OPTICS OF CONDUCTIVE KERATOPLASTY: IMPLICATIONS FOR PRESBYOPIA MANAGEMENT

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ABSTRACT

Purpose: To define the corneal optics of conductive keratoplasty (CK) and assess the clinical implications for hyperopia and presbyopia management.

Methods: Four analyses were done. (1) Multifocal effects: In a prospective study of CK, uncorrected visual acuity (UCVA) for a given refractive error in 72 postoperative eyes was compared to control eyes. (2) Surgically induced astigmatism (SIA): 203 eyes were analyzed for magnitude and axis of SIA. (3) Higher-order optical aberrations: Corneal higher-order optical aberrations were assessed for 36 eyes after CK and a similar patient population after hyperopic laser in situ keratomileusis (LASIK). (4) Presbyopia clinical trial: Visual acuity, refractive result, and patient questionnaires were analyzed for 150 subjects in a prospective, multicenter clinical trial of presbyopia management with CK.

Results: (1) 63% and 82% of eyes after CK had better UCVA at distance and near, respectively, than controls. (2) The mean SIA was 0.23 diopter (D) steepening at 175° ($P < .001$); mean magnitude was 0.66 D (SD, 0.43 D). (3) After CK, composite fourth- and sixth-order spherical aberration increased; change in (Z^{12}) spherical aberration alone was not statistically significant. When compared to hyperopic LASIK, there was a statistically significant increase in composite fourth- and sixth-order spherical aberration ($P < .01$) and spherical aberration (Z^{12}) alone ($P < .02$); spherical aberration change was more prolate after CK. (4) After the CK monovision procedure, 80% of patients had J3 or better binocular UCVA at near; 84% of patients were satisfied. Satisfaction was associated with near UCVA of J3 or better in the monovision eye ($P = .001$) and subjectively good postoperative depth perception ($P = .038$).

Conclusions: CK seems to produce functional corneal multifocality with definable introduction of SIA and higher-order optical aberrations, and development of a more prolate corneal contour. These optical factors may militate toward improved near vision function.

Trans Am Ophthalmol Soc 2005;103:412-456

INTRODUCTION

Over the past decade, removal of corneal tissue with 193-nm excimer laser energy has been successfully used for treatment of refractive errors by means of the laser in situ keratomileusis (LASIK)[1-4] and photorefractive keratectomy (PRK) procedures.[5-17] Excimer lasers are able to ablate corneal tissue with minimal thermal or mechanical effects. Using this tissue sculpting methodology, LASIK and PRK correct nearsightedness, farsightedness, and astigmatism by changing the surface curvature of the cornea.[18-20] The resulting optics, including corneal topography, surgically induced astigmatism (SIA), corneal multifocality, and wavefront aberration profile, have been explored in some detail.

The correction of presbyopia is more problematic, both practically and theoretically. A physiologic approach aimed at crystalline lens function remains in its infancy. Most clinical efforts, therefore, have been directed toward optical arrangements, all of which hope to achieve simultaneous near and distance acuity. One general approach includes contact lenses and intraocular lenses of a variety of bifocal and multifocal designs. The other, commonly referred to as "monovision," achieves depth of focus with differential corrections on each eye, whether achieved with glasses, contact lenses, or surgery.

Conductive keratoplasty (CK) is a relatively new corneal steepening procedure for the correction of hyperopia and management of presbyopia. In a series of studies, this thesis first will investigate the optics of the CK procedure, in general. These analyses will look at putative corneal multifocality, SIA, and the optical aberrational profile of the cornea after CK. Clinical implications of these findings will be explored. The second part will present results of a multicentered clinical trial of CK to achieve a monovision-type correction of presbyopia, with attention to the optics findings considered in the previous sections.

BACKGROUND OF THERMOKERATOPLASTY

Biochemistry and Biophysics

Collagen makes up 71% of the dry weight of the cornea. The collagen molecule consists of three polypeptide chains conformationally wrapped together in a triple helix. There are a number of collagen types, based on the amino acid composition, degree of glycosylation, and the state of aggregation of the chains. Produced by keratocytes, Type I collagen is the major constituent of the corneal stroma, although small amounts of Type III collagen are also present.[21]

In the intracellular steps of collagen biosynthesis, the three polypeptide chains of the triple helix, each termed pro-alpha chains, first are synthesized. Proline and lysine on the chains next undergo hydroxylation and glycosylation. The three pro-alpha chains fold into

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into individual helices and then combine to form a triple helix. This molecule, termed procollagen, is secreted from the cell. Outside the cell, enzymes cleave the terminal peptide from the chains, resulting in a molecule termed tropocollagen. This is the fundamental unit of the collagen fibril. Tropocollagen molecules, which are approximately 300 nm in length, aggregate with a stagger of about one-fourth overlap between adjacent molecules, giving a characteristic banding pattern, typically 640 angstrom units in the fibrous collagens. Adjacent chains are covalently cross-linked by lysine oxidation.[22] Collagen, therefore, contains both intramolecular and intermolecular cross-links. As will be seen, it is the former that are important in understanding collagen shrinkage.

Composed of these cross-linked triple helical molecules of tropocollagen, corneal collagen fibrils measure approximately 25 to 35 nm in diameter and are spaced in uniform intervals of approximately 30 nm between adjacent fibrils. Corneal transparency results from the small size of the fibrils and their uniform architectural spacing (less than a wavelength of light). Bundles of these collagen fibrils, each extending the width of the cornea and oriented parallel to one another, compose the corneal stromal lamellae. The bundles are approximately 2.0 μm thick and 9 to 260 μm wide. There are approximately 200 to 250 lamellae in the cornea. The more posterior corneal lamellae have a regular orthogonal layering, with collagen bundles of adjacent lamellae at right angles to each other. Lamellae in the anterior third of the stroma have a more oblique layering.[23] This difference in ultrastructure of the anterior and posterior cornea potentially could affect the collagen shrinkage procedures to be discussed.

Types I, II, and III collagen are known to shrink up to one third when heated from approximately 50°C to 70°C.[24] This results from a breaking of intrapeptide hydrogen bonds of the triple helix, with consequent breakdown of the structure and rearrangement of the triple helix into a random chain configuration. As the intramolecular cross-links within the triple helix are broken, the long chains shorten and take on a more random orientation, with only intertropocollagen cross-links remaining.[25] Associated with this shrinkage in the direction parallel to the long axis of the fiber, there is a swelling perpendicular to the fiber.[26]

The degree and architecture of collagen contraction are a function of the temperature, time, and profile of the application.[27] At temperatures of less than 50°C, there are minimal biomechanical effects.[28] Above 50°C, contraction occurs; the rate of shrinkage maximizes at approximately 70°C. Beyond 70° to 100° C, the collagen turns to gelatin and there is irreversible necrosis and permanent destruction of the corneal tissue.[29]

Collagen shrinkage underpins the refractive surgery procedures to be discussed. In theory, shrinking the collagen lamellae will decrease the chord length of the cornea in the meridian of application, hence steepening the cornea in that axis.[30] Indeed, calculations suggest that there will be a meridional steepening of 1 diopter (D) for each 23 μm of decreased chord length.[31] In addition, focal shrinkage in a hemimeridian would be expected to move the cornea apex away from the application.[32]

History of Clinical Thermokeratoplasty

The idea of thermokeratoplasty, the refractive reshaping of the cornea from the application of heat, has been attempted in a number of ways for over 100 years. Lans,[33] in 1889, applied burns to the peripheral surface of a rabbit cornea and noted the induction of astigmatism. In the 20th century, thermokeratoplasty using heated probes was used in an attempt to induce flattening of the keratoconic cornea.[34-40] However, such interventions generally were unsuccessful, resulting in unpredictable outcomes, regression, and corneal scarring. For instance, Keates and Dingle[36] treated nine eyes with a 5-mm metal probe heated to 120°C. Despite a marked initial flattening, keratometer levels returned to pretreatment levels in seven eyes, and one eye showed stromal scarring and neovascular ingrowth. In contrast, Aquavella and colleagues[35] did find an improvement in corneal hydrops in six eyes treated.

In related work, Gasset and coworkers[34] developed a thermokeratoplasty apparatus consisting of a stainless steel tip with a thermocouple placed within its head. With this instrument, the temperature could be monitored throughout the procedure. In experiments with fresh enucleated pig eye corneal strips, they found that the average shrinkage temperature was 65°C and the amount of shrinkage varied from 40% to 50%. In addition, they showed that with the probe at 130°C, the average temperature increase at the level of the corneal endothelium was 22°C. Using this instrument, they treated 15 keratoconic eyes with probe temperatures varying from 90°C to 150°C with different lengths of application. They found that results were more predictable in the eyes treated with higher temperatures. In later work, Gasset and Kaufman[39] treated 59 keratoconic eyes with a similar probe at 115°C. Initial results were encouraging; of these, only three went on to penetrating keratoplasty because of corneal opacity, and the investigators recommended clinical use of the procedure.

