that accommodation is reduced, while the AC/A ratio is increased in myopic children, prior to the onset of myopia *(Gwiazda et al., 2005)*. On the contrary, the results of a longitudinal study conducted by Mutti and colleagues indicated that the increased accommodation lag is not noticeable in myopic children, until the onset of myopia *(Mutti et al., 2006)*. Though, in all of the aforementioned studies, it was verified that the increased accommodation lag was not noticeable in myopic adults, as it was noticeable in myopic children. This is due to the pause of the myopia development *(Gwiazda et al., 2005, Mutti et al., 2006, Abbott et al., 1998)*. Hence, the accommodation lag is not considered as the main reason for the development of myopia, albeit its role constitutes a topic for further research.

The theories refer to the relation between near work and accommodation lag showing that the development of the myopic eye is a result of the defocus to the central retina. Nevertheless, recent studies proved that the defocus of the peripheral retina significantly contributes to the myopic eye growth *(Smith et al., 2005)*. Smith et al have demonstrated that the peripheral form deprivation (i.e. placing diffuser lenses in front of the eyes, compellingly reducing the light reaches the retina) may induce growth of myopic eye in a monkey infant, even when the foveal vision is unlimited. Additionally, the recovery of such induced refractive errors was held after removing the diffuser lenses, even in the case of a surgically ablated fovea *(Smith et al., 2005)*. Despite the attention paid to defocus, the researchers support that myopic eye growth is simply a result of the physiological eye growth, which is restricted equatorially. As an effect, the eye grows in an axial direction leading to the development of an ovate ocular shape and consequently to a myopic refractive error *(Mutti et al., 2012)*.

The accommodation lag is defined as the difference between the dioptric power of the accommodation stimulus and the measured accommodation response of the subject. For example, if a target is placed at a distance of 0.25m from the subject's eyes or 4 D of accommodation, and the subject accommodates 3.50 D, then this subject is characterized by an accommodation lag of +0.50 D. However, in some cases the subject over-accommodate (e.g. 4.50 D), which means that the subject is characterized by an accommodation lead (e.g. -0.50 D).

The accommodation lag is regularly illustrated over a range of dioptric stimuli by an accommodation stimulus-response function. The 1:1 line represents the correspondence of the accommodation response with the accommodation stimulus (i.e. when the subject accurately accommodates at every stimulus level without any accommodation lag or lead to be present).

The non-linear part of the curve (1), which is close to the 0 D stimulus is directly affected by the tonic accommodation and DoF, generating a lead of accommodation. Though, the largest part of such function is described by the linear part of the function (2), which represents the accommodation response that it is increased approximately up to the same percentage of the accommodation stimulus. In this way, the slope of this part is close to 1 D, which depicts a constant condition of accommodation lag; apparently because the accommodation system solely needs to bring the object into the range of the DoF, so that any additional accommodation effort is useless. The upper limits of the curve (3), where the slope levels off and gradually reduces, constitute the limit of the amplitude of accommodation of the subject. Thus, the subject is not more able to generate the accommodation needed for matching the stimulus target and the lag, which is significantly increased.

Figure 1.5: *Representation of the accommodative response to stimulus function. (Adopted from (Ciuffreda, 2006)). The numbers correspond to the various zones as they described previously on this section.*

In conclusion, all of the aforementioned evidence support the correlation between the myopic refractive error and the thickness of the ciliary body *(Oliveira et al., 2005, Muftuoglu et al., 2009)*, near work *(Angle and Wissmann, 1980, Richler and Bear, 1980, Zylbermann et al., 1993, Zadnik et al., 1994)* and the accommodation lag *(Gwiazda et al., 1993, Gwiazda et al., 1995, Gwiazda et al., 1999)*. Consequently, it is identified that the function of the ciliary muscle during the accommodation process of the eye is taken into account in studies referring to near work *(Angle and Wissmann, 1980, Richler and Bear, 1980, Zylbermann et al., 1993, Zadnik et al., 1994)* and accommodation lag *(Gwiazda et al., 1993, Gwiazda et al., 1995, Gwiazda et al., 1999)*. While, the physiological structure of the eye provides a potential source of equatorial eye growth restriction, as it is recommended by the CLEERE Study Group *(Mutti et al., 2000)*.

1.2 Objectives

The visual performance of the human eye has not been fully characterised yet. The understanding of the mechanism of accommodation is vital for the visual performance of the human eye, as the mechanism of accommodation has an essential contribution to it. Retinal image quality also influences the visual performance of the human eye, as well as the resolution of the images formed on the retina. The retinal image quality is described by the optical signals, namely ocular aberrations.

The aim of this Thesis is to investigate the interaction between the crystalline lens response and the ocular aberrations, with a view of using the wavefront aberrations of the eye. In order to achieve the aim of the study the following objectives need to be accomplished:

1. Estimation of the relationship between accommodation of the eye and wavefront aberrations of the eye under different conditions, along with their influence on the retinal image quality.
2. Assessment of the changes of the anatomic structures, those occur with accommodation, in the anterior eye segment in terms of axial lengths, crystalline lens curvature and ciliary muscle area and their contribution to the visual performance.
3. Apply the predetermined aberrations to the eye with the aid of an adaptive optics system and evaluate their efficiency to the retinal image quality by selectively extracting them.

CHAPTER 2

The Ocular Aberrations and Analysis of the Wavefront

2.1 Quality of Vision

The quality of vision is dependent on three aspects; the attribution of the optical media of the eye that influence on the retinal image quality, the proper function of the retina and the image processing that takes place on the cortex of the brain. The optical factors that are responsible for the image quality are the ocular aberrations (i.e. monochromatic, chromatic, low and higher order aberrations), diffraction, pupil size, and scattering of the optical media and the accommodative ability of the eye. In this way, a weakness in production of a perfect image is caused, as the perfect representation of a point of the object at a corresponding point of the image is prevented. Hence, the perfect point image of a point source of an optical system is never achieved, providing a pattern of a central brighter ring that is surrounded by gradually reduced luminance concentric rings (airy disc).

Figure 2.1: *On the left is displayed the perfect point image of a point source, while on the right is displayed the airy disk (i.e. the point image of a point source surrounded by gradually reduced luminance concentric rings) (Adopted from (Lombardo and Lombardo, 2010) and modified).*

2.2 Ocular Aberrations

In an optical system, as it is the eye, some errors or aberrations are presented in focus, which is not due to faulty manufacture of the optical, but the geometry of the diffractive surfaces *(Artal et al., 2001)*. The aberrations increase as long as the pupil diameter increases. As a result, the larger area of the optical system of the eye enters the visual field and leads to the deformation of the light. The increase in pupil diameter results in an increase of visual acuity, due to the phenomenon of diffraction and in a reduction of visual acuity due to the increase of the monochromatic aberrations. The ideal pupil diameter is about 2.5mm.

The ocular aberrations are divided into:

i. monochromatic low and high order aberrations (seen when looking at a wavelength)
ii. chromatic aberrations (seen when looking at the colour effects of light dispersion)

2.2.1 Monochromatic aberrations

The monochromatic aberrations for a specific wavelength are different from those of another wavelength.

The monochromatic aberrations are divided into low and high order according to the Zernike coefficient (see section 2.4). Those that have a factor of up to two are described as low-order aberrations (LOA), while those that have a factor of two or more are described as high-order aberrations (HOA). It has been found that the importance of the aberration is reduced when the order increases.

The monochromatic aberrations show a wide variation in the population. For a pupil size of 6 mm, the total ocular aberrations are distributed as follows: the low-order aberrations (i.e. the 2nd order aberrations of sphere and cylinder) contributes to 92%, while from the aberrations of high order, the third order (coma) contributes to 58%, the fourth order (spherical) contributes to 38% and the fifth order contributes to 7% *(Guirao et al., 2002)*.

Figure 2.2: *(a) Proportionate contribution of the low-order aberrations to the population and (b) Proportionate contribution of the higher-order aberrations to the population.*

2.2.1.1 Monochromatic Low Order Aberrations

The monochromatic low-order aberrations (i.e. 1st and 2nd order) are composed of the simple refractive errors; myopia, hyperopia (sphere) and astigmatism (cylinder), which are corrected by using sphere and cylindrical lenses, respectively. The existence of these refractive error influence on the accurate focusing of the rays onto the fovea of the retina, and thus this effects on the sharpness of the image.

2.2.1.2 Monochromatic High-Order Aberrations

The monochromatic aberrations of high order (i.e. 3rd, 4th, 5th, etc.) are referred to the deformations that the light rays suffer from, when passing through an optical system, in which the simple refractive errors have been corrected.

The monochromatic high-order aberrations include the spherical aberration, coma, field distortion (i.e. pincushion and barrel distortion) and the curvature of the field.

Spherical Aberration

The spherical aberration is characterized as the phenomenon in which the light rays are refracted at different heights of a spherical surface, intersecting the optical axis at different points (when the peripheral part of the surface is of different power in comparison to the central one).

The rays are focused on a different point, which evenly is removed from the paraxial focal point, but it maintains the symmetry of the light beam (a spot is generated with its size to be less than the position of the minimum circle of confusion).

Figure 2.3: *Schematic layout of the positive spherical aberration (Adopted from (Animations for physics and astronomy, 2013)).*

Spherical aberration is divided into positive and negative. It is considered as positive when the rays from the periphery of the spherical surface are focused ahead of those rays coming from the center of the spherical surface (the central part of the lens is less powerful than the peripheral one). The opposite applies for the negative spherical aberration. The peripheral rays are focused further away from the central ones (the central part of the lens is visually stronger from the peripheral one).

The spherical aberration is described as that of the cornea and the crystalline lens. The corneal spherical aberration is positive, while that of the crystalline lens is negative in its non-accommodation condition. During accommodation the spherical aberration of the crystalline lens becomes more negative, in order to better focus on the image.

Image 2.1: *Simulations of vision in the (a) absence of the spherical aberration and (b) presence of the spherical aberration (Adopted from (Nikon Vision Co., 2011)).*

The spherical aberration is categorised into two types, the longitudinal and transverse. The longitudinal spherical aberration refers to the distance of the beam intersection point and the optical axis of the paraxial focal point. The transverse spherical aberration is defined as the distance of the point of intersection of the beam from the paraxial focal point, in the level of passing through the paraxial focal point and it is vertical to the optical axis.

Clearly, the extent of the aberration depends on the shape of the lens and its size. In the eye, the spherical aberration is mainly introduced from the back surface of the cornea, but it is offset by the crystalline lens.

Figure 2.4: *Schematic layout of the Longitudinal and Transverse spherical aberration (Adopted from (Animations for physics and astronomy, 2013)).*

Coma

Coma is defined as the deviation presented magnified, when a light beam passes through a lens or a system with coma, forming an angle with the optical axis of the lens.

The rays passing through the periphery of the lens are depicted in different heights from those passing through the center of the lens.

Figure 2.5: *Diagrammatic representation of the aberration namely coma (Adopted from (Nikon Vision Co., 2011)).*

Image 2.2: *Simulations of vision in the (a) absence of coma, (b) presence of coma (Adopted from (Nikon Vision Co., 2011)).*

Distortion of the field

Distortion is the inability of a lens or an optical system to reproduce the shape of an image that it is exactly the same as that of the object (the linear magnification of the lens is not uniform across the surface).

Figure 2.6: *Diagrammatic representation on (left) the positive field distortion (i.e. pincushion distortion) and (right) the negative field distortion (i.e. barrel distortion) (Adopted from the (Nikon Vision Co., 2011)).*

There are two types of distortion; the pincushion distortion and the barrel distortion. It is possible that the image points are in precise focus on the correct plane of the image, but they occupy positions either closer or farther from the axis than the ideal positions.

Image 2.3: *Simulations of vision in the (a) absence of field distortion, (b) pincushion type distortion and (c) barrel type distortion (Adopted from the (Nikon Vision Co., 2011)).*

Curvature of the field

Curvature of the field is defined the ability of an optical system to focus the points of the image on a curved surface (not straight), and thus the image of a flat object is curved.