Both Arentsen and colleagues[37] and Aquavella and colleagues[40,41] investigated corneal morphology after these types of thermokeratoplasty procedures. The former found epithelial necrosis, degeneration of keratocytes, and endothelial edema early, with longstanding epithelial basement membrane changes. The latter showed epithelial thinning, bullous keratopathy, thickening of the epithelial basement membrane, and frequent destruction of Bowman's layer. Moreover, some eyes showed aseptic stromal necrosis, stromal scarring, and a persistent inflammatory infiltrate. Fogle and coworkers[42] found persistent defects of the epithelial basement membrane by electron microscopic evaluation and suggested that this could be associated with clinical recurrent epithelial erosions.

In a further attempt to treat hyperopia and astigmatism, thermokeratoplasty again was attempted by other investigators.[43-46] Their technical innovation involved heating the cornea to a greater depth than achieved in earlier attempts at the thermokeratoplasty procedure. In this effort, they used an instrument developed by S. Fyodorov, MD, and the Moscow Research Institute for Eye Microsurgery, in which a nichrome wire probe was heated to 600°C for 0.3 seconds. The probe depth was set by ultrasonic pachymetry of the cornea, generally to 90% of corneal thickness. Applications were made in a series of radial spots in the corneal midperiphery in a surgical strategy they termed *radial thermal keratoplasty*. Prescient of more recent thermokeratoplasty experiences, the amount of correction was found to be governed by the central clear optical zone, the number of radial rays, and the number of spots per ray. For the treatment of astigmatism, meridional applications of a variety of patterns were used.

As with earlier approaches, the Fyodorov technique caused complications, including corneal erosions, corneal folds, induced astigmatism, peripheral corneal neovascularization, and corneal pannus. In a rabbit study using the Fyodorov instrument, Feldman and coworkers[47] found burns to 90% depth and an early retrocorneal membrane as well as a 300-µm-diameter area of endothelial cell damage under each burn. Similarly, the Fyodorov technique was confounded by lack of predictability and regression of effect. In a series by these same investigators,[48] there was an 80% regression in effect at 1 year. Charpentier and colleagues,[49] similarly, showed a 55% regression of effect and suggested that the regression was related to remodeling of the stroma over time.

Holmium-YAG Laser Thermokeratoplasty

In an effort to better control collagen shrinkage and, thus, in theory make thermokeratoplasty an efficacious and predictable corneal refractive procedure, the pulsed holmium:YAG (Ho:YAG) laser has been investigated and used on a relatively widespread clinical basis. All Ho:YAG lasers for collagen shrinkage operate in the infrared spectrum at a wavelength of approximately 2 µm, corresponding to the maximal absorption coefficient of water. Energy uptake heats the water in the tissue to the proper temperature for collagen shrinkage.

Seiler and coworkers[50] used a laser platform with a wavelength of 2.06 µm, pulse duration of approximately 200 µsec, and repetition rate of 4 Hz. Laser energy was delivered via a flexible fiberoptic and handheld applicator. A sapphire lens system was mounted at the applicator tip to focus the beam approximately 400 µm in front of the handpiece. Using this system, the surgeon manually placed spots in one or a series of concentric rings on the cornea. These investigators found that corneal steepening increased above a threshold of 10 mJ per pulse and was constant between 15 and 35 mJ per pulse. They demonstrated hyperopic changes up to 5.0 D in cadaver and four blind human eyes, which remained stable for 4 months. On histologic examination, they found that the coagulation profile was that of an inverted cone with the most posterior aspect of the coagulation approximately 50 µm from Descemet's membrane.

The first Ho:YAG thermokeratoplasty device for general clinical use was manufactured by Summit Technology (Waltham, Massachusetts). As in Seiler's initial work, it delivered energy to the corneal surface using a fiberoptic and a handheld probe, which was applied by the surgeon in annular rings of concentric focal spots. Laser parameters were wavelength 2.06 µm, pulse duration 300 µsec, and repetition rate 15 Hz with a pulse power of approximately 19 mJ. Durrie and colleagues51 reported Phase II results in 1994. In this study, one or two concentric rings of eight spots were placed. Each treatment spot received 25 laser pulses to raise the temperature in that location to approximately 60°C. Single zone treatments were done at diameters of 7.0 or 7.5 mm, and double zone treatments were done at 7.0 mm and 9.0 mm, or 6.5 mm and 9.0 mm. Attempted corrections ranged from 1.0 to 4.0 D. At the 6-month follow-up visit, 75% of 24 eyes had uncorrected near visual acuity of J2 or better, and 79% were within ±1.00 D of attempted correction, but these investigators noted that regression of effect was the rule. In general, results using this laser were generally disappointing secondary both to regression of effect and induced astigmatism. One group reported an approximately 50% regression at 2 years follow-up as well as induced astigmatism of +1.25 to 2.5 D in 23% of treated eyes at the 6-month postoperative examination.[52]

Some of these unpredictable outcomes were thought to be secondary to the manual nature of the laser applications. The surgeon needed to hold the probe perpendicular to the cornea, place consistent pressure at each spot, and ensure proper spot location, all nontrivial efforts. Decentered or irregular treatment sites, thus resulting, were suggested as possible causes of poor results.[50]

In an effort to circumvent the surgical problems inherent in a handheld application device, attention was turned to the development of a noncontact Ho:YAG device. In early work, Moreira and associates[53] used an MOI-1 laser (Medical Optics Corporation, Carlsbad, California), which delivered 2.1-µm laser energy in 8-µsec pulses with pulse energy variable from 4 to 50 µJ. Targeting was accomplished with a dual-beam helium-neon aiming laser. They performed procedures on 40 human cadaver eyes using a ring of 32 spots and reported central corneal steepening. As in other studies of thermokeratoplasty, they found a greater corneal steepening effect with small optical zone diameters.

Building on this work, a noncontact pulsed Ho:YAG manufactured by Sunrise Technologies (Fremont, California) recently has been investigated, has received US Food and Drug Administration (FDA) approval, and has been used clinically in fairly broad application. In this technique, an annulus of laser spots is delivered concurrently via a slit-lamp delivery system.[25,54-57] Similar to the Summit laser, the Sunrise Ho-YAG laser uses a wavelength of 2.10 µm. Parel and associates[25,54,55] described basic work using the Sunrise gLASE 210. It used a lasing medium of chromium sensitized thulium holmium doped YAG crystal. The pulse width was 250 µsec with a 5-Hz repetition rate. Radiant exposure was 18.0 J/cm^2. Eight concentric spots were delivered via a slit-lamp delivery system using a monofilament fiber, polyprism, and mask. They produced treatment patterns of eight to 32 spots with spot sizes of 150 to 600 µm. In a cadaver eye study using a single-pulse, eight-spot, 3-mm ring, they found that the peak effect was at a radiant exposure of 26 J/cm^2, and that 18 J/cm^2 was the minimum exposure giving consistent changes in corneal curvature. They reported that an optical zone of 3 mm flattened the cornea and that zones of 5 mm and more steepened the cornea. These investigators then performed a histologic study in human cadaver eyes, and owl, monkey, rabbit, and cat eyes at various radiant exposures. They found epithelial and endothelial damage at 8 J/cm^2 using 25 pulses and at 18.01 J/cm^2 using 5 pulses. No endothelial damage was observed with a single spot at 18.01 J/cm^2. As in the previously discussed studies using the Summit Technology handheld platform, the histologic lesion in all cases was a cone, with a broader area of collagen contraction in the anterior cornea, tapering posteriorly. The volume of contracture increased with radiant exposure and the number of laser pulses. They found no lesion on histology with a radiant exposure setting below 10.26 J/cm^2. Other reports confirm the conical nature of the shrinkage lesion.[58]

Using noncontact Ho:YAG lasers, other investigators have described a thermal gradient through the depth of the treatment site with an approximately Gaussian distribution.[59] This likely leads to the architecture of contraction found on histologic examination.

They suggest, furthermore, that differential hydration of the corneal surface and corneal tissue layers could affect the temperature gradient. And, similarly, shrinking and dehydration may induce variation of the optical and thermal properties of the cornea during irradiation, all leading potentially to nonpredictable responses.