Figure 2.7: *Diagrammatic representation of the curvature of the field (Adopted from (Nikon Vision Co., 2011)).*

Image 2.4: *Simulations of vision in the (a) absence of the curvature of the field and (b) presence of the curvature of the field (Adopted from (Nikon Vision Co., 2011)).*

2.2.2 Chromatic Aberrations

The chromatic aberrations are a result of the refractive index that depends on the wavelength, but with each wavelength to have a different focal point. Therefore, when the white light passes through an optical system, each wavelength is focused on a different point, causing blur of the formed image. Chromatic aberration is divided into the longitudinal and transverse chromatic aberration.

Image 2.5: *Simulations of vision in the (a) absence of chromatic aberration and (b) presence of chromatic aberration (Adopted from (Nikon Vision Co., 2011)).*

Figure 2.8: *Diagrammatic representation on the (top) of the longitudinal chromatic aberration and (bottom) of the transverse chromatic aberration (Adopted from (Nikon Vision Co., 2011)).*

2.3 Analysis of the wavefront

Several methods have been developed, in order to measure the ocular aberrations *(Moreno-Barriuso et al., 2001)*. Nowadays, it is very common to use methods to measure the wavefront as it is beneficial to map the optical errors and the refractive power of the eye. Using sophisticated instruments namely wavefront analyzers, it is feasible to accurately measure and particularly record all of the optical aberrations of the eye *(Thibos et al., 2002b)*. The display is in the form of a colour map.

Figure 2.9*: Schematic layout of the propagation of the wavefront (Adopted from (Scratchapixel, 2011) and modified).*

This method has particular principles. More specifically, a light source generates radiating light waves (as when a stone falls in water). The top of the formed wave circularly moves away from the source. The curve that follows the peak of the wave, as it is formed every moment, is called wavefront. When the light comes from a point source, the wavefront has a spherical shape. As the wavefront moves away from the source, a part of its surface progressively flattens and eventually turns over to a plane wavefront.

Figure 2.10: *Types of wavefront.*

When the light propagates and passes through optical media with different refractive index (e.g. air, cornea), is delayed. Nevertheless, the frequency remains the same. Additionally, when the light passes through a material, which is optically denser in some areas (those with higher refractive index), it delays further to reach them, resulting to a more curved wavefront in such areas in comparison to the others (less optically denser areas).

Figure 2.11: *Representation of the Optical Path Difference (OPL) due to difference in the refractive index and thickness of the material.*

2.3.1 Methods of measuring aberrations

The main methods that have been developed for measuring the ocular aberrations are the following:

Retinal Ray Tracing (RRT)

In this method, the beam of a laser diode is introduced into the eye parallel to its optical axis, sequentially from different points of entry (scan). The beam will not pass through the retina at its intersection with the line of sight, but it will pass through elsewhere and it will create a secondary source of scattered radiation. This is due to the existence of aberrations into the eye. The direction of the propagating returning wave depends on the position of the secondary source. The distance of the center of the secondary source from the fovea gives the transverse aberration for the entry point of the beam *(Molebny et al., 2000, Pallikaris et al., 2000)*.

***Figure 2.12**: (Left) The external retinal ray tracing aberrometer (Adopted from (Tracey Technologies, 2016)) and (Right) the internal schematic layout of the system (Adopted from (Castillo-Gómez et al., 2012)).*

The deviation of the returned radiation from the original is illustrated in a position detector using an appropriate lens system. Then the signal from the position detector is translated into digital information and the deviations of all the beams form the colour map of the wavefront.

***Figure 2.13:** Sample of the wavefront colour map of the retinal ray tracing aberrometer (Adopted from (Molebny et al., 2000)).*

To obtain a measurement 95 different entry points are used, and the total time required for sequentially scanning these points is around 20 msec.

Tscherning

In this method, the laser beams are not successively entering from different points, but they are all entrained and detected simultaneously. The light in the form of square grid is presented vertically through the aperture of the pupil, and it is focused on the retina *(Mrochen et al., 2000)*. The focused grid is deformed from the various aberrations, due to the anomalies of the ocular media. In the retina a two-dimensional image is displayed including the deformations of the initial grid.

Figure 2.14: *The square grid in an (a) ideal optical system and (b) optical system with aberrations (Adopted from (Mrochen et al., 2000)).*

In order to clearly match the points of intersection of the entry beams with the spots on the retina, the beams are focused before the retina using a lens. Then, all the secondary sources are illustrated on a highly sensitive CCD camera, and thereafter through the digital processing, the deviations of the original image of the grid are evaluated with the image modelled for the path through the eye. Such deviations are displayed with colour maps.

Figure 2.15: *(Left) The external Tscherning aberrometer (Adopted from (Alcon, 2016)) and (Right) the internal schematic layout of the system (Adopted from (Kaschke et al., 2014) and modified).*

Shack-Hartmann

In this method, a light shaping diffusor (LSD) is used for the light beam that enters the eye from the opening of the pupil. The beam is reflected from the retina and as a second light source exits the eye. The path of the beam through the eye is subjected to a similar distortion of the errors and imperfections of the ocular media, which passes and terminates in an array of lenses. The array of lenses, through which passes the outgoing beam, consists of a grid of small lenses, each of them focus on a small part of the wavefront onto a sensor (Charge Coupled Device-CCD) *(Liang et al., 1994, Liang and Williams, 1997)*.

Figure 2.16: *Diagrammatic representation of the Shack-Hartmann sensor (Adopted from (Thorlabs Inc., 2016)).*

The deviation of each point from the ideal focal point of each lens on the CCD is an indication of the slope of the wavefront at that point. These slopes correspond to the deviations from the ideal wavefront and they are illustrated in a format of colour map.

Figure 2.17: *(Left) The external Shack-Hartmann aberrometer (Adopted from (Imagine Eyes, 2012)) and (Right) the internal schematic layout of the system.*

2.4 Assessment of the aberrations

The best known way of expressing and quantifying the aberrations of an optical system is in the form of the wavefront aberration (wave aberrations).

The wavefront $W(\rho, \theta)$ can be described from the Zernike polynomials classification *(Thibos et al., 2002a)* as follows:

$$W(\rho,\theta) = \sum_{n,m} C_n^m \, Z_n^m \, (\rho,\theta),$$

where the C_n^m factor derives from the spread of the Zernike Z_n^m polynomial.

The spread in polar coordinates is given according to the following:

$$Z_n^m(\rho,\theta) = \begin{cases} N_n^m \, R_n^{|m|} \, (\rho) \sin(m\,\theta), \; for & m < 0 \\ N_n^m \, R_n^{|m|} \, (\rho) \cos(m\,\theta), \; for & m \geq 0 \end{cases},$$

where ρ is the radius and θ is the angle.

The Zernike polynomials are orthogonal and normalized. They form the basis of the space of the continuous functions that are defined inside the unit circle.

The index n describes the order of the aberration (radial term) and the index m describes the angular term.

As more polynomial terms are added to the aforementioned sum so much is increased the accuracy with which the wavefront is approached. In ophthalmology, given the limited accuracy of the wavefront analyzers for measuring ocular aberrations, commonly used terms up to 4th or 6th order.

The Zernike coefficients can be positive or negative numbers. The measurement unit that is used for the Zernike coefficients is the micro-meter (μm).

The terms of the coefficients of the Zernike polynomials are approximately related to the common aberrations. For example the C_2^{-2} and C_2^2 are connected with the astigmatism (i.e. 45°/135°, 90°/180° respectively), the C_2^0 is connected with the defocus (i.e myopia, hypermetropia), the C_4^0 is connected with the spherical aberration, the C_3^{-1} and C_3^{1} are connected with the coma, the C_3^{-3} and C_3^{3} are connected with the trefoil, etc.

***Table 2.1:** Classification of the Zernike coefficients from zero up to fourth order.*

***Figure 2.18:** Schematic representation of the Zernike polynomials (i.e. 2nd, 3rd and 4th order) (Adopted from (Sener, 2015).*

To evaluate the errors, it is commonly used either directly the value of the coefficient of the Zernike polynomial, corresponding to the amount of the error or the Root Mean Square (RMS) value. The RMS is a parameter which is used to express the amount of an optical error, and refers to the deviation of an optical system from the ideal. The higher the RMS value of an optical system, the greater the errors of the optical system.

The RMS value is calculated according to the following formula:

$$RMS = \sqrt{\sum_{n.m}(C_n^m)^2},$$

where C_n^m are the coefficients of the Zernike polynomials.

Another metric that is used for the expression of the aberrations is the Point Spread Function (PSF). This function exhibits how a point source is seen from a patient, who suffers from every aberration separately. For example, a person with coma sees rays around a point source, while a person with high spherical aberration sees halos around it.

***Figure 2.19**: Schematic representation of the Point Spread Function (PSF) under the influence of each aberration (Adopted from (Opticaltechnologies, 2009).*

CHAPTER 3

Assessing the accommodation response after near visual tasks using different handheld electronic devices

3.1 Introduction

The use of computers and digital electronic devices for both professional and non-professional activities has become more prevalent in the modern society, worldwide *(Bababekova et al., 2011)*. It has been proved that approximately 75% of the companies have incorporated in their workplace the use of desktop computers, universally *(Hayes et al., 2007)*. Viewing from digital electronic screens is no longer restricted exclusively to desktop computer located on the workplace. The visual requirements -from laptops, tablets, electronic book readers, smartphones and more electronic devices- have, nowadays, been expanded outside the workplace to either the home places or to any other location as portable equipment *(Bababekova et al., 2011)*.

Individuals of all ages show preference in using handheld electronic devices (e.g. smartphones, tablets) for written communication (e.g. text messaging, e-mail, internet access). This results to the eventual replacement of the hardcopy printed materials, as the use of electronic devices have become an integral part of the individuals' daily life *(Hue et al., 2014)*.

Nevertheless, the relatively small screen and text size of such devices require close working distances, which affect the accommodation needed from the crystalline lens *(Collier and Rosenfield, 2011)*. This is required for having a clear and sharp vision in such distances *(Harb et al., 2006)*. To achieve this, the continuous contraction of the extraocular and ciliary muscles of the eye is needed. Thus, the prolonged use of such devices in close working distances may cause the development of harmful symptoms such as eyestrain, ocular discomfort, dry eye, diplopia, and blurry vision *(Thomson, 1998).*

Nonetheless, accommodation is one of the most important visual processes of the human eye, and thus several new optical instruments have been designed to appraise the accommodation process (e.g. biometric and optical methods) over the past years *(Ramasubramanian and Glasser, 2015)*. One of the most widely accepted and powerful instrument to evaluate the dynamic components of accommodation is the wavefront aberrometer *(Ehmer et al., 2008)*. So far, it is well known that accommodation process has a direct effect on the wavefront of the human eye. Using a wavefront aberrometer, which describes the wavefront at every point of the eye’s pupil diameter, the changes in the wavefront can be easily assessed *(Zhou et al., 2015, Li et al., 2011)*.

Due to the proliferation of electronic devices in the last decade studies have been conducted *(Mills and Weldon, 1987)* to detect whether viewing from electronic screens influences on the optical quality of the human eye. Although, up to now, a definitive conclusion has not been established. Additionally, to assess the accommodation process of the human eye, it is preferable to use a non-invasive way (i.e. wavefront sensing aberrometry).

Therefore, the aim of this study was to assess the accommodation response after short reading periods, using a tablet and a smartphone, as well as to determine potential differences in accommodation response at various stimulus vergences with a Hartmann-Shack aberrometer.

3.2 Methods

3.2.1 Subjects

Eighteen young adult subjects (mean age: 28 ± 1.9 years, range: 25 to 30 years) participated in the study. Astigmatism was limited to ≤ 1.00 D, and anisometropia < 2.00 D. All subjects had normal corrected visual acuity (20/20 or better), no ocular pathology, no binocular vision anomalies, no previous conducted ocular surgery, and normal clinical amplitudes of accommodation for their ages. Informed consent was obtained from each subject after providing a verbal explanation of the nature and possible consequences of the study.