Despite such observations, clincial studies on poorly sighted eyes suggested potential safety and efficacy of the noncontact Ho:YAG technique.[56] Koch and colleagues[57] reported results of a Phase IIA clinical trial of the Sun 1000 Corneal Shaping System (Sunrise Technologies, Inc, Fremont, California) in 28 patients for the correction of hyperopia up to +3.88 D. They used one or two ring treatments of eight spots each with diameters of 6.0 or 6.0 and 7.0 mm, respectively. Laser parameters included a wavelength of 2.13 μm, pulse duration of 250 μsec, and nominal spot diameter, containing approximately 90% of the energy per spot, of approximately 615 μm. Laser pulse energies ranged from 208 to 242 mJ, and 10 pulses of laser light at a repetition rate of 5 Hz were used; thus, treatments took 2 seconds. Results at 2 years showed that the mean change in spherical equivalent refraction was –0.53 D in the one-ring group and –1.48 D in the two-ring group. Regression between 1 and 2 years was 0.01 D and 0.16 D in the two groups, respectively.

Regression of effect, however, has confounded the laser thermokeratoplasty technique and largely has led to its decreased clinical use today.[60] In his 1996 American Ophthalmological Society thesis, Koch,[61] in a study of corneal histology of Ho-YAG laser thermokeratoplasty, suggested that the epithelial and stromal wound healing response could account for such regression over time.

Other Thermokeratoplasty Lasers

CO_2 Laser Thermokeratoplasty. CO_2 lasers operate at a wavelength of approximately 10.6 μm. Chandonnet and coworkers[62] demonstrated flattening of the corneal dome using a pulsed CO_2 laser beam. Similar to the strategy of other thermokeratoplasty procedures, they placed annular rings at 7 mm and 5.5 mm. However, attempts at thermokeratoplasty using CO_2 lasers have generally resulted in poor predictability and regression of effect. It has been suggested that this is secondary to the superficial penetration depth of this long laser wavelength.[63,64]

Diode Laser Thermokeratoplasty. With wavelengths similar to Ho:YAG lasers, diode lasers operating at infrared wavelengths have been studied for collagen shrinkage procedures. Brinkman and coworkers[65] used a tunable continuous-wave diode laser at a wavelength of 1.845 to 1.871 μm. Laser powers of between 125 and 200 mW were used. Application times were 5 to 10 seconds. With this laser, they placed spots in annular rings using both contact and noncontact delivery systems and demonstrated refractive changes up to 10 D. Moreover, they showed increased refractive change with increased irradiation time and with smaller-diameter optical zone applications. These investigators suggest that diode lasers have advantages over Ho-YAG lasers, including more uniform collagen heating and greater reliability.

CONDUCTIVE KERATOPLASTY

Background

In an effort to develop a thermokeratoplasty procedure that affords more predictable corneal steepening and long-term stability, recent efforts have been directed at the application of high-frequency, low-energy electric current to shrink corneal collagen. This approach, in theory, combines the advantages of deep corneal penetration of the original Fyodorov technique with a controllable, predictable, and uniform heat application throughout the stromal depth. Initially developed by Mendez and associates,[65] the *conductive keratoplasty* instrument and procedure were developed by Refractec, Inc (Irvine, California). Premarket approval for the device was given by the FDA in 2002. The 1-year results of the prospective, multicenter clinical trial of CK for hyperopia have been previously published.[67]

The CK Equipment

The Viewpoint CK system (Refractec, Inc, Irvine, California) was used in all studies to be presented in this thesis. The instrument has two main components.

The first component is a console to generate radiofrequency (RF) energy (Figure 1). The second is a sterile, disposable, medical-grade 420 series stainless steel probe designed for corneal application, which is inserted into a reusable handpiece (Figure 2). The probe's dimensions are 450 μm in length and 90 μm in diameter. Proper depth of application is ensured by an insulated Teflon-coated governor 450 μm from the probe tip. This insulated cowl also prevents loss of current. The handpiece connects to the console with a cable, and the electric circuit is completed with a metal lid speculum, which returns via a cable to the console. The instrument is activated by the surgeon using a foot pedal.

In the CK procedure, RF energy is produced at a fundamental frequency of 350 kHz. The current is pulsed with a nominal pulse repetition rate of 7.8 kHz and pulse voltage time constant of 14 μsec. During each application, RF energy is delivered for 0.6 seconds at an energy level of 0.6 W. A cooling period of at least 0.4 seconds is required to stabilize the collagen dimensional changes.[68]

The Biophysics of Conductive Keratoplasty

The basic principle of CK is similar to many monopolar electrosurgical devices. The inherent electrical impedance of the corneal stroma results in heating of the tissue. Thus, unlike previous attempts at thermokeratoplasty, CK relies on indirect, rather than direct, heating of the corneal collagen. A temperature of approximately 65°C at the point of application is targeted.

During CK application, the tissue impedance increases as collagen denaturation occurs. This, in theory, autoregulates the amount, spatial distribution, and ultimate footprint of thermal energy, since current will flow to areas of less resistance.[68] If true in practice, this could result in a more homogeneous architecture of stromal collagen shrinkage.

FIGURE 1

Conductive keratoplasty console. Note handpiece and integrated metal lid speculum.

FIGURE 2

Conductive keratoplasty probe, 90 µm in diameter and 450 µm in length; note the insulated governor.

Histology of Conductive Keratoplasty

As part of preclinical trials of CK, six eyes scheduled for penetrating keratoplasty underwent CK 24 to 48 hours before surgery. Thereafter, histology was performed on the excised corneal buttons (FDA Protocol RCS-001-HYP). On light microscopy, the CK footprint was either V- or U-shaped and extended for approximately 80% of corneal depth (Figure 3). A bullous separation or total absence of epithelium at the site of application was noted. Remaining epithelial cells were abnormal, with necrotic, shrunken nuclei. Bowman's layer remained intact. There was edema between stromal lamellae, collagen disorganization, and a decreased number of keratocytes in the treated area. The surrounding stroma appeared normal. There were no inflammatory cells within the area of CK application, and Descemet's membrane remained unchanged.

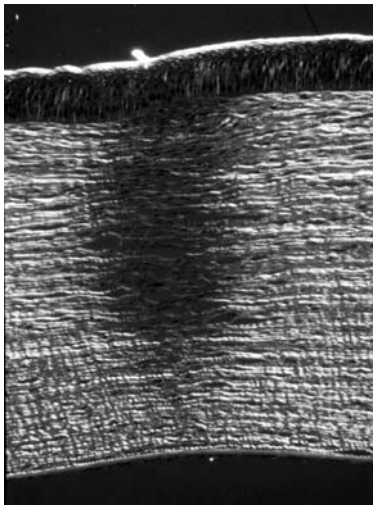

FIGURE 3

Histology using polarized light microscopy showing conductive keratoplasty lesion in pig cornea taken 1 week after surgery. Total corneal thickness is approximately 650 µm. Note relatively cylindrical architecture of collagen shrinkage profile. Width is approximately 250 µm and depth approximately 500 µm.

The Biomechanics of Conductive Keratoplasty

The basic theory of CK is similar to that of the other thermokeratoplasty procedures heretofore discussed. A 360° ring of CK application will contract collagen circumferentially in the midperiphery and result in decrease in chord length along all meridians with consequent central steepening (Figures 4A, 4B, and 4C). Circumferential corneal stromal contracture is seen by clinical biomicrosopy as striae between adjacent application spots (Figure 5).

As noted before, calculations suggest that there will be a meridional steepening of 1 D for each 23 μm of decreased chord length.[31] Placido disc imagery (Figure 6) and elevation corneal topography (Figure 7) show that this central steepening is associated with midperipheral flattening. The flattest areas are seen directly over the spot applications. This is analogous to the commonly recognized surgical observation of steepening distal to a tight corneal suture with focal flattening over the suture itself.[30] This biomechanical explanation of the topographic finding is supported by a finite element analysis model published by Moreira and coworkers.[53] Based on a theoretical 12% collagen shrinkage as a result of heat application to 75% corneal thickness, their analysis similarly predicts peripheral flattening concomitant with the central steepening effect.

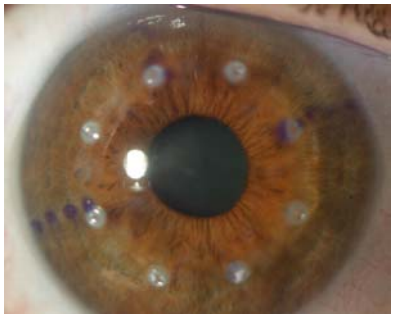

FIGURE 4A

Immediate postoperative eight-spot conductive keratopathy.