3.2.2 Equipment

The crx1 instrument (Imagine Eyes, Orsay, France) was used to measure the wavefront aberrations of each subject's eye (Figure 3.1).

Figure 3.1: *Schematic layout of the instrument used as a wavefront aberrometer.*

The crx1 employs a square array of 1024 microlenses and a near-infrared light source with a wavelength of 850 nm. An internal microdisplay is used to project the target, while the Badal system is employed to change its vergence. To control the accommodation process, a Maltese cross is used as the target. A precise alignment of the subject's pupil is required, and these parameters are controlled with an additional Charge Coupled Device (CCD) camera. Head movements are reduced employing a chin and forehead rest.

Prior to data collection, a commercially available software, namely HASO-CSO (Imagine Eyes, Orsay, France) is used to totally correct the internal aberrations. Hence, during the wavefront measurement an aberration-free optical system was maintained. Consequently, the wavefront aberrometer is capable of obtaining the ocular aberrations as Zernike coefficients up to 8th order.

Despite this, the Zernike coefficients up to 6th order considered in the present study. Likewise, the wavefront data might be used to calculate the wavefront refraction, based on the least square fit of a spherical-cylindrical surface *(Tarrant et al., 2010a)*.

An iPad mini and an iPhone 4S (Apple Inc., California, USA) were employed to perform the visual tasks. These devices are characterized by a screen size of 7.9 and 4.5 inches corresponding to the iPad mini and iPhone 4S, respectively. The relative small screen and text size of such handheld electronic devices were suitable for visually stressing the accommodation state of the eye.

3.2.3 Reading task

The reading material consisted of a text with black letters on a white background. The text was displayed on both iPad mini and iPhone 4S screens with a font size corresponding to a 20/20 of visual acuity. To calculate the correspondence of the text displayed on both iPad and iPhone 4S screens, it was estimated the minimum separation between two lines that a subject with visual acuity equal to 1.0 could identify. This value was expressed as an angle of 1 minute of arc (1/60 of a degree). Prior to that, the height of a letter (e.g. capital X) was measured, employing an electronic digital calliper for both electronic devices. In the end, the height correspondence (in mm) was estimated, resulting to a font size of 5 and 3 (in TNR-Times New Roman), for the iPad and iPhone 4S, respectively.

Both devices were placed at a distance of 0.25 m from the subject's eyes. On average, the luminance of the screen of both devices was adjusted to be constant and equal to 200 cd/m^2. Subjects were instructed to read silently the text for 10 min.

3.2.4 Experimental procedure

The experiment was divided into three conditions, each followed by a different accommodation state. In the first condition the accommodation state of the eye was relaxed, whereas in the two other conditions it was visually stressed. To achieve this, reading tasks were performed with the two previously described electronic devices. More specifically, a text for reading was displayed on both iPad mini and iPhone 4S. In all conditions the tasks were performed monocularly, to solely assess accommodation and not convergence.

The accommodation responses were measured under three different conditions: (i) relaxed, (ii) after reading 10 min on an iPad mini, and (iii) after reading 10 min on an iPhone 4S. After completing each condition, three measurements of accommodation response were monocularly acquired at the stimulus vergences of 0, 1, 2, 3 and 4 D, employing the irx3 Hartmann-Shack aberrometer. Thus, 15 wavefront measurements were recorded per accommodation state, with a total of 45 measurements for each eye. The subject was allowed to blink prior recording a measurement, to avoid increased tear film aberration that might otherwise have occurred during an extended inter-blink interval *(Montes-Mico et al., 2005)*. In each of the aforementioned conditions the measurements were collected in different days by randomly providing the devices to the subjects.

3.2.5 Data analysis

The wavefront data were exported as Zernike coefficients up to 6th order, rescaled to a 3 mm pupil size using the method described by Schwiegerling *(Schwiegerling, 2002)*. The Zernike polynomials are orthogonal, and thus Zernike defocus is independent of the higher order aberrations and their certain interaction, which mainly influences on the retinal image quality. Therefore, to solely identify the response of the eyes to the accommodation stimuli the Zernike defocus is commonly used *(Tarrant et al., 2010a, He et al., 2000)*. In the present study, the accommodation response was determined from the measured wavefront, using the least squares fitting procedure provided by the Zernike defocus, which is further known as a surface fitting procedure. The accommodation response was estimated in diopters employing the following Equation:

$$M = \frac{C_2^0 4\sqrt{3}}{r^2}, (1)$$

where C_2^0 is the second-order Zernike coefficient for defocus in μm and *r* is the pupil radius in mm *(Thibos et al., 2004)*.

To identify the image quality changes during accommodation the spherical aberration was analysed for all conditions, as it has been proved that is the main higher-order aberration contributes to that *(Tarrant et al., 2010a)*. The same applies for coma, which is subjected to various changes during accommodation *(He et al., 2000)*. Hence, the sum of the third and fifth order Zernike coefficients, as well as the fourth order Zernike coefficient were utilized to calculate the RMS Coma-like and spherical aberrations, respectively.

Using the IBM SPSS Statistics software v22.0 (Armonk, NY, USA), a 1-way ANOVA was performed to identify the influence on the accommodation response of each device. Then, a post-hoc analysis (Tukey HSD-Honest Significant Difference) was conducted, to determine the significantly different mean values for each condition. A p-value less than 0.05 was considered to be statistically significant.

3.3 Results

To obtain the values of the accommodation response, the second-order Zernike coefficient (defocus) was converted into diopters, employing the previously described formula (Equation 1). The Figure 3.2 exhibits the average of 3 consecutive measurements, for each condition and stimulus vergence considered in this study.

Figure 3.2: *Comparison between the different accommodation states (±SD) for each condition and stimulus vergence (D). The dashed line shows the theoretical response of the accommodation process (equal accommodation response for each stimulus vergence).*

It was anticipated that the accommodation response would be described as the inverse of a fixed distance, by the formula $A = \frac{1}{d}$, in which A refers to accommodation (in Diopters) at a certain distance *d* (in meters). All of the obtained accommodation responses have a shift with respect to the theoretical line, demonstrating that a certain value of lag was present for all stimulus vergences. This is also evident in the data collected by Ciuffreda et al *(Ciuffreda, 2006)* . Although, a greater lag of accommodation was found in the present study (Figure 3.3).

Figure 3.3: *Lag of accommodation obtained for all conditions compared with the replotted data of Ciuffreda et al (Ciuffreda, 2006).*

When analysing the higher-order aberrations a moderate, but gradually increasing RMS coma-like with accommodation state at each stimulus vergence was obtained for all the subjects, as it is illustrated on Figure 3.4. Additionally, it was verified that as the accommodation demand was increasing (i.e. with the stimulus vergences), the spherical aberration was decreasing (i.e. reducing its positive value), as it is exhibited in Figure 3.5. As already mentioned, a statistical analysis was conducted to estimate the variance over the different stimulus vergences for the three accommodation conditions. In conclusion, any statistical difference (*p*>0.05) was found comparing the different conditions.

Figure 3. 4: *The root mean square derived from the third-order and fifth-order coma aberration.*

Figure 3.5: *The spherical aberration pattern in relation to the different stimulus vergences and conditions for a single subject.*

3.4 Discussion

In the present study, the accommodation response was assessed after short reading periods, using a tablet and a smartphone. This was achieved using a Hartmann-Shack aberrometer and different stimulus vergences.

It is well known that during the past years a large amount of handheld electronic devices have been placed on the market, with the tablets and smartphones being the most adopted electronic devices of the modern society, along with the personal computers. Several studies have demonstrated the massive increase in the use of such electronic devices in the individuals' daily life. For example, a study conducted by Takeda et al *(Takeda et al., 1988*) exhibited that in United States of America (USA) the percentage of adopting Visual Display Terminal Operators (VDTOs) raised from 30% to 60% over 5 years. Though, it is well stated that a high degree of visual strain is directly connected with these VDTOs, as it was proved by the same study. In particular, the degradation of accommodation reported after sustained work with VDTOs, showed a strong correlation between visual demanding task, depletion of accommodation and visual fatigue. Therefore, employing such technology for reading task, an excellent near visual acuity is required, as it is strongly associated with the accommodation process.

Moreover, Sheedy and Shaw McMinn suggested that a subject should have a near visual acuity approximately three times higher than the needed, in order to easily read a text on an electronic display *(Sheedy and Shaw-McMinn, 2003)*. Nonetheless, Bababekova et al stated that, the previously described rule does not coincide with any objective evidence *(Bababekova et al., 2011)*. Thus, the authors recommended a clear association between the pixel density of a certain electronic device (e.g. pixel/mm) and the number of pixels per letter height; a parameter taken into account in this study.

Despite the near visual acuity, additional parameters, such as depth-of-focus (DoF), pupil diameter and wavefront aberrations, are associated with the accommodation process, as well. In particular, Tucker et al have proved that the smaller the pupil diameter is, the greater the DoF and the lesser the wavefront aberrations of the eye *(Tucker and Charman, 1975)*. Hence, for the experimental procedure of this study, a pupil diameter of 3mm was selected.

It is well established that the eye wavefront is essentially formed by the wavefront of both cornea and crystalline lens *(Pierscionek et al., 2001, He et al., 2003)*, and thus it is affected by the accommodation process. For this reason, in the current study a wavefront aberrometer was employed to calculate the total eye wavefront. Another factor that led to the use of this instrument is that it objectively evaluates the accommodation process *(Li et al., 2011)*, bypassing the limitations provided by the subjective evaluation of the accommodation process (e.g. non-differentiation of a passive DoF, a change in ocular aberrations or accommodation power).

To estimate the accommodation response at different stimulus vergences for all conditions the defocus aberration was employed. The findings of each condition were only compared within the groups of the subjects. The obtained accommodation responses demonstrated a lag of accommodation for all stimulus vergences and conditions. These results are in agreement with those obtained by Ciuffreda et al *(Ciuffreda, 2006)*, although a greater lag of accommodation is evident in the current study.

Additionally, several parameters were taken into account, to maintain the good subject's visual performance. Particularly, the ambient illumination affects the visual performance and causes visual fatigue *(Lee et al., 2011)*. Hence, a fixed ambient illumination to 300 lux was fixed during the experiments, to prevent any reduction of the contrast of the displays employed and any glare interfered with the near visual tasks. Furthermore, the screen reflectivity influences on the image quality, meaning that higher visual performance has been recorded with lower screen reflectance coefficient *(Liu et al., 2014)*. Consequently, two electronic devices produced by the same company were employed, to reduce any potential differences in terms of data and screen technology or reflectivity.

Both visual tasks performed at a distance of 0.25 m, as it is the common reading distance corresponds to the subjects' age *(Leung et al., 2011)*; a closest distance could further altered the accommodation response. For this reason, a selection of a visual task (e.g. watching a video, playing a game, etc.) over a range of various distances could be interested to be evaluated in the future.

To our knowledge, the current study did not aim to correlate the accommodation response after reading a text on a hardcopy printed material and an electronic device. Although, a study conducted by Hue et al. intended to compare the performance of subjects, when reading from a printed material and two types of hand held electronic devices (i.e. Amazon Kindle e-reader, Apple iPod) *(Hue et al., 2014)*. In particular, the authors found that the reading speed was significantly lower when reading from the iPod, in comparison to that observed when reading from the printed material. This was attributed to the relatively small screen of such electronic device. Additionally, no differences in reading speed were found when reading from the Kindle and printed material.

Another finding of this study was a moderate, but gradually increasing RMS coma-like with accommodation state, which was previously described by Cheng et al *(Cheng et al., 2004)*. The authors reported a relative influence on the RMS coma-like, due to the vertical shift of the lens throughout the accommodation process. López-Gil et al. found that the increase of the third-order aberration was dependent on the subjects' variability *(Lopez-Gil et al., 2008)*. Nevertheless, findings of additional studies did not yield that the presence of third-order aberrations may play a crucial role in the accommodation response *(Lopez-Gil et al., 2007)*.