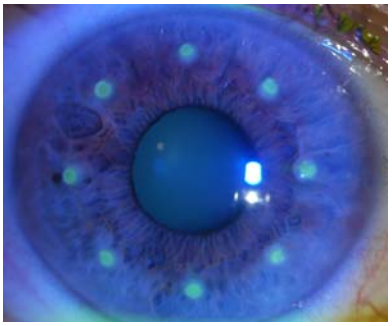

FIGURE 4B

Immediate post-operative conductive keratopathy (CK); note fluorescein stain over CK spots.

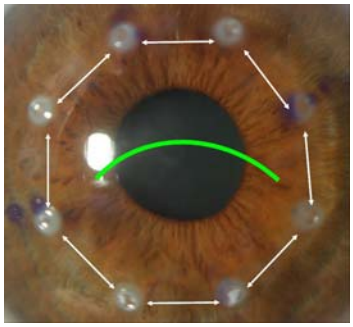

FIGURE 4C

Schematic depicting circumferential collagen contracture. The resulting "pursestring" effect causes central steepening.

FIGURE 5

Conductive keratoplasty spots immediately after application. Note striae of collagen contracture connecting spots.

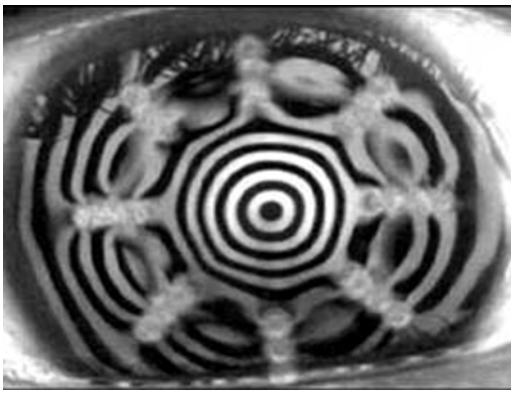

FIGURE 6

Placido disc image immediately after conductive keratoplasty shows central steeping and relative flattening directly over the thermokeratoplasty spots.

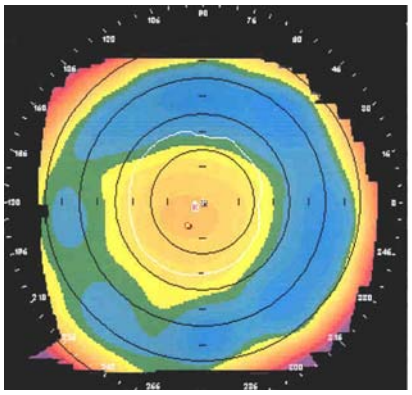

FIGURE 7

Elevation corneal topography after conductive keratoplasty (CK) shows a generally prolate optical contour with central steepening and relative flattening in the periphery. Note flatter areas (darker blue) directly over the eight meridians of CK application.

The Conductive Keratoplasty Nomogram

Earlier clinical trials have determined a general nomogram to define the expected corneal steepening after CK.[69] This nomogram was used in all studies presented herein.

The effect of CK is determined generally by three criteria: (1) number of spot applications, (2) number of rings of applications, and (3) diameter of application rings (Figure 8).

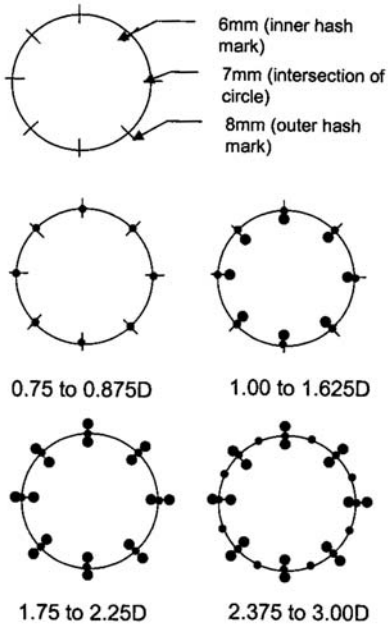

FIGURE 8

Conductive keratoplasty nomogram. Eight-spot annuli are placed at diameters of 6, 7, and 8 mm concentric with the entrance pupil: eight spots @ 7 mm = +0.75 to +0.875 D of correction; eight spots @ 6 mm and eight spots @ 7 mm = +1.00 to +1.625 D; eight spots @ 6 mm, eight spots @ 7 mm, and eight spots @ 8 mm = +1.75 to +2.25 D; adding eight more spots @ 7 mm = +2.375 to +3.00 D.

Rings of eight evenly spaced spots can be placed at 6 mm, 7 mm, and 8 mm. In addition, a second ring of eight spots can be placed at 7 mm. Thus treatments consist of eight, 16, 24, or 32 spots. Using a single ring of eight spots at a 7-mm diameter gives an expected correction of 0.75 to 0.875 D. Adding a second ring at a 6-mm diameter gives a correction of 1.0 to 1.625 D. Adding a third ring at 8 mm gives 1.75 to 2.25 D. Finally, adding eight spots at the 7-mm diameter gives an expected correction of 2.375 to 3.00 D.

Results of Phase III Clinical Trial

Conductive keratoplasty has been approved by the FDA for the correction of hyperopia of 0.75 to 3.00 D in eyes with preoperative astigmatism of less than 0.75 D. General clinical trial results have been published.[67,69,70] The most complete study with longest follow-up to date was performed by McDonald and colleagues.[67] This analyzed 1-year safety, efficacy, and stability of 355 eyes treated in the Phase III prospective, multicenter US clinical trial of CK for hyperopia.

In this study, mean age was 55.3 years (range, 40 to 74 years). The average cycloplegic refraction spherical equivalent was +1.86 D (range, +0.75 to +4.00 D), and the average manifest refraction spherical equivalent (MRSE) was +1.80 D (range, +0.38 to +3.75 D).

With regard to efficacy outcomes at 1 year, UCVA was ≤20/20 in 56%, ≤20/25 in 75%, and ≤20/40 in 92%. Sixty-three percent of eyes were ±0.50 D of attempted correction, and 89% were within ±1.0 D. Considering stability of the cycloplegic spherical equivalent refraction, there was an initial overcorrection followed by regression of effect on average. There was a mean change of +0.25 ± 0.50 D (confidence interval [CI], 0.19, 0.31) between months 3 and 6, +0.11 ± 0.41 D (CI, 0.07, 0.15) between months 6 and 9, and +0.11 ± 0.35 D (CI, 0.07, 0.15) between months 9 and 12. Thus, mild regression, on average, continued through 1 year.

With regard to safety outcomes at 1 year, seven eyes (2%) lost 2 logMAR Snellen lines of best spectacle-corrected visual acuity (BSCVA), but no eye lost more than 2 lines. Endothelial cell counts were unchanged by the procedure.

Table 1 summarizes the Phase III safety and efficacy data for the CK procedure. The reader is referred to the previously published study for details.[67]

TABLE 1. PHASE III CLINICAL TRIAL OF CONDUCTIVE KERATOPLASTY FOR HYPEROPIA CORRECTION: ONE-YEAR SAFETY AND EFFICACY DATA (n = 355)*

VARIABLE	PREOPERATIVE	1 YEAR
UCVA		
≤20/20	1% (5)	56% (178)
≤20/25	—	75% (240)
≤20/40	26% (96)	92% (294)
Predictability (achieved versus attempted MRSE)		
±0.50 D	—	63% (199)
±1.00 D	—	89% (282)
Stability (change MRSE)		
Months 3 to 6	—	0.25D ± 0.50 D (CI 0.19, 0.31)
Months 6 to 9	—	0.11D ± 0.41 D (CI 0.07, 0.15)
Months 9 to 12	—	0.11 D ± 0.35 D CI (0.07, 0.15)
Loss BSCVA		
2 Line loss	—	2% (7)
>2 Line loss	—	0% (0)

*Abstracted from McDonald et al[67] (n = 355).
BSCVA = best spectacle-corrected visual acuity; CI = confidence interval; MRSE = manifest refraction spherical equivalent; UCVA = uncorrected visual acuity at distance.

Thesis Design and Rationale

Although some of the data presented herein derives from the aforementioned Phase III patient cohort, the purpose of this thesis is not to reiterate the general results of CK, but to analyze the corneal optics of CK and clinical outcomes of the procedure as they relate to the management of presbyopia.