Additionally, it is widely established that spherical aberration is most linked to accommodation *(Zhou et al., 2015, Tarrant et al., 2010a, Thibos et al., 2013)*. Mostly, it has been identified that an increase in accommodation demand causes a decrease in spherical aberration. This is due to the conicity of the lens, which may also be originated by the function of the ciliary muscle *(Lopez-Gil and Fernandez-Sanchez, 2010, Dubbelman et al., 2003b)*. The findings of this study comes to an agreement with the aforementioned evidence (Figure 3.5). In particular, a change in the spherical aberration was identified with the increase in stimulus vergences. Nevertheless, due to the inter-subject variability obtained from the mean of all the subjects, it was not found any additional tendency as that previously described in the literature.

In summary, in the present study no significant differences were found in the accommodation responses for all the conditions and stimulus vergences considered. This may be due to the youth of subjects' eyes, and further to their normal level of amplitude of accommodation, corresponding to their age. Future work should consist of larger reading periods, as well as greater sample of participants with a wide range of different ages, in order to establish a comparison with the results obtained by this study.

CHAPTER 4

In-vivo OCT assessment of anterior segment lengths, lens curvature and ciliary muscle with accommodation

4.1 Introduction

The accommodation of the human eye is a very highly fluctuant and dynamic process. According to the most widely accepted theory of Helmholtz *(Helmholtz, 1855b)*, accommodation is a muscle-induced activity. Specifically, the ciliary muscle contracts, causing the release of the zonular fibers, allowing the crystalline lens to increase its curvature and thickness, leading to an increase/change in its refractive power to focus on close targets (i.e. known as accommodative demand) *(Helmholtz, 1855b)*. The efficiency of this process declines with age, as the crystalline lens loses its elasticity and the activity of the ciliary muscle deteriorates, leading to presbyopia *(Atchison, 1995, Pardue and Sivak, 2000, Tamm et al., 1992, Wyatt, 1993, Stark, 1988, Strenk et al., 2005)*. Nevertheless, this theory may not entirely explain the development of presbyopia, as the in vivo crystalline lens response to ciliary muscle contraction still remains under investigation, mainly due to visualization difficulties faced over the past decades *(Lossing et al., 2012)*.

Nowadays, recent improvements in imaging technology provide advances that have contributed to further understand the accommodation of the human eye, in terms of the simultaneous biometrical changes occur in the crystalline lens and ciliary muscle during it *(Lossing et al., 2012)*. This will lead to the upgrade of the eye care services provided to the patients, and further to the upgrade of the entire visual system of the human eye. As so far there are young and elder people, which are presented in the daily clinical practice facing accommodative dysfunctions, but having to choose between limited solutions of reading additions or implanting accommodative Intraocular Lenses (IOLs), to temporally inhibit such dysfunctions. Despite this, it has also been recorded in the literature that multiple companies are working to develop efficient accommodative IOLs, which rely on the action of the ciliary muscle; however, there is still limited understanding of the presbyopic ciliary muscle function *(Glasser, 2008)*.

In addition to presbyopia, there are other types of accommodative dysfunctions that they are equally significant to that of presbyopia, and which negatively influence on the quality of individual's daily life. This is due to the rapid increase of activities that require clear vision at closer distances such as the use of computers, electronic readers, tablets, smartphones, etc. Such accommodative dysfunctions are associated with accommodative anomalies giving symptoms as blurred vision, headache, ocular discomfort and loss of concentration throughout a task; however, the source of these anomalies remains unknown *(Lossing et al., 2012, Hokoda, 1985, Hoffman et al., 1973)*. This also applies in cases of myopia onset, where an increased accommodative lag is evident, without being identified yet the source of such anomaly in the accommodative process/system. Therefore, as already stated it is imperative to conduct further research on understanding the gradual decline of the accommodative process and how this may be related to accommodative dysfunctions and/or myopia onset *(Lossing et al., 2012, Mutti et al., 2006)*.

To achieve this, it is essential to visualize and make measurements on the changes that take place to both anterior crystalline lens and ciliary muscle with accommodation. Different studies have used different methods like magnetic resonance imaging (MRI), ultrasound biomicroscopy (UBM), and anterior segment optical coherence tomography (OCT) to visualize these changes *(Oliveira et al., 2005, Sheppard and Davies, 2010, Stachs et al., 2002, Strenk et al., 2006)*. The present study uses the imaging capabilities of the Visante® *Omni* OCT to develop a protocol that measures the changes occur to the anterior curvature of the crystalline lens and the ciliary muscle thickness at different accommodative demands. We chose this method as it is a non-contact, non-invasive imaging technology, easy to operate, which provides us with high resolution images of both anterior crystalline lens curvature and ciliary muscle, maintaining at the same time its high speed capability *(Lossing et al., 2012)*.

4.2 Methods

4.2.1 Subjects

Twenty-five right eyes of healthy adults aged from 20 to 45 years (29.5 ± 6.7 years) were included in this study. The refractive error of the patients was obtained with dry autorefraction. The averaged refractive error was -0.77 ± 1.90 diopters (D). The subjects had enough amplitude of accommodation (at least -3.00 D), which was evaluated monocularly by the Donders' method. Their best-corrected visual acuity evaluated with the LogMAR chart was at least 20/20 in Snellen equivalent. The subjects had no ocular abnormality or systemic condition, no ocular surgery history and they all presented clear intraocular media. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia. The patients were informed about the details of the study, and signed a formal consent after written and verbal explanation of the implications.

4.2.2 Measurement device and parameters

The device used for the measurement was the Visante® *Omni* system (Carl Zeiss AG, Oberkochen, Germany) (Image 4.1). This device combines OCT technology together with Placido disk topography in order to obtain advanced corneal and anterior segment measurements. It is a non-contact diagnostic instrument that acquires and analyses detailed cross-sectional tomographic images of the anterior segment. It uses low-coherence interferometry, in order to obtain the captures. Infrared light of 1310 nm is sent along an optical path that reaches the eye together with another reference path of the interferometer. Both paths are then combined at the photodetector in order to determine the axial depth of the tissue thanks to the reflectivity signal.

The device allows the examiner to adjust the vergence of the visual target by means of a set of internal lenses, which is useful to evaluate the changes with accommodation. Taking this into account, all the measurements were taken for the stimulus presented at 0 D relative to the patient's far point (referred as the “unaccommodated state” from now on) and for the accommodated eye with increasing stimuli at -1.0 D, -2.0 D and -3.0 D vergences. All the captures were performed at the horizontal meridian.

Image 4.1: *The Visante® Omni system (Carl Zeiss AG, Oberkochen, Germany) used in this study.*

The used software of the Visante® OCT (version 3.0) disposes of a set of different scan types. Three of them were used in this study: the “Enhanced anterior segment single”, the “Raw Image”, and the “Raw Image HR” modes. The “Enhaced anterior segment single” mode catches four different tomograms composed by 256 A-Scan primitive lines, that represent a total area of 16 mm in width and 6 mm in depth, and averages them out. This mode requires the examiner to take the capture centred on the cornea. It then processes the final image in order to detect the anterior and posterior corneal surfaces and fits two limiting lines matching them. This adjustment is useful in order to reshape the tomograms so it is possible to obtain corrected and real physical distances. This mode was used to capture the central corneal thickness (CCT) and the central anterior chamber depth (ACD). Normally, the anterior segment length (ASL) is defined as the distance from the central anterior corneal surface to the posterior surface of the lens. In this work, this measurement was included but it was considered from the posterior surface of the cornea (endothelium) to the posterior surface of the lens in order to evaluate the change in position of the posterior pole of the crystalline lens without adding extra variability due to the corneal measurements.

With the “Raw image” mode, getting images deeper into the eye is possible to fully get the lens thickness. This mode is composed of 256 primitive A-Scans, which also represent a total area of 16 mm in width and 6 mm in depth. This mode was used to capture the images to obtain the central lens thickness (CLT). Additionally, the “Raw Image HR” mode works similarly but with higher resolution. This mode yields images of 512 primitive A-Scans, which represent a total area of 10 mm in width and 3 mm in depth. It was used to capture the central anterior lens curvature (ALC) and central posterior lens curvature (PLC), as well as the ciliary muscle area (CMA) at the temporal region.

Since any of the raw modes corrects the image for the refractive indices of the ocular media, all the measurements for all the vergences were obtained in pixels and the differences among accommodative stimuli comparisons were performed this way. With this method, we are assuming that the uncorrected images for all patients represent similar distances for the same number of pixels. All the captured images were exported from the Visante® into external software. The axial measurements like CCT, ACD and CLT were analysed by means of ImageJ, a public domain software for image processing and analysis developed by Wayne Rasband (National Institute of Health, USA). The CCT was considered from the central corneal anterior surface or epithelium to the central posterior surface or endothelium. The ACD was considered from the central corneal endothelium to the anterior surface of the lens. The CLT was extracted from the central anterior surface to its central posterior surface. (Figure 4.1).

Figure 4.1: *Parameters being measured with the Visante® Omni OCT equipment. A-Central corneal thickness. B-Anterior chamber depth. C-Crystalline lens thickness. The ASL parameter was calculated as the sum of B and C distances. These distances were measured at the horizontal meridian.*

Regarding the central curvatures of the lens, the ALC and PLC measurements were obtained adjusting a circumference to the central area moving aside a fixed number of pixels from the centre. This was performed selecting 3 points on the surfaces after applying smooth and sobel filters to the images to enhance the limits of both surfaces. (Figure 4.2). For this purpose, MATLAB (MathWorks, USA) was used. The CMA was obtained also by ImageJ applying a smooth image processing filter and then enhancing the contrast. (Figure 4.3).

Figure 4.2: *Processed image of the crystalline lens anterior surface at the horizontal meridian in order to measure its curvature: (A) the original image and (B) the processed image with measurement.*

Figure 4.3: *Processed image of the ciliary muscle at the temporal portion of the horizontal meridian in order to measure its cross-sectional area: (A) the original image and (B) the processed image with measurement.*

4.2.3 Experimental procedure

The patients were requested to keep their fixation on the instrument visual target before capturing. To avoid affecting the measurement during the acquisition process, the patients were also requested to blink before starting the exam and to open wide until the measurements were finished. All the measurements for each patient that took part of the study were obtained during a single session.

4.2.4 Statistical analysis

The statistical analysis was performed with SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). Each measurement was extracted three times per image and a mean value was calculated. A repeated measurement analysis of variance (rANOVA) was performed to investigate significant differences among stimuli vergences for each parameter. The normality of data sets was assessed by the Shapiro-Wilk test. The ANOVA procedure based on the F statistic is robust under the breach of the normality assumption, provided that the data samples have no important asymmetries or similar distribution shapes *(Tan, 1982)*. Prior to the rANOVA, the sphericity assumption was checked with the Mauchly's sphericity test. The Greenhouse-Geisser correction was applied in those cases in which sphericity test did not turn out to be statistically significant *(Box, 1954)*. The Bonferroni method was used as a post-hoc test for comparisons among groups when the rANOVA revealed significant differences between measurements. This procedure allows obtaining the significance level for paired differences between the individual conditions. The statistical significance limit was defined as $p < 0.05$.

4.3 Results

Regarding the central axial measurements that were analysed, the variations of the CCT were not found to be statistically significant among any of the considered pair comparisons, i.e., any accommodation stimuli (-1.0 D, -2.0 D or -3.0 D) induced any change in this parameter with respect to the unaccommodated state or between accommodative states ($p>0.05$). When considering the ACD measurements, the accommodation involved a significant reduction ($p<0.05$) for every pair comparison. This reduction of the ACD was bigger the higher the stimulus vergence was set. Moving deeper into the eye, a significant increasing of the CLT was also found with accommodation at any stimulus vergence comparisons. The lens increased its thickness the higher the stimulus was set. With regards the ASL, statistically significant differences were also found for every pair comparison.