In this effort, four analyses were undertaken by the author. The data in these studies derived from two multicenter, prospective clinical trials of CK, the aforementioned one for the correction of hyperopia and another for the management of presbyopia, both sponsored by Refractec, Inc (Irvine, California). The first study was envisioned by the author to ascertain the presence of possible "multifocal" clinical effects after CK, following the design of a study, previously published, demonstrating such an outcome after PRK.[71] The study cohort consisted of patients enrolled in the clinical trial of CK for hyperopia and treated at one study site by the author. The second and third studies were then conceived and designed by the author in an attempt to define potential causes of this "functional multifocality" after CK by analyzing SIA and wavefront-derived higher-order aberrations of the cornea. Again, the study cohort consisted of patients enrolled in the multicenter clinical trial of CK for hyperopia; the astigmatism data was taken from patients treated at all of the study sites and the aberration data was obtained only from those patients treated at one study site by the author. Finally, given the clinical implications of the first three studies, an analysis of the multicenter study of CK for presbyopia was undertaken with particular regard to the possible interplay of post-CK optics with the study outcomes found. All patients entered in this clinical trial were treated at sites different from that of the author; data analysis then was performed independently by the author.

METHODS

CONDUCTIVE KERATOPLASTY

The standard CK surgical technique was used for all studies presented in this thesis and is the technique suggested for clinical use today.

The CK Surgical Procedure

Before each operating session, the CK instrument was calibrated per the manufacturer's recommended procedure. After the patient was supine on the operating table, the operative field was prepared in a sterile fashion with povidone iodine. A patch was taped over the nontreated eye to facilitate coaxial fixation by the patient. Tetracaine drops were instilled three times to achieve topical anesthesia. A lid speculum was placed.

All procedures were centered over the entrance pupil as suggested by Uozato and Guyton.[72] The patient was asked to look at a coaxial fixation target, and a CK marking instrument (Katena Products, Denville, New Jersey) coated with gentian violet or methylene blue was placed centered on the pupil. This instrument has a 7.0-mm central ring and eight radial posts extending to the 6.0-mm and 8.0-mm optical zones to guide spot placement. Cellulose sponges were used to remove any residual fluid from the surface.

The CK procedure is shown in Figure 9. Starting with the innermost ring of the planned procedure, CK spots were applied using the gentian violet template as a guide. Treatment proceeded from the innermost 6-mm ring to the outermost 8-mm ring. In a 32-spot treatment, the final eight spots were placed at 7 mm after the first three rings were completed. For each ring, spots were applied consecutively 90° from one another.

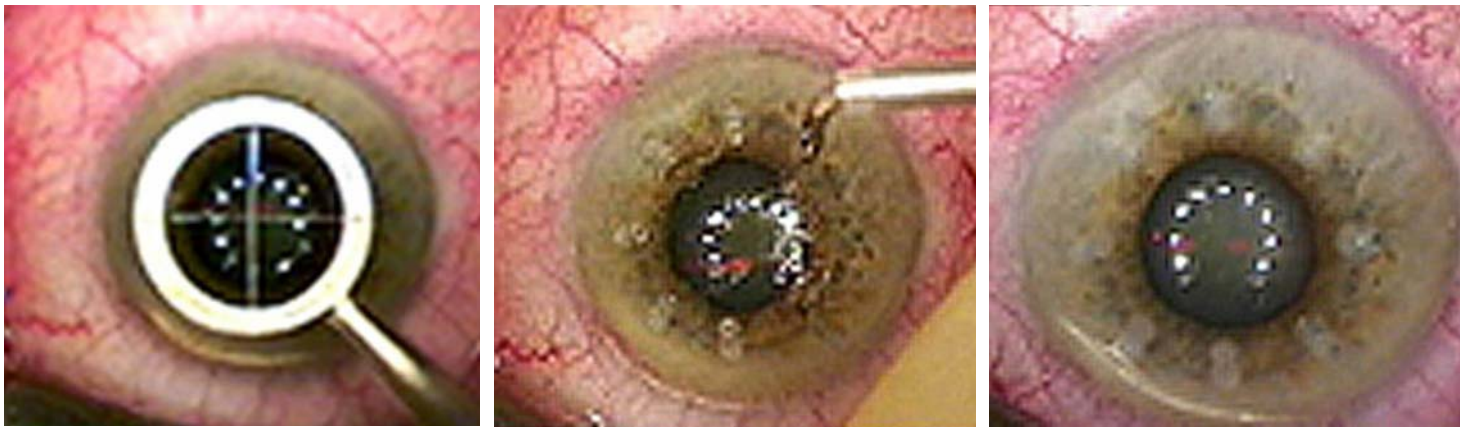

FIGURE 9

The conductive keratoplasty (CK) procedure. Left, Marker with gentian violet placed over the line of sight. Center, CK probe applied, taking care to enter cornea perpendicularly. Right, Completed two-ring, 16-spot CK procedure.

Care was taken to assure that the probe was placed perpendicular to the cornea. Enough force was applied to the tip to assure maximum penetration depth up to the stop. After each ring was applied, the probe tip was inspected under the microscope and any

epithelial debris carefully cleaned with a cellulose sponge.

All eyes received treatment as determined by the nomogram described earlier.

Postoperative Management

At the end of the procedure, nonpreserved lubricating drops and diclofenac sodium 0.1% (Ciba Vision Ophthalmics, Duluth, Georgia) were applied and the lid speculum was removed. No postoperative medications except for nonpreserved lubricants were used.

STUDY 1. PUTATIVE MULTIFOCAL CORNEAL EFFECTS AFTER CONDUCTIVE KERATOPLASTY

Study Background

In previous studies of radial keratotomy and laser refractive surgery, uncorrected visual acuity (UCVA) was better than expected compared with postoperative refractions.[71,73] This outcome has been attributed to a putative multifocal corneal contour resulting from surgery.[71,74] In this study, similarly, the association between uncorrected distance and near visual acuity with postoperative refractive error in CK subjects is explored. In particular, distance and near UCVA after CK is compared with the UCVA of untreated control eyes of similar hyperopic and myopic refractive error. Hypothetically, as suggested in the previous published studies,[71,73,74] a finding that UCVA is better than would be expected given a postoperative refractive error may suggest the possibility of induced corneal mulifocality with a consequent enhanced depth of field. If indeed true, clinically this may militate toward an improvement in near vision after CK, both for hyperopia correction and for monovision (Figure 10).

This study was done as part of a Phase III multicenter clinical trial of the Refractec ViewPoint CK System (Refractec, Inc, Irvine, California) for the treatment of hyperopia conducted in accordance with FDA regulations.75 Approvals from appropriate institutional review boards were obtained, and all patients gave informed consent. The data analyzed in this substudy are from 72 eyes of 37 patients all treated at a single center and operated on by a single surgeon. Data were taken at the 6-month follow-up examination.

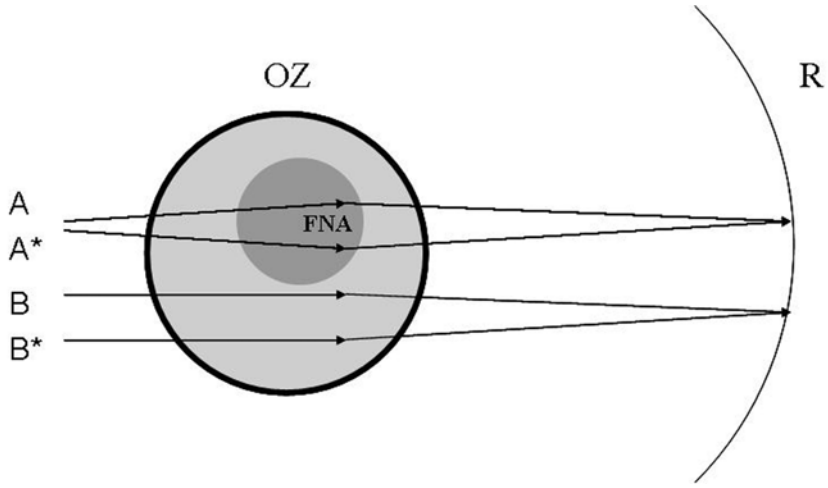

FIGURE 10

Schematic depicting multifocal effect of cornea after conductive keratoplasty. Nearpoint rays A and A* pass through a "focal nearpoint area" (FNA) on the optical zone (OZ) and are focused on the retina (R), composing near "signal." Distance rays B and B* pass through a flatter area of the optical zone giving concurrent distance focus.

Patient Entry Criteria

All patients conformed to standardized patient entry criteria under an FDA investigational device exemption granted to Refractec, Inc. Entry criteria included spherical hyperopia of +1.0 to +3.0 D and ≤0.75 D of refractive astigmatism as expressed in minus cylinder form as measured by cycloplegic refraction. The cycloplegic spherical equivalent needed to be ≥ +0.75 D. In order to exclude patients with latent hyperopia, the manifest and cycloplegic refraction spherical equivalent could not differ by more than 0.5 D.

Before preoperative evaluation, patients were required to discontinue rigid contact lens wear for at least 3 weeks and soft contact lens wear for at least 2 weeks. All patients were 21 years of age or older and needed to have BSCVA of 20/40 or better. Exclusion criteria included a history of strabismus or strabismus surgery, cataracts, uncontrollable blepharitis, corneal erosions, corneal epithelial basement membrane dystrophy, irregular astigmatism, any previous corneal or intraocular surgery, and a history of herpes simplex or herpes zoster keratitis. Additional exclusion criteria included a history of steroid-responsive rise in intraocular pressure, glaucoma, preoperative intraocular pressure greater than 21 mm Hg, or the presence of narrow anterior chamber angles; diabetes or autoimmune diseases; the use of corticosteroids, immunosuppressive agents, or any ophthalmic medication other than artificial tears; a history of

keloid formation; and pregnancy. Patients were required to have a peripheral corneal thickness of ≥560 µm.

No retreatments were performed in this study.

Data Acquisition and Analysis

Distance (6.0 m) UCVA was measured under controlled lighting conditions using a back-illuminated ETDRS chart (Lighthouse for the Blind, New York, New York). Near visual acuity was obtained using a Rosenbaum pocket vision screener held at 14 inches in standard lighting conditions. All visual acuity measurements were converted to the logarithm of the minimum angle of resolution (logMAR) scale, and mean visual acuities were derived by the method of Holladay and Prager using logMAR acuities.[76]

Each subject's refraction was determined using a fogging technique "pushing plus (+)" to achieve the refraction with the most (+) power consistent with the subject's best visual acuity. Cycloplegic refractions were performed at least 30 minutes after instillation of 1 or 2 drops of cyclopentolate hydrochloride 1% (Cyclogyl; Alcon Laboratories, Fort Worth, Texas). The manifest and cycloplegic refractions were recorded preoperatively and then approximately 6 months postoperatively.

Preoperative visual acuity and refraction served as controls. Thus, the expected, unaided visual acuity at a given refractive error in the hyperopic presbyopic population was known. To determine control values for myopic refractions, eight subjects outside of the study were analyzed with artificially induced myopia.[71] To achieve a fixed degree of artificial myopia, the subject's left eye was covered and (+) lenses were placed in front of the right eye until fogging was achieved. The highest (+) lens retaining 20/20 visual acuity was assigned as the emmetropic starting point. Increasing (+) lenses were placed in increments of 0.50 D, and visual acuity was measured for each point. The average visual acuity of the eight subjects at each "myopic" refractive point was calculated using logMAR acuities. Similar examination and lighting conditions were used for this myopic group as with the CK eyes.

Postoperative UCVA of the CK treated eyes was then compared to the expected UCVA of controls with similar refractive error.

STUDY 2. SURGICALLY INDUCED ASTIGMATISM AFTER CONDUCTIVE KERATOPLASTY

Study Background

In an effort to further define the change in corneal contour after CK, an analysis of SIA was performed. The data in this substudy, consisting of results from 203 eyes derived from six study centers, were from the 1-year follow-up visit.

Patient Entry Criteria

Patient entry criteria were as described in study 1. Subjects were required preoperatively to have ≤0.75 D of refractive astigmatism. No retreatments were performed in this study.

Data Acquisition and Analysis

Data were entered at each investigational site onto standardized data collection forms by either the investigator or trained technicians. Statistical analysis was performed using Excel (Microsoft, Inc, Seattle, Washington) and the Statistical Analysis System 6.07 (SAS Institute, Inc, Cary, North Carolina).

Astigmatism Calculations. The absolute change in astigmatism was calculated by taking the difference between the magnitude of astigmatism preoperatively and postoperatively without regard to axis. To more rigorously assess SIA, vectoral analysis was performed.[77] The following formula was used to calculate the vectoral change in astigmatism[78]:

$$\text{Magnitude} = \sqrt{(x^2 + y^2)}$$

$$\text{Axis} = \begin{cases} 1/2\text{Tan}^{-1}(y/x), \text{ if } x>0 \\ 1/2(\text{Tan}^{-1}(y/x) + 180), \text{ if } x<0 \end{cases}$$

Where $x = D_2\text{Cos}2A_2 - D_1\text{Cos}2A_1$

$y = D_2\text{Sin}2A_2 - D_1\text{Sin}2A_1$

D_1 = preoperative plus cylinder in D at axis A1

D_2 = postoperative plus cylinder in D at axis A2

For a graphic representation of these results (Figure 11), data points were converted to Cartesian coordinates and the axis of cylinder values were doubled to give a doubled angle plot as described by Holladay and coworkers.[79] Thus, when plotted on an x-y graph, steepening toward 90° (induced with-the-rule) is represented by points on the negative x-axis and steepening toward 180° (induced against-the-rule) is represented by points on the positive x-axis.

The average induced vectoral astigmatism was calculated by taking the mean of the x values and y values, respectively, and calculating the induced astigmatism using the equation above. This yields the centroid of the individual data and is best to describe the average vectoral *axis* of SIA.[79] To best analyze the vectoral *magnitude* of SIA, the average of the absolute values of the x and y

coordinates, respectively, first were taken, and then the magnitude was determined using the equation for the calculation of induced astigmatism given above. Conversion to absolute values is necessary, since the coordinates are signed positive or negative functions that would tend to cancel each other if simply averaged, thus understating the actual mean magnitude of SIA.

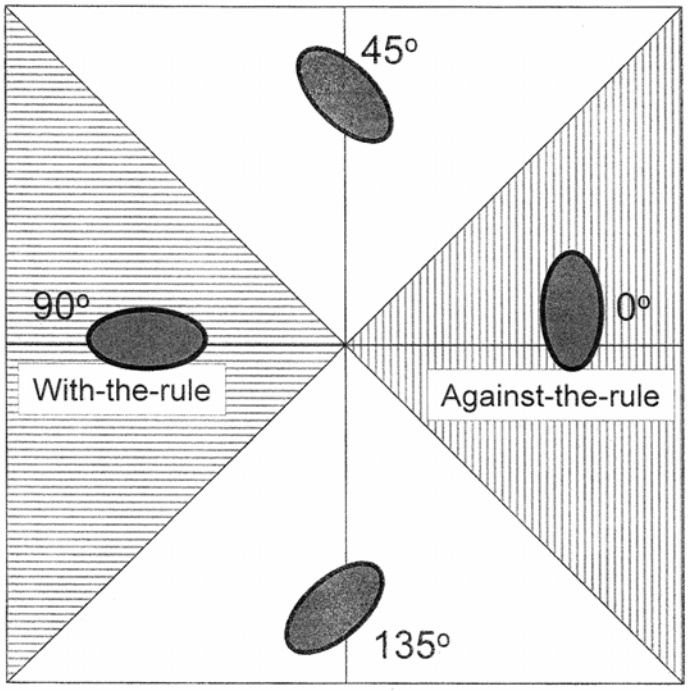

FIGURE 11

Schematic explaining astigmatism charting methodology. The axis of induced plus cylinder is plotted. By convention in this study, points from 0 to 22.5° and 157.5° to 180° (vertical cross-hatch) were considered induced against-the-rule astigmatism and points from 67.5° to 112.5° (horizontal cross-hatch) denoted induced with-the-rule astigmatism. Other points are considered astigmatism induced at an oblique axis—points above the horizontal meridian tend toward steepening at 45°, and points below the horizontal tend toward steepening at 135°.

Analysis of Axis of SIA. The following methodology was used to compare the axis of SIA. The axis of induced astigmatism (presented as induced plus cylinder between 0 and 180°) was divided into four subsets: 0° to 22.5° and 157.5° to 180° (induced against-the-rule astigmatism), 67.5° to 112.5° (induced with-the-rule astigmatism), 22.5° to 67.5°, and 112.5° to 157.5° (astigmatism induced in an oblique direction). Using these stratifications, comparison of vectoral direction of SIA between preoperative and postoperative values was determined by a chi-square test.