Table 4.1: *Pair comparisons for which there were found statistically significant differences (*p<0.05). CCT: central corneal thickness. ACD: Anterior chamber depth. CLT: Crystalline lens thickness. ASL: Anterior segment length. ALC: Anterior lens curvature. PLC: Posterior lens curvature. CMA: Ciliary muscle area.*

With respect to the ALC measurements, the curvature showed a statistically significant increasing with accommodation also for every accommodative stimulus with respect to the 0.0 D vergence, as well as between accommodative stimuli. Its trend was to increase with higher accommodation. In contrast, the PLC only registered a significant steepening of its surface while the stimulus vergence was set to -3.0 D ($p<0.05$) with respect to the unaccommodated state. There was also a significant difference between accommodative stimuli -1.0 and -3.0 D. Regardless there were some pair comparisons without statistically significant differences, the trend was also to increase its curvature (or reduce its radius) with higher accommodative stimuli.

Finally, there were also statistical differences among all the pair comparisons for the CMA. A bigger increase in the area of the muscle was observed with increasing accommodative stimuli.

Table 4.1 summarizes all the statistically significant differences that were found among stimuli comparisons for every studied parameter. Table 4.2 shows all the results (mean ± standard deviation) extracted from the images of the anterior eye segment with Visante® *Omni* at all stimulus vergences: 0.0 D, -1.0 D, -2.0 D and -3.0 D.

Table 4.2: *Results (mean ± standard deviation) in pixels extracted from the images of the anterior eye segment with Visante® Omni at stimulus vergences 0.0 D, -1.0 D, -2.0 D and -3.0 D. CCT: central corneal thickness. ACD: Anterior chamber depth. CLT: Crystalline lens thickness. ASL: Anterior segment length. ALC: Anterior lens curvature. PLC: Posterior lens curvature. CMA: Ciliary muscle area.*

4.4 Discussion

Evaluating the anterior eye segment and the variations of the anatomic structures is feasible thanks to the non-invasive technique known as anterior segment OCT. In this sense, this technique provides a useful tool for clinicians since a better comprehension of the mechanisms that involve the eye structures can be achieved *(Ramos et al., 2009, Farouk et al., 2015, Radhakrishnan et al., 2001)*. Since it was introduced in the clinical practice, it has been used to analyse the structures such as the cornea, the anterior chamber, or the crystalline lens among others. This has crucial importance for taking clinical decisions such as on special contact lens fittings like in keratoconus or post-LASIK corneas, as well as for cataract surgery and for the planning of a pseudophakic or phakic IOL implantation *(Doors et al., 2010, Doors et al., 2009)*. But rather than just considering the eye as a static organ, it has to be taken into account that it is in constant adjustment of its refractive power throughout the day in order to let us focus on objects at different distances. This is known as accommodation, and during this process, the anatomical configuration of the eye changes *(Baikoff et al., 2004)*. The crystalline lens takes the main role in this process and adjusts its refractive power by adapting its shape as a response to a near stimulus in order to get a clear image on the retina. This fact involves secondary anatomical changes in the anterior segment of the eye *(Dominguez-Vicent et al., 2014b, Richdale et al., 2008a, Malyugin et al., 2012, Ciuffreda, 2006)*.

In this research, we evaluated a set of central axial measurements and the effect of accommodation on them. Specifically, the CCT, the ACD, the CLT and the ASL were evaluated at different stimulus vergences corresponding to 0.0 D, -1.0 D, -2.0 D and -3.0 D. The CCT was not altered during accommodation at any stimulus ($p>0.05$). Nevertheless, although the CCT does not seem to be affected, other changes in the shape of the cornea have been investigated in the presence of accommodation. Some other studies have evaluated by means of corneal topographers the changes in its curvature with accommodation. In this regard, Yasuda et al. found statistically significant differences in the maximum K-values for the central 3.0 mm, 5.0 mm and 7.0 mm by a mean of 0.62

D *(Yasuda et al., 2003)*. Similarly, He et al. found changes in the corneal surface with a placido-based videokeratographer during accommodation that suggested an increase in the peripheral curvature with flattening at the vertex *(He et al., 2003)*.

As for the ACD measurements, there were found statistically significant differences for every pair comparison. The ACD was reduced with accommodation and this reduction was bigger the higher the stimulus was set. A pilot study carried out by Del Águila et al. analysed the changes in the ACD at different parts of the anterior chamber with a Scheimpflug camera rotating system *(Dominguez-Vicent et al., 2014a)*. They analysed the variations with accommodation for the ACD at the central position, as well as at the superior-inferior and temporal-inferior pairs 2 mm away from the centre. They also found a reduction of the mean ACD value with accommodation at all positions with bigger reduction the higher the stimulus up to -4.0 D. The reduction of the ACD with accommodation in a given patient is an important parameter to consider when an anterior chamber phakic IOL is going to be implanted into the eye, since its nearness to the corneal endothelium and the push-up of the ocular structures with accommodation could induce cell loss due to peripheral contact *(Coullet et al., 2007, Kim et al., 2008)*. The anterior segment OCT device used in this study includes a set of embedded functions that allow simulating preoperatively how a phakic IOL would fit into the eye of the patient. This can be simulated at different accommodative stimuli, which helps practitioners to observe the changes of the ACD in order to assess the feasibility of this procedure *(Doors et al., 2009)*.

With regards the CLT, there were also found statistically significant changes for every group. The CLT was increased the higher the accommodative stimulus up to the maximum vergence studied in this work. This behaviour is well known as one the main implications during the process of accommodation. Other publications have evaluated the change in the thickness of the crystalline lens, with findings in accordance to our reported data *(Richdale et al., 2008a, Dubbelman et al., 2003a)*. Furthermore, the ASL calculated parameter, as it was mentioned, was considered from the corneal endothelium to the posterior surface of the lens as the addition of the ACD and CLT values. The point of including this measurement is to assess the change in position of the posterior pole of the crystalline lens. The bigger this distance is, the more it would have moved backwards. The change of the anterior surface of the lens is directly related to the change in ACD, since the anterior chamber is reduced or expanded proportionally to the displacement of its anterior surface assuming that the cornea does not change its position during accommodation. The values of our study for the ASL showed significant changes with accommodation for all the comparisons. This indicates that the posterior surface of the lens is moving backwards with accommodation. This is in accordance with the results of Dubbelman et al., who used a Scheimpflug device and also found that the increase in the lens thickness with accommodation is higher than the decrease in the ACD *(Dubbelman et al., 2005)*. However, since the ASL has a lower absolute variation than the ACD, this means that this posterior movement is smaller than that of the anterior lens surface, which carries a more significant accommodative component by getting closer to the cornea. In fact, besides increasing its thickness, the crystalline lens moves forward, which plays an important role in increasing refractive power of the accommodated eye *(He et al., 2014)*.

Nevertheless, it has to be taken into account that the accommodation provided by the crystalline lens is not only due to the increasing thickness of its structure or to its movement changing the distance to the cornea, but also, a change in shape occurs which would increase its power by steepening its curvature radii. For this reason, the curvature radii of the central area of the anterior and posterior surfaces of the crystalline lens were analysed. As for the ALC, it was found that the curvature changes with accommodation are significantly different among all pair comparisons and that it increases with higher accommodative stimulus. However, regarding the PLC measurements, there were only found statistically significant differences between the -3.0 D stimulus with respect to the unaccommodated state, as well as between -1.0 D and -3.0 D stimuli ($p<0.05$). Nonetheless, the trend was also to increase its curvature with increasing accommodation. This analysis of the anterior and back surfaces of the crystalline lens indicates that the changes in curvature in order to increase its power are more relevant in the anterior surface. Indeed, Dubbleman et al. also reported that during accommodation there is an increase in both the anterior and the posterior lens curvatures, although the change in the latter is much smaller *(Dubbelman et al., 2005)*. Regarding the change in curvature of the 3 mm central zone, they found that both surfaces steepen, indicating that the lens power increases due to the more convex shape of the lens for approximately 64% steepening of the ALC, and 36% of the PLC. They also studied the change in the conic constant during accommodation of the anterior lens surface, determining that this value decreases with accommodation. This fact indicates that the lens surface becomes more curved and hyperbolic, besides moving towards the cornea.

The CMA was also studied as a significant parameter affected by accommodation, although still nowadays little is known about its exact behaviour during contraction and there are some limitations with its imaging and measurement *(Bailey, 2011b)*. It is known that the ciliary muscle relaxes or contracts to enable the lens to change its shape for focusing. Our results showed statistically significant differences with accommodation for the CMA as a cross-sectional area measurement ($p<0.05$). Besides, this parameter showed an increase the higher the accommodative stimulus was set, since it has to make a bigger effort with higher stimuli to allow focusing. Lossing et al. analysed the changes in the ciliary muscle thickness with accommodation in young adults *(Lossing et al., 2012)*. With their method, they confirmed that it is possible to examine the action of the ciliary muscle with accommodation by means of Visante® OCT, and that it seems to be a thickening of the anterior part and a thinning of the posterior portion of the ciliary muscle. However, the methods for measuring the ciliary muscle still has to be improved and the results should be considered carefully.

Our findings provide extra useful information about the accommodation mechanism analysed through the OCT technology that can be useful for practitioners in order to achieve a better understanding of this process and to help them make their clinical decisions. Not only this, getting to know better this mechanism allows also designing new strategies in order to provide optical solutions for the correction of presbyopia. The recent and future advances in imaging technology will improve the examination of those changes of the ocular anatomy with accommodation.

CHAPTER 5

Crystalline lens and ciliary muscle assessment with accommodation: aging effects

5.1 Introduction

The human eye is formed by complex structures that make use of different mechanisms in order to achieve a proper visual function. Many of these functions are altered as the eye ages. One of them is the adjustment of the refractive power of the crystalline lens, which let us focus on objects at different distances, known as accommodation. According to the most widely accepted theory of accommodation of Helmholtz, this mechanism is a muscle-induced activity *(Helmholtz, 1855a)*. The crystalline lens is a transparent and flexible structure with a biconvex shape that lies in the capsular bag, which is connected through the zonular fibres to the ciliary muscle. Specifically, when the ciliary muscle contracts, it causes the release of the zonular fibres, which allows the crystalline lens to increase its size and curvature of its surfaces, increasing its refractive power.

With aging, the lens becomes less flexible, which leads to a visual condition known as presbyopia *(Strenk et al., 2005)*. In presbyopia, the ability of the crystalline lens to modify its size and shape is reduced, decreasing the level of accommodation. Additionally, changes in the ciliary muscle related to age have been observed *(Tamm et al., 1992, Strenk et al., 1999)*. Furthermore, the increasingly social demand for tasks that require different working distances (far, intermediate, and near vision) motivate the research on the correction of presbyopia. A better understanding about the alterations in the accommodation mechanism with aging may lead to develop new optical solutions and/or improve the existing ones. This is particularly important, since the lack of accommodation leads to a decreasing of the quality of life *(Luo et al., 2008)*.

To achieve this, it is crucial to image the structures of interest in the anterior segment. Recent research on anterior segment visualization and quantification of anatomical parameters has been performed using different methods such as ultrasound biomicroscopy, magnetic resonance imaging (MRI) or anterior segment optical coherence tomography (OCT) *(Leung et al., 2005, Dada et al., 2007, Strenk et al., 2010, Ursea and Silverman, 2010)*. In this work, the OCT technology provided by the Visante *Omni*® device (Carl Zeiss AG, Oberkochen, Germany) was chosen as the best method in order to image and quantify the ocular structures, since the changes occurring during accommodation can be precisely evaluated without any contact with the ocular structure. Additionally, the instrument includes the possibility of manually setting the vergence of an accommodative stimulus.

For all of this, the present study aims to assess by OCT the main structures that take part in the process of accommodation at different age groups.