Procedure Decentration Analysis and Other Associations of SIA. Vector-analyzed SIA was also analyzed with respect to eye treated (right or left), number of CK spots applied, and CK procedure decentration. To determine procedure decentration, the method of Schwartz-Goldstein and associates[80] was used. In short, topography data acquisition was accomplished by a trained technician with the Orbscan (Bausch & Lomb, Rochester, New York). Two types of maps, either the normalized differential power map (32 eyes) or the postoperative anterior elevation map (32 eyes), were used, depending on which afforded the best visualization of the optical zone. The normalized scale differential topography power map was derived from subtracting preoperative from postoperative corneal topography maps. To analyze centration, it was assumed that the largest width of ablation in the horizontal and vertical directions represented the corresponding borders of the ablation zone. A transparent grid with a Cartesian coordinate system was placed over the generally circular orange optical zone on the topography elevation map. The grid was manipulated until its center was located at the midpoint of the horizontal diameter of the optical zone. The computer cursor was aligned with this point. While maintaining the horizontal position of the grid, this process was repeated for the vertical meridian. The computer cursor was again positioned beneath the center of the grid, now situated at the center of the optical zone. The legend on the topography map then indicated the distance (r) to the nearest 0.01 mm and the angle (θ, in meridian degrees) of the optical zone center from the corneal vertex. Measurements were recorded consistently such that negative values represented the temporal direction and positive values represented the nasal direction in right eyes. Conversely, negative values

represented the nasal direction and positive values represented the temporal direction in left eyes. Using these coordinates, the distance of the optical zone center both from the pupil center and the corneal vertex was calculated to the nearest 0.01 mm. For this study, the corneal vertex was defined as the center of the reflected rings of the topography unit; the pupil center was determined by the pupil-finding software of the topography system.

To evaluate whether decentration from the corneal vertex was different from decentration from the pupil center, a paired Student's *t* test was performed. In addition, decentration from the pupil center was tested for randomness by first converting the length and angle of decentration from polar coordinates (r, θ) to Cartesian coordinates (X, Y) in millimeter units. The X and Y coordinates of decentration, respectively, then were tested for randomness by comparing the sum of the X's and Y's to zero using Wilcoxon signed-rank tests. This analysis was performed for right and left eyes both separately and combined. Sixty-four eyes from a single study site had available data and were entered in this decentration substudy.

Clinical Sequelae of SIA. To analyze the implications of induced cylinder with regard to clinical outcomes, a comparison of eyes with ≥1.0 D to those with <1.0 D of absolute induced astigmatism was undertaken. Outcomes of refractive sphere, refractive cylinder, UCVA, BSCVA, change in BSCVA, and subjective glare, halo, and patient satisfaction were investigated. The latter three were obtained from self-administered patient questionnaires, with possible rankings of 0 to 4 (low to high magnitude) for glare and halo and 1 to 5 for satisfaction. Mean visual acuity again was calculated using logMAR values. Significant associations were determined by Student's *t* test.

STUDY 3. HIGHER-ORDER OPTICAL ABERRATIONS AFTER CONDUCTIVE KERATOPLASTY AND HYPEROPIC LASIK

Study Background

The success of refractive surgical procedures traditionally has been measured by Snellen visual acuity and achieved postoperative refractive correction. These are the outcomes assessed in past studies of CK and in studies 1 and 2 of this thesis. However, evaluations of the corneal shape before and after refractive surgical procedures have shown, in general, that higher-order optical aberrations are typically introduced despite elimination of spherocylindrical refractive errors (defocus and astigmatism).[81-89] These surgically induced aberrations may impact the optical quality of the cornea and have been correlated with postoperative visual performance.[90-96]

Higher-order aberrations can be quantified using the Zernike polynomial. Just as any curve in geometry can be approximated by a polynomial function, the Zernike polynomial is a mathematical transformation that describes an optical component's wavefront curve (for example, that of the cornea) as a series of orthogonal elementary aberration functions over a unit circle or circular pupil.[97,98] The terms in the polynomial expansion are numbered Z_n , where *n* is the radial order, and Z^f, where *f* is the meridional frequency; ie, Z_n corresponds to a given order of the polynomial component of the wavefront function, and Z^f is an angular component within a specific order. Astigmatism and defocus are second-order Zernike terms, whereas spherical aberration and coma are higher-order Zernike terms. In normal human eyes, higher radial orders account for less magnitude in the description of the wavefront. Spherical aberration is described by fourth- and sixth-order Zernike terms, and coma is described by third- and fifth-order terms. Specifically, the fourth radial order term Z^{12} is the spherical aberration term of greatest clinical impact, and the third radial order terms Z^7 and Z^8, respectively, are vertical and horizontal coma terms of greatest clinical impact.

With regard to optical aberrations, most clinical investigation, to date, has been on patients undergoing surgical treatments for myopia. For hyperopic procedures, there have been few studies looking at changes in wavefront aberrations related to surgery and the influence these changes may have on the optical quality of the cornea.[86] To our knowledge, no studies have addressed these changes in CK-treated eyes, nor have there been comparisons of such outcomes between CK and LASIK.

Therefore, in an effort to further investigate corneal optics and to identify and quantitate putative corneal multifocality after CK, higher-order corneal wavefront aberrations (third- to sixth-order) were evaluated before and after surgery. In addition, to distinguish potentially important clinical differences between the postsurgical wavefront profile of CK and that of hyperopic LASIK, a similar population of LASIK eyes was studied and the two procedures were compared with regard to overall, spherical, and coma-like aberrations.

As in studies 1 and 2, the CK portion of this study was done as part of a Phase III multicenter clinical trial of the Refractec Viewpoint Conductive Keratoplasty System for the treatment of hyperopia. The data analyzed in this substudy of CK are from 36 eyes of 20 patients all treated at a single center and operated on by a single surgeon. The LASIK portion of the study was done retrospectively, analyzing 38 eyes of 24 patients from a patient cohort described below.

Patient Entry Criteria

For CK eyes, patient entry criteria were the same as for study 2 described above. LASIK data was taken retrospectively from a database of a similar population of patients who were more than 40 years old with hyperopia of +0.75 to 3.25 D (spherical equivalent) and ≤0.75 D of regular astigmatism. Comparison of baseline characteristics of the CK and LASIK groups is shown in Table 2. As for CK, all LASIK patients had been treated at the same center by the same surgeon.

TABLE 2. CORNEAL WAVEFRONT HIGHER-ORDER ABERRATIONS AFTER CONDUCTIVE KERATOPLASTY (CK) AND HYPEROPIC LASIK: BASELINE CHARACTERISTICS OF STUDY POPULATIONS

CHARACTERISTIC	CK	LASIK
No. of patients	20	24
No. of eyes (right, left)	36 (18, 18)	38 (17, 21)
Males	4	14
Females	16	10
Mean age (SD) (years)	56.8 (4.7)	59.4 (6.7)
Age range (years)	49 to 65	40 to 73
Mean preoperative MRSE (SD) (D)	1.98 (0.619)	1.90 (0.522)
MRSE range (D)	0.75 to 3.00	1.00 to 3.00
Mean preoperative CRSE (SD) (D)	1.89 (0.522)	1.95 (0.622)

CRSE = cycloplegic refraction spherical equivalent; D = diopters; MRSE = manifest refraction spherical equivalent; SD = standard deviation.

Surgical Procedures

The CK procedure was done as described previously.

LASIK was performed using the LADARVision excimer laser platform (Alcon Laboratories, Inc, Fort Worth, Texas). A lamellar flap with a nasally placed hinge was prepared with the SKBM microkeratome (Alcon Laboratories, Inc, Fort Worth, Texas) with a nominal flap diameter of 9.5 mm and nominal flap thickness of 160 µm. The flap was then positioned to the side and laser ablation was performed. A 6.0-mm optical zone with a 1.5-mm blend zone was used in all cases. All procedures were centered over the entrance pupil as for CK. The centration procedure and its accuracy in general are published elsewhere.[80] At the end of the procedure, a LASIK cannula/spatula combined instrument with filtered balanced salt solution was used to reposition the corneal flap. Approximately 2 minutes were allowed to ensure proper adherence of the flap.

Postoperatively, antibiotic (ofloxacin, ciprofloxacin, or levofloxacin) and corticosteroid drops (prednisolone acetate 1%) were administered four times daily for 1 week and then discontinued. Nonpreserved lubricants were used as needed.

Data Acquisition and Analysis

Videokeratography using the Orbscan II (Baush & Lomb Surgical, Salt Lake City, Utah) was measured before and after surgery for all eyes. On average, videokeratography was performed 92.7 (SD, 25.0) days postoperatively. Topography maps were analyzed using the CTView 4.0 software (Sarver & Associates Inc, Merritt Island, Florida), and the cornea wavefront aberration was described as a Zernike polynomial expansion up to the sixth order. A 4-mm pupil was used for analysis for analogy to the physiologic pupil in this older, hyperopic population.