5.2 Methods

5.2.1 Subjects

A total of 14 subjects were included in this study. These were divided into two groups. The first group consisted of young healthy patients (3 males and 4 females) aged from 20 to 25 (mean 23.0 ± 2.2 years) whose mean spherical equivalent refractive error was -0.6 ± 2.8 diopters (D). The second group was compound of adult subjects (6 males and 1 female) aged 35 to 40 (mean 39.0 ± 1.5 years) with a spherical equivalent error of -0.2 ± 2.0 D. For all cases, the refractive error was obtained with dry autorefraction.

The subjects had enough amplitude of accommodation (at least 3.00 D), which was assessed monocularly by the Donders' method. Their best-corrected visual acuity evaluated with the LogMAR chart was at least 20/20 in Snellen equivalent. The subjects had no ocular abnormality or systemic condition, no ocular surgery history and they all presented clear intraocular media. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia. The patients were informed about the details of the study and signed a formal consent after written and verbal explanation of the implications.

5.2.2 Measurement device and parameters

The equipment that was used in this study for the visualization of the ocular structures is the Visante® *Omni*. This device combines OCT technology together with Placido disk topography to obtain advanced anterior segment measurements. It is a non-contact diagnostic instrument which acquires and analyses detailed cross-sectional tomographic images of the anterior eye segment. In order to obtain the captures, it makes use of low-coherence interferometry. Specifically, infrared light of 1310 nm is sent along an optical path that reaches the eye together with another reference path of the interferometer. Then, both paths are combined at the photodetector in order to determine the axial depth of the tissue thanks to the reflectivity signal.

Furthermore, the device allows the examiner to adjust the vergence of the visual target with a set of internal lenses. This is useful in order to evaluate the changes of the structures that occur with accommodation. Taking this into account, all the measurements were taken for the stimulus presented at 0.0 D for each patient (also referred as the unaccommodated state). This stimulus distance was considered to be relative to the subject's far point. In other words, the 0.0 D vergence was not the same for every patient, but it was presented at a vergence corresponding to the subject's far point. Additionally, the measurements were also obtained for the accommodated eye at -3.0 D of vergence. All the captures were performed at the horizontal meridian.

The software of the Visante® OCT (version 3.0) has a set of different scan types. In this study, the "Raw Image" and the "Raw Image HR" modes were used. The "Raw image" mode is able to get images deep into the eye, since it doesn't require the examiner to take the capture centred on the cornea. This mode is composed of 256 primitive A-Scans which represent a total area of 16 mm in width and 6 mm in depth. It was used to obtain the central lens thickness (CLT). Additionally, the "Raw Image HR" mode works similarly but at a higher resolution. This mode yields images of 512 primitive A-Scans which represent a total area of 10 mm in width and 3 mm in depth. It was used to capture the central apparent anterior lens curvature radius (ALC), as well as the ciliary muscle area (CMA) at the nasal region.

Due to the fact that these modes do not correct the images for the refractive indices of the ocular media, the measurements were obtained in pixels and the measurement comparisons were performed in pixels.

The captured images were exported from the Visante® into the external software. The CLT and the CMA were measured by ImageJ, developed by Wayne Rasband (National Institute of Health, USA). The CLT was considered as the axial distance from the central anterior surface to the central posterior surface. The CMA was obtained also by ImageJ applying a smooth image processing filter and then enhancing the contrast. Regarding the ALC, it was obtained adjusting a circumference to three points on the lens anterior surface, one central and two more moving aside to the left and to the right the same number of pixels from the centre (150 pixels, corresponding to approximately 1.5 mm taking as a reference a model eye with known dimensions). This was performed selecting these points on the surfaces after applying smooth and Sobel filters to the images in order to enhance the limits. Figure 5.1 represents different captures showing how these parameters were measured.

Figure 5.1: *Captures showing the parameters being measured: (A) central lens thickness, with the raw mode (B) Apparent anterior lens curvature, with the high-resolution raw mode and (C) Ciliary muscle area, with the high-resolution raw mode.*

5.2.3 Experimental procedure

The patients were requested to keep their fixation on the instrument visual target before capturing. They were also requested to blink before starting the exam and to open wide until the measurements were obtained. All the measurements for each patient that took part of the study were captured during a single session.

5.2.4 Statistical analysis

The statistical analysis was performed with SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). Each measurement was obtained three times per image and a mean and a standard deviation value were calculated. Due to the limited number of subjects in each sample, the non-parametric Mann Whitney U test for two independent samples was used. This procedure allows getting the significance level between two different groups or samples for a given parameter. The statistical significance level was set as $p<0.05$. Prior to analysis of the parameters of interest, the spherical equivalent of the groups was checked for significant differences, which were not found in our samples. Additionally, box-and-whisker plots were generated and represented for each parameter.

It has to be taken into account that this work is concerned to evaluate whether there are or not significant differences in some of the anterior segment measurements between two different age groups, and not to assess the changes with accommodation. For this reason, the comparisons were performed for the same accommodative state of the eye between groups and not between different accommodative stimuli, which some other works have extensively evaluated.

5.3 Results

With respect to the CLT, there were found statistically significant differences between both age groups for the unaccommodated state of the eye ($p<0.05$). Specifically, the thickness was found to be larger in the group with ages ranging from 35 to 40 years old than in that of younger subjects. Nevertheless, when considering the ALC of the crystalline lens, there were not found any statistically significant differences. As for the CMA the same outcome was observed, without significant differences. Nonetheless, even though there were not found significant differences, the radius of the ALC was found to be smaller in the adult group, whereas the CMA yielded slightly higher values for the young adults group.

Figure 5.2: *Box-and-whisker plot of the data set for the central lens thickness in both age groups at stimulus vergences 0.0 D (unaccommodated eye) and -3.0 D (accommodated eye). The measurements are represented in pixels.*

Regarding the accommodated state considering a stimulus vergence of -3.0 D, the results followed the same behaviour as with respect to the unaccommodated eye, showing a significant increase in the CLT of those adult patients. Again, as with respect to the unaccommodated state, although the ALC did not show significant differences with -3.0 D of vergence, the radius yielded smaller values in average for the adult group. The CMA was found to be slightly bigger in the young adults group.

Figure 5.3: *Box-and-whisker plot of the data set for the apparent anterior lens curvature radius in both age groups at stimulus vergences 0.0 D (unaccommodated eye) and -3.0 D (accommodated eye). The measurements are represented in pixels.*

Figure 5.4: *Box-and-whisker plot of the data set for the ciliary muscle cross-sectional area of the nasal region in both age groups at stimulus vergences 0.0 D (unaccommodated eye) and -3.0 D (accommodated eye). The measurements are represented in pixels.*

Figures 5.2, 5.3 and 5.4 represent the box-and-whisker plots for the data set of our samples in relation to the CLT, ALC and CMA, respectively. Table 5.1 summarizes the results as a mean ± standard deviation that were obtained for each group in every parameter that was considered, and points out those statistically significant differences found.

Table 5.1: *Results (mean ± standard deviation) extracted from the images of the anterior eye segment with Visante® Omni at stimulus vergences 0.0 and -3.0 D and the associated p-values among group comparisons. CLT: Crystalline lens thickness (pixels), ALC: Anterior lens curvature radius (pixels), CMA: Ciliary muscle area (pixels^2). * means statistically significant differences.*

5.4 Discussion

With aging, the human body goes through several changes that have an impact on our functions and thus, in our quality of life. The eye is no different, being presbyopia one of these conditions affecting the ocular function. In this paper, we analysed some of the anatomical parameters of the crystalline lens and the ciliary muscle in two different age groups by means of OCT technology in order to elucidate how they are affected by aging. Two different stimuli were included (unaccommodated and accommodated state), in order to analyse the possible differences between both age groups at each stimulus and thus observe whether these differences were more visible with accommodation.

It is already known that accommodation is one the physiological functions that are more rapidly lost. With aging, the crystalline lens suffers from several transformations as part of the aging process. These changes include a loss of the elasticity of the capsule. Additionally, the cortex decreases its elasticity and the nucleus hardens, modifying the ability of the lens to change its shape and achieve the proper refractive state required in order to focus on objects at different distances *(Strenk et al., 2005)*. Some in vivo studies that have been carried out decades ago already showed that the total volume of the lens increases with age, thus increasing the CLT *(Brown, 1974)*. Indeed, in light of our results, the difference in CLT between age groups was found to be statistically significant, which is in agreement with those previous findings. Also, the radii of curvature can be reduced with aging as a result of the total growth of the lens. In fact, the experiment of Brown in 1974 demonstrated that the aging lens becomes more convex *(Richdale et al., 2008b)*. Brown found out that the curvature radius of the anterior surface of the lens changed from 15 mm to 8.5 mm between ages 20 and 80, in average. However, our study did not show any significant variation with regard to the ALC measurements between the age groups as assessed considering the device limitations in the measurements. Nevertheless, these findings could mean that the first signs of the aging of the lens are more noticeable in its thickness, continuing to modify its shape and steepening its curvature radius as age increases, since the maximum age limit that was considered in this study was 40. Richdale et al. *(Richdale et al., 2008b)* carried out a study including subjects with ages ranging from 35 to 50 also using the Visante OCT in order to determine its feasibility to measure the changes in lens thickness with aging. In their work, they validated the Visante OCT system showing an increasing in thickness of the lens which is also consistent with previous findings and with ours.

Some other works have evaluated the changes of the lens with aging. Barraquer et al. *(Barraquer et al., 2006b)* investigated the variations in the thickness of the lens capsule along its perimeter as a function of age. In their study, donor lenses of humans aged 12 to 103 were evaluated. They found that the studied capsules were thicker in the anterior part, and that it increased continuously in thickness with age. Specifically, the anterior midperiphery central to the zonular insertion yielded the maximum thickness, whereas the midperipheral zone decreases after the seventh decade. They did not found posterior peripheral thickening in average. In fact, they concluded that the posterior capsule becomes thinner with age. Other studies carried out by Dubbleman et al. *(Dubbelman and Van der Heijde, 2001, Dubbelman et al., 2003a)* have evaluated the shape of the aging human lens. They measured the curvature of the lens in subjects, whose age ranged from 16 to 65 years, by means of Scheimpflug images and corrected them for distortion due to the fact that they are obliquely captured. They observed a decrease of the anterior and posterior lens radius as well. The thickness of the cortical layers of the lens and how they change with age was also analysed. Their results showed that aging increases the thickness of the cortex 7 times more than that of the nucleus. A significant thickening of the nucleus was also observed with age, although this thickening was much smaller than that of the cortex. Glasser et al. (Glasser and Campbell, 1998a, Glasser and Campbell, 1999) also investigated those changes of the human crystalline lens related to age. They included 27 enucleated human lenses of subjects whose age ranged from 10 to 87 years. In their case, they used a stretching device and a scanning laser to obtain precise measurements of the focal length of the lenses, similar to that technique Fisher had previously used *(Fisher, 1977)*. Measuring the focal length at the maximum stretching force, the lenses younger than 50 years showed significant changes, whereas the older lenses did not yield any change in the focal length with stretching. Their results give additional evidence for predominantly lens-based theories of presbyopia. All these changes of the crystalline lens related to age would imply a tendency to myopia with aging but this actually does not happen and it is known as the crystalline paradox, which is accompanied by changes in the gradient refractive index of the lens with increasing age *(Dubbelman and Van der Heijde, 2001)*.

On the other hand, although the crystalline lens is crucial during accommodation, its activity is muscle-induced. Otherwise, without the ciliary muscle contractions and relaxations, the lens would not be able to modify its shape in order to change its refractive power by means of the zonular fibres. This feeds some other theories, following that of Duane-Fincham *(Duane, 1922, Fincham, 1937*), which have suggested that a component related to presbyopia is given by the ciliary muscle deterioration with age in addition to the loss of lens elasticity. Tamm et al. *(Tamm et al., 1992)* studied the age-related changes in the human ciliary muscle of enucleated eyes of subjects aged 33 to 87. Their results showed that the total area and the length of the muscle yielded a significant decrease with age. In fact, presbyopia is more likely to be a multifactorial condition in which main changes in the lens may be combined with other factors, such as changes in the ciliary muscle or the vitreous, which could have an impact on the amplitude of accommodation. However, although the in vitro measurements provide comprehensive descriptions of the structures, the changes could differ from in vivo conditions due to the effect of other factors such as the intraocular pressure or the vitreous. Strenk et al. *(Strenk et al., 1999)* used high-resolution MRI in order to measure in vivo the relationship between the ciliary muscle contraction and the lens response with increasing age. Their findings showed that the contraction of the muscle was present in all subjects up to age 83, although it was slightly reduced with aging. In the present study, the CMA was also studied as a significant parameter that may be affected with aging, although it is worth mentioning that still nowadays little is known about its exact behaviour during contraction and there are some limitations with its imaging and in vivo measurement

(Bailey, 2011a). Nonetheless, Lossing et al. *(Lossing et al., 2012)* confirmed that it is possible to examine the action of the ciliary muscle with accommodation by means of Visante® OCT. Taking these facts into account, our results of the CMA as a cross-sectional area measurement with OCT technology did not show any statistically significant difference in relation to age for any of the accommodative states that were included in this study ($p>0.05$). Nevertheless, Lossing et al. *(Lossing et al., 2012)* observed that it seems to be a thickening of the anterior part and a thinning of the posterior portion of the ciliary muscle with accommodation. Concerning to age, they did not assess the possible anatomical differences or variations of the action of the muscle in different age groups, and yet few studies have been carried out on this topic due in part to the current limitations. For this reason, the methods for measuring the ciliary muscle still have to be improved and the results should be considered carefully.

In summary, our findings provide extra useful information about the aging process of the crystalline lens and the ciliary muscle structures. It was shown that the thickness of the lens is increased with aging, whereas there were not found any significant differences in the anterior curvature radius or the ciliary muscle size of those subjects in our samples. Additionally, the small size of the samples for the considered parameters or the current limitations of the imaging techniques should be taken into account, above all those related to the ciliary muscle. For these reasons, further investigation should be carried out on this topic in order to clarify those possible variations with age in the ciliary muscle action and to elucidate to what extent it affects the ability of the lens to change its shape. With this information, new designs leading to correct presbyopia or maybe new methods aimed at delaying its appearance could be achieved in order to improve the quality of life of presbyopes.

CHAPTER 6

The effect of even and odd higher order aberrations on the accommodation response

6.1 Introduction

It is well known that the eye is capable of changing its power in order to focus on objects that are placed on different distances *(Southhall, 1925)*. The change in focus of the human eye is known as accommodation and it is vital for the improvement of the retinal image quality *(López-Gil et al., 2013)* and for the appreciation of the details of the objects *(Heath, 1956)*.

There are several cues that activate the accommodation mechanism of the eye in order to have a proper accommodation response *(Vinas et al., 2015)*. These cues are characterized by either subjective *(Kruger and Pola, 1985)* (e.g. distance of the object) or objective *(Fernandez and Artal, 2005)* (e.g. longitudinal chromatic aberration (LCA)) parameters that influence on the retinal image quality *(Chen et al., 2006)*.

Defocus has been proved to be caused from an incorrect accommodation response and it is possible to be characterized by a positive or negative sign, which is dependent on whether the plane of the image is ahead of or behind the retina *(Kruger et al., 2003, Thibos et al., 2013)*.

It has been demonstrated that LCA continues to provide a directional signal for accommodation at large pupil sizes despite higher levels of monochromatic aberrations. Large individual differences in accommodation to LCA are a hallmark of accommodation in normal trichromatic observers *(Seidemann and Schaeffel, 2002, Kruger, 2012, Kruger et al., 1997a, Rucker and Kruger, 2004)*.

Nevertheless, there have been cases in which the accommodation ability was not lost when the cues of the LCA were artificially removed *(Metlapally et al., 2014)*. This indicates the co-existence of additional optical cues, which play a role in the accommodation response *(Kruger et al., 1997b)*.

The monochromatic aberrations (except from defocus) are also considered as optical cues. This is due to the form of a different retinal image, which also depends on the defocus (as it happens in the case of the LCA). Moreover, some aberrations have a greater contribution to the accommodation response than others. This is evident in a study conducted by Wilson et al *(Wilson et* *al., 2002)* according to which the optical system is capable of differentiating the changes between the PSF of the positively and negatively induced defocus in the presence of monochromatic aberrations. In particular, the even-order aberrations are intertwined with the ability to distinguish between the negative and positive defocus, in comparison to the total aberrations. On the contrary, the odd-order aberrations are not intertwined with such ability *(Wilson et al., 2002, Wang et al., 2011)*. Nonetheless, it is still under research the exact role of the different aberrations in the accommodation response of the eye and whether the even and odd-order aberrations contribute as a signed cue to the direction of defocus or not.

Therefore, the aim of this study is to further investigate how the monochromatic aberrations influence on the accommodation response of the eye. To achieve this, an adaptive optics system was used in order to measure the accommodation response of the subjects' eyes under different conditions: with the natural aberrations being present, and with the odd and even-order aberrations being corrected.

6.2 Methods

6.2.1 Subjects

Eight young adult subjects (mean age: 31 ± 5.24 years, range: 26 to 40 years) who could accommodate under monochromatic light conditions participated in the study. The averaged spherical equivalent refractive error was -1.00 ± 2.37 diopters (D). Astigmatism was limited to ≤ 1.00 D, and anisometropia < 2.00 D. All subjects had normal corrected visual acuity (20/20 or better), no ocular pathology, no binocular vision anomalies, no previous conducted ocular surgery, and normal clinical amplitudes of accommodation for their ages (at least 4 D). The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia. The subjects were verbally informed about the details and possible consequences of the study, and a signed formal consent was obtained from each subject.

6.2.2 Equipment

The crx1 adaptive optics visual simulator (Imagine Eyes, Orsay, France) was used to measure and correct the wavefront aberrations of each subject’s eye (Figure 6.1). The system is composed of a Hartmann-Shack wavefront sensor and a deformable mirror. The wavefront sensor employs a square array of 1024 microlenses and a near-infrared light source with a wavelength of 850 nm. An internal microdisplay is used to project the target, while the Badal system is employed to change its vergence (in other words, accommodation demand). To control the accommodation process, a monochromatic Maltese cross (550 ± 5 nm) is used as the target. A precise alignment of the subject’s pupil is required, and these parameters are controlled with an additional Charge Coupled Device (CCD) camera. Head movements are reduced employing a chin and forehead rest.

Furthermore, the deformable mirror is comprised of 52 independent magnetic actuators, which are used to either correct or modify the wavefront aberrations *(Perez-Vives et al., 2013, Ruiz-*

Alcocer et al., 2012, Madrid-Costa et al., 2012). Prior to data collection, a customized software based on commercially available routines (Imagine Eyes, Orsay, France) was used to control the deformable mirror and reshape it from its normally flat surface to the desired one.

Figure 6.1: *Schematic layout of the crx-1 adaptive optics visual simulator used to measure and correct the wavefront aberrations of the subject's eye.*

In this study, the Zernike coefficients of each individual up to and including 6th order were considered and partially corrected to meet the conditions tested (i.e. natural aberrations present, odd and even order aberrations separately corrected).

6.2.3 Experimental procedure

The experiment was divided into three conditions, each having different wavefront aberrations present. In the first condition the subject's natural aberrations were present, whereas in the two other conditions the subject's odd and even-order aberrations were respectively corrected. To achieve this, a customized software was made and implemented into the adaptive optics system. This software was further controlling the deformable mirror of the system in order to correct the aberrations corresponding to each condition. In all conditions the measurements were performed monocularly and obtained from the dominant eye of each subject.

The measurements were acquired under three different conditions: (i) natural aberrations were present, (ii) odd order aberrations were corrected, and (iii) even order aberrations were corrected. In each condition, three measurements were acquired at the accommodation demand from 0 to 4 D, with a step of 0.5 D. Thus, 27 wavefront measurements were recorded per condition, with a total of 81 measurements for each eye. The subject was allowed to blink prior recording a measurement, to avoid increased tear film aberration that might otherwise have occurred during an extended inter-blink interval *(Montes-Mico et al., 2005)*. Subjects were also allowed to rest between trials.

6.2.4 Data analysis

The wavefront data were exported as Zernike coefficients up to 6th order. To solely identify the accommodation response of the eyes to the accommodation stimuli, the Zernike defocus was used *(Tarrant et al., 2010b, He et al., 2000)*. The accommodation response was estimated in diopters employing the following Equation:

$$AR = AD - \frac{C_2^0 4\sqrt{3}}{r^2}, (1)$$

where AR is the accommodation response, AD is the accommodation demand, C_2^0 is the second-order Zernike coefficient for defocus in µm and r is the pupil radius in mm *(Thibos et al., 2004)*.

Data corresponding to each one of the three conditions were fitted to linear models using Matlab 2015b (MathWorks Natick, MA). For each regression analysis, the intercept, the slope, the determination coefficient, and the *p*-value were obtained. An additional ANCOVA analysis was performed to elucidate whether the slopes of the three different conditions were different. A *p*-value of less than 0.05 was considered to be statistically significant.

6.3 Results

To obtain the values of the accommodation response, the second-order Zernike coefficient (defocus) was converted into diopters, employing the previously described formula (Equation 1). Then, the mean of three consecutive measurements was displayed for each condition and accommodation demand considered in this study.

Figure 6.2: *The mean accommodation response obtained with the normal aberrations being present in the subjects' eye. Each data point represents the mean ± standard deviation (SD) of each accommodation demand. The dashed line displays the theoretical accommodation response.*

Figure 6.2 exhibits the mean accommodation response obtained from all eight subjects for each accommodation demand with the natural aberrations being present, starting from 0 D and ending at 4 D of accommodation demand, utilizing a step of 0.5 D. The accommodation responses were acquired when the natural aberrations were present. The dashed line shows the theoretical response of the accommodation process (i.e. equal accommodation response for each accommodation demand). In this case, there was a difference towards the same direction between all accommodation responses and the theoretical line, demonstrating that a certain value of lag was present for all subjects and accommodation demands.

The mean accommodation responses acquired when the odd and even-order aberrations were removed, are displayed in Figures 6.3 and 6.4, respectively. Both figures illustrate the mean accommodation response of all subjects and accommodation demands. In both figures, the obtained accommodation responses are similar indicating a similar accommodative lag for both conditions in association with the theoretical line. Nevertheless, in Figure 6.4 the lag of accommodation is greater for the accommodation demands of 1.5 D, 3 D, 3.5 D and 4.0 D, in comparison to that obtained in Figure 6.3 for the same accommodation demands.

Figure 6.3: *The mean accommodation response obtained with the odd order asymmetric aberrations being corrected in the subjects' eye. Each data point represents the mean ± standard deviation (SD) of each accommodation demand. The dashed line displays the theoretical accommodation response.*

As already mentioned, a statistical analysis was conducted to analyze if the measurements obtained for the three different conditions were statistically different or not.

Figure 6.4: The mean accommodation response obtained with the even order asymmetric aberrations being corrected in the subjects' eye. Each data point represents the mean ± standard deviation (SD) of each accommodation demand. The dashed line displays the theoretical accommodation response.

Table 6.1 summarizes the results obtained for the regression analysis performed for each condition. The referred accommodation demand of 0 D corresponds to the far point of each subject's eye, hence its non-accommodated state. Therefore, this accommodation demand was excluded from the statistical analysis. All the *p*-values for the three linear regression analysis were statistically significant ($p < 0.001$). The minimum determination coefficient (R^2), equal to 0.88, was obtained for the condition in which the even-order aberrations were corrected. The ANCOVA analysis revealed that the slopes of the accommodative responses for the three conditions were not significantly different from each other ($p = 0.26$).

Table 6.1: *Results obtained for the regression analysis performed for each condition.*

6.4 Discussion

During the past fourteen years, several studies have been conducted to identify the possible use of the high-order aberrations on accommodation *(Fernandez and Artal, 2005, Chen et al., 2006, Wilson et al., 2002, Fernandez and Artal, 2002)*. Nevertheless, all of these studies came up with different results. An additional study conducted by López-Gil et al *(Lopez-Gil et al., 2007)* examined once again the effect of the high-order aberrations, but exclusively the effect of inducing third-order aberrations on the accommodation using customized contact lenses. On the other hand, Gambra et al *(Gambra et al., 2010)* employed targets, which were blurred with a certain amount of specific high-order aberrations to identify their influence on accommodation. Although, in all of the aforementioned studies there were differences in the methodology employed to perform the different experiments, they all had one common parameter; they all developed their experiments in order to study the dynamic accommodation response. Moreover, the number of participants varied between five to ten among these studies, with one study having only two participants *(Fernandez and Artal, 2005)*. Additionally, in two studies, some aspects of latency and speed of the dynamic accommodation response were explored after the partial *(Fernandez and Artal, 2005)* and complete *(Chen et al., 2006)* correction of the ocular aberrations using an adaptive optics system, whereas in two other studies the gain and phase of the dynamic accommodation response were examined by inducing ocular aberrations *(Lopez-Gil et al., 2007, Gambra et al., 2010)*. A fifth study investigated the capability of perceiving changes between the PSF of the positive and negative induced defocus, but it did not record accommodation *(Wilson et al., 2002).*

In the present study, we selected a different approach to study the effect of the ocular aberrations on the static accommodation response. This study was designed in this way in order to show the potential of such approach for future research. More specifically, we selected to assess the differences in accommodation with natural aberrations being present in the subjects' eyes and with the odd and even-order aberrations being respectively corrected. This was achieved by employing an adaptive optics visual simulator and several accommodation demands ranging from 0 D to 4 D, with a step of 0.5 D. Additionally, we chose to study solely the changes that occur in defocus when a total of natural, even and odd-high order aberrations are present in the eye. In this way the changes in accommodation response can be adequately assessed for all conditions and accommodation demands.

Our results indicate that in the presence and absence of high-order aberrations, the static accommodation response is not altered. Although, we were expecting that the interactions between the natural and corrected aberrations may play a role in the precision of accommodation, such as worse precision in accommodation in the absence of some ocular normal aberrations; in our study this is not evident. In particular, according to our statistical analysis we found that the obtained accommodation responses were not significantly different between the three conditions. In other words, we would suggest that our results show that the accuracy of accommodation response remains unaffected with the correction of the odd and even-order aberrations. This aspect of our results is in agreement with the corresponding aspect of the results obtained in three previous conducted studies on the dynamic accommodation response *(Fernandez and Artal, 2005, Chen et al., 2006, Lopez-Gil et al., 2007)*. Therefore, from these results we conclude that if the higher-order aberrations were helping the visual system to choose the right direction of accommodation, then with their correction the accommodation performance would have been reduced.

Moreover, our results yielded a certain value of accommodation lag for all conditions and accommodation demands. According to previous studies, a general accommodation lag was expected as our subjects were seeing a Maltese cross. Using more demanding stimuli, like small letters, significantly reduces the lag in the accommodation response *(López-Gil et al., 2013)*. Once again, the differences in accommodation lag between the different conditions were not significantly different for each accommodation demand. Nonetheless, a slightly increased accommodation lag is noticed in the even-order corrected condition for the accommodation demand of 1.5 D, 3 D, 3.5 D and 4 D in comparison to the lag obtained in the two other conditions for the same accommodation demands.

Furthermore, in this study we used a monochromatic Maltese cross in order to impair the use of the LCA by the accommodation system, as it is well known that commonly it is used as cue for accommodation. This way, we can focus exclusively in the effect of the correction of the monochromatic aberrations on the accommodation response. We selected only subjects who were able to appropriately accommodate under monochromatic light, despite the great reduction in information provided by the LCA and monochromatic aberrations, respectively. In particular, in their case is indicated that by accommodating in monochromatic light the LCA is not used as a cue of accommodation. Additionally, no difficulties in accommodating were faced in the conditions of correcting the odd and even-order aberrations (in other words, the partial correction of the higher-order aberrations), as it has happened to previous conducted studies *(Chen et al., 2006).*

Overall, neither of the subjects' responses was worse without the odd and even-order aberrations nor it was unchanged. Chen et al *(Chen et al., 2006)* suggested that in such case the accommodation response does not improve as it is not affected by the increase in the rate of change in image quality with focus error produced with the removal of the high order aberrations.

In summary, we measured the static accommodation response of the subjects' eyes with the natural aberrations and with the odd and even-order aberrations corrected using an adaptive optics system. Our results indicate that when LCA is eliminated as cue, all of the subjects who are able to accommodate under monochromatic light are capable of accommodating properly despite the elimination of the odd and even high-order aberrations. For all subjects, there is no significant difference in the accommodation response with the natural aberrations or without the odd and even-order aberrations. In our study we suggest that the odd and even-order aberrations do not provide aid for accommodation, as the accommodation response of all subjects was not affected by the partial correction of these aberrations. Nevertheless, still is under question the actual role of the monochromatic aberrations in the accommodation mechanism. Therefore, further research is needed using a larger number of subjects in order to increase our knowledge in this topic.

CHAPTER 7

Conclusions and Future work

7.1 Conclusions

The aim of this Thesis was to assess the crystalline lens response to different optical signals using different technologies. This field of study has been proved to be wide and hence provided us with multiple alternatives of studying the topic under different points of views. In particular, we have investigated both the physiological and anatomical changes that occur in the human eye with accommodation. To achieve this, we performed different-purposed research studies selecting subjects of different age to participate, as well as employing powerful technologies such as wavefront sensing, optical coherence tomography and adaptive optics to establish our results. From the different research studies we performed, we may conclude to the following:

1. The accommodation response of young adults is not affected when they shortly read from electronic devices with relative small screen and text size in neither of the different accommodation demands that they may use. This is due to the youth of subjects' eyes, and further to their normal level of amplitude of accommodation corresponding to their age.
2. There are significant variations in the anterior segment structures, such as in anterior chamber depth, central lens thickness, anterior segment length, anterior lens curvature, posterior lens curvature and in ciliary muscle area which occur with the accommodation process. These changes apply for the different demands of accommodation that an individual may use.
3. There are significant anatomical changes that occur in the anterior segment of the eye, in terms of lens thickness, anterior lens curvature radius and ciliary muscle area with accommodation and aging. These anatomical changes are noticed in the different accommodation demands that an individual may use.

4. When longitudinal chromatic aberration is eliminated as a cue for accommodation, all of our subjects were capable of accommodating in the right direction despite the elimination of the odd and even higher-order aberrations.
5. There were no significant differences in the accommodation response with the natural aberrations or without the odd and even higher-order aberrations. This suggests that the odd and even higher-order aberrations do not provide the sign of defocus for accommodation, as the accommodation response of all subjects was not affected by the partial correction of these aberrations.

The outcomes of this Thesis help to extent our knowledge on three wide known research fields: ocular accommodation, ocular aberrations and ageing eye. This can be also useful for practitioners in order to achieve a better understanding in these areas, which can help them to make their best clinical decisions. In addition, the findings from this Thesis also provide potentially useful approaches for designing either optical solutions to correct presbyopia or new methods aiming to delay the appearance of presbyopia.

7.2 Future work

The conclusions of this Thesis that were discussed on the previous section could lead the work to the establishment of future research and potential studies. We cite below potential future studies that may evolve from the research studies conducted. More specifically:

1. Future work should consist of larger reading periods using electronic devices with relatively small screen and text size, as well as greater sample of participants with a wide range of different ages, in order to establish a comparison with the results obtained by this study.
2. Further investigation should be carried out on the topic of the changes that occur in ocular anatomy with accommodation, in order to clarify those possible variations that take place with age in the ciliary muscle action and to elucidate to what extent it affects the ability of the lens to change its shape.
3. Despite the several studies that have been carried out regarding the actual role of the monochromatic higher-order aberrations in the accommodation mechanism, this still remains under question. Therefore, further research is needed in studying the effect of each monochromatic aberration separately on accommodation using a larger number of subjects.

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Appendix A

Appendix A

This PhD Thesis has resulted in the following peer-reviewed publications:

1. Moulakaki, A. I., Recchioni, A., Del Águila-Carrasco, A. J., Esteve-Taboada, J. J. & Montés-Micó, R. Assessing the accommodation response after near visual tasks using different handheld electronic devices. Accepted for publication in *Arquivos Brasileiros de Oftalmologia*.
2. Monsálvez-Romín, D., Moulakaki, A. I., Esteve-Taboada, J. J. & Montés-Micó, R. In vivo OCT assessment of anterior segment lengths, lens curvature and ciliary muscle with accommodation. Submitted for publication (in peer-review process).
3. Monsálvez-Romín, D., Moulakaki, A. I., Esteve-Taboada, J. J. & Montés-Micó, R. Crystalline lens and ciliary muscle assessment with accommodation: aging effects. Submitted for publication (in peer-review process).
4. Moulakaki, A. I., Del Águila-Carrasco, A. J., Esteve-Taboada, J. J. & Montés-Micó, R. The effect of even and odd order aberrations on the accommodation response. Submitted for publication (in peer-review process).

Parts of the present Thesis have been presented to the following scientific congresses:

1. Moulakaki, A. I., Montés-Micó, R., Esteve-Taboada, J. J., Ferrer-Blasco, T., Madrid-Costa, D., Marin-Franch, I. & Del Águila-Carrasco, A. J. (2014). Age-related changes in the accommodative response of the human eye. Communicated at the *XXXII European Society of Cataract and Refractive Surgeons (ESCRS)* congress, London, United Kingdom.
2. Moulakaki, A. I., Montés-Micó, R., Esteve-Taboada, J. J., Madrid-Costa, D. & Ferrer-Blasco, T. (2014). Effects of age on the dynamic components of accommodation. Communicated at the *XXXII European Society of Cataract and Refractive Surgeons (ESCRS)* congress, London, United Kingdom.
3. Moulakaki, A. I., Recchioni, A., Del Águila-Carrasco, A. J., Esteve-Taboada, J. J. & Montés-Micó, R. (2015). Assessment of accommodation response over sustained near visual tasks using a

Hartmann-Shack sensor. Communicated at the *Optometry Congress (OC'15)*, Ageing Eye Annual Meeting, Valencia, Spain.

4. Moulakaki, A. I., Recchioni, A., Del Águila-Carrasco, A. J., Esteve-Taboada, J. J. & Montés-Micó, R. (2015). Assessment of accommodation response after short near visual tasks using a Hartmann-Shack aberrometer. Communicated at the *XXXIII European Society of Cataract and Refractive Surgeons (ESCRS)* congress, Barcelona, Spain.
5. Recchioni, A., Moulakaki, A. I., Esteve-Taboada, J. J., Del Águila-Carrasco, A. J., & Montés-Micó, R. (2015). Evaluation of the accommodation response under different accommodative demands after short-term near visual tasks, using a Hartmann-Shack aberrometer. Communicated at the *XXXIII European Society of Cataract and Refractive Surgeons (ESCRS)* congress, Barcelona, Spain.
6. Moulakaki, A. I., Recchioni, A., Del Águila-Carrasco, A. J., Esteve-Taboada, J. J. & Montés-Micó, R. (2015). Alternative assessement of the accommodation response using a Hartmann-Shack aberrometer. Communicated at the *International OSA Network of Students (IONS)* congress, Valencia, Spain.
7. Moulakaki, A. I., Recchioni, A., Del Águila-Carrasco, A. J., Esteve-Taboada, J. J. & Montés-Micó, R. (2016). Evaluación alternativa de la respuesta acomodativa utilizando un aberrómetro Hartmann-Shack. Communicated at the *24 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica*, Madrid, Spain.