The root mean square (RMS) was used to assess the magnitude of wavefront error. Wavefront error differences before and after surgery were evaluated. Due to the nonsymmetric pattern of aberrations, right and left eyes also were analyzed independently for each procedure (17 right and 21 left for LASIK; 18 right and 18 left for CK).[87] In addition to composite third- to sixth-order aberrations, spherical aberration and coma specifically were assessed for all eyes. For ease of discussion, the convention used by Oshika and coworkers[85] was adopted; spherical aberrations (fourth and sixth orders) were combined and considered together as spherical-like aberrations while comas (third and fifth orders) were similarly considered as composite coma-like aberrations. In addition, spherical aberration (Z^{12}) was evaluated alone, which, on account of its symmetric nature, was not separately analyzed for left and right eyes within each treatment cohort. Independent analyses of vertical (Z^{7}) and horizontal (Z^{8}) coma components were also performed.

Statistical significance was determined using a Student's *t* test, paired for analysis between preoperative and postoperative data and matched for intergroup assessment of CK compared with LASIK-treated eyes. A P value $\leq .05$ was considered significant.

STUDY 4. MULTICENTER STUDY OF PRESBYOPIA CORRECTION USING CONDUCTIVE KERATOPLASTY

Study Background

In an attempt to analyze the clinical safety and effectiveness of CK for the treatment of presbyopia by the method of monovision correction, this prospective, multicenter trial studied 150 consecutive subjects. The treatment plan was designed to achieve a refractive target of –1.0 to –2.0 D in the nondominant eye. Emmetropic patients underwent CK in the nondominant eye only, whereas hyperopic patients underwent bilateral CK consisting of a hyperopic correction of up to 2.0 D in the dominant eye (with a target of plano) and a monovision correction of up to 3.0 D in the nondominant eye (with a target of –1.0 to –2.0 D). This study was done as

part of a Phase III multicenter clinical trial of the Refractec Viewpoint Conductive Keratoplasty system (Refractec, Inc, Irvine, California) for the treatment of presbyopia. Approvals from appropriate institutional review boards were obtained, and all patients gave informed consent. In this thesis, results are presented of a consistent cohort of the 150 patients enrolled in the trial for whom data was available at all applicable time points through the 12-month follow-up visit.

Patient Entry Criteria

All patients conformed to standardized patient entry criteria under an FDA investigational device exemption granted to Refractec, Inc. Entry criteria included a cycloplegic spherical equivalent manifest refraction of –0.50 to +2.0 D and ≤0.75 D of refractive astigmatism as expressed in minus cylinder form. Patients needed correctable distance visual acuity to at least 20/40 in both eyes, and near visual acuity correctable to at least J3 in the nondominant eye. Before preoperative evaluation, patients were required to discontinue rigid contact lens wear for at least 3 weeks and soft contact lens wear for at least 2 weeks. All patients were 40 years of age or older and needed to require a presbyopic add of +1.00 to +2.00 D. All patients required a documented history of successful monovision with contact lenses or the satisfactory completion of a contact lens trial of monovision. Exclusion criteria were similar to those described in study 1 previously described.

Ocular dominance was determined by sighting tests. The power of the monovision contact lens (either previously utilized or resulting from the monovision trial) was the targeted power for the correction of the nondominant eye. This power was determined at the discretion of the surgeon using one or a combination of the following: Plus lenses were added while the patient looked at a reduced Snellen target held at 40 cm until the patient achieved the greatest clarity of the 20/20 letters; a plus power equal to one-half the patient's accommodative amplitude was used; or results of binocular cross-cylinder testing at 14 inches were used.

Conductive Keratoplasty Procedure

The CK procedure was as described above. All eyes received treatment as determined by the standard nomogram. In addition to the nomogram spots, at the surgeon's discretion and genererally based on intraoperative keratometry, an additional spot could be placed in the flat axis.

In this study, retreatments were allowed for qualified eyes that were undercorrected following the initial procedure. For the nondominant emmetropic eye, this was defined as a residual spherical equivalent of ≥0.75 D from the attempted monovision correction and uncorrected near visual acuity worse than J3**.** For the dominant hyperopic eye, this was defined as a residual spherical equivalent of ≥0.75 D from the attempted hyperopic correction and uncorrected distance visual acuity worse than 20/25**.** Retreatment procedures in both cases were not performed sooner than 3 months after the primary procedure. Retreatments also required a stable refraction, defined as MRSE within 0.50 D on two consecutive visits at least 3 months apart.

Retreatments were performed using the standard CK treatment nomogram for additional spherical correction, up to a total of 32 spots. Eyes originally receiving 32 spots were not eligible for retreatment.

Postoperative Management

At the end of the procedure, nonpreserved lubricating drops and diclofenac sodium 0.1% (Ciba Vision Ophthalmics, Duluth, Georgia) were applied and the lid speculum was removed. No postoperative medications except for nonpreserved lubricants were used.

Data Acquisition and Analysis

Examinations and Testing. Per the investigational protocol, patients were examined preoperatively, and postoperatively at 1 day, 1 week, and 1, 3, 6, 9, 12, and 24 months. For the purpose of this thesis, data were analyzed at the 3- and 12-month postoperative visits. For those patients who underwent retreatment, the 3- and 12-month data were taken with regard to the retreatment date.

For hyperopic eyes treated for distance correction, monocular and binocular distance visual acuity, uncorrected and best spectacle-corrected, was measured under controlled lighting conditions using a back-illuminated ETDRS chart (Lighthouse for the Blind, New York, New York). For hyperopic and emmetropic eyes treated for near correction, monocular and binocular near visual acuity, uncorrected and best spectacle-corrected, was measured using the Rosenbaum pocket vision screener at 14 inches. Best-corrected visual acuity was determined with the patient's manifest refraction at distance. For near best-corrected acuity, a nearpoint add was placed over the patient's manifest refraction.

Cycloplegic refractions were performed at least 30 minutes after instillation of one or two drops of cyclopentolate hydrochloride 1% (Cyclogyl; Alcon Laboratories, Fort Worth, Texas) or tropicamide 1% (for postoperative visits only) with two applications 5 minutes apart.

Subjective Patient Questionnaires. Self-administered subjective questionnaires were used to investigate patient's perceptions of (1) overall satisfaction with the CK presbyopia procedure, (2) quality of overall vision, and (3) quality of depth perception. For the overall satisfaction and quality of vision variables, data were available only at the 12-month postoperative visit.

Satisfaction was ranked on a scale of 1 to 5 (1 = very dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, 5 = very satisfied). In addition to descriptive statistics, preoperative and postoperative characteristics were analyzed for associations with patient subjective satisfaction. To do this, patients were pooled into those who were dissatisfied or neutral (scores of 1, 2, or 3) and those who were satisfied (scores of 4 or 5). Preoperative characteristics included gender, age, and binocular (hyperopia correction one eye, monovision correction one eye) versus monocular (monovision correction only) treatment plan. Postoperative characteristics included monocular and binocular near UCVA, monocular and binocular distance UCVA, subjective grading of quality of postoperative depth perception, and preoperative to postoperative change in subjective depth perception. With regard to near UCVA, patients were stratified to those with J3 or better and those with worse than J3 acuity. For distance UCVA, patients were stratified to those with

20/40 or better and those with worse than 20/40. Grading of depth perception was on a scale of 1 to 5 as described below, and patients with grades 1 to 3 were pooled and compared to those with grades 4 to 5. For the change in depth perception analysis, all patients with decreased depth perception were pooled and compared to those who remained the same or improved. Statistical associations were tested with chi-square tests.

Quality of vision was ranked on a scale of 0 to 4 (0 = no improvement, 1 = slight improvement, 2 = moderate improvement, 3 = marked improvement, 4 = extreme improvement). As described above for the satisfaction outcome, patients were pooled into those with scores of 0 to 2 and those with scores of 3 to 4 for analysis of potential associations with postoperative outcomes. For the depth perception variable, patients ranked the subjective quality of their depth perception both preoperatively and postoperatively on a scale of 1 to 5 (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

In any monovision type of surgical goal, a predominant concern is loss of distance vision. Therefore, patients also were asked to compare their (1) distance, (2) intermediate, and (3) near vision before and after CK. These were ranked on a scale of 1 to 5 (1 = significantly worse, 2 = worse, 3 = same, 4 = better, 5 = significantly better). Similarly, to ascertain the functional impact of the CK procedure, patients were asked if they could perform common visual tasks without glasses before and after surgery. These included seeing (1) street signs, (2) books on a shelf, (3) computer screens, (4) menus, (5) knitting, sewing, and performing crafts, (6) newspaper print, and (7) fine print. Patients were asked to answer yes or no to each.

Data were entered at each investigational site onto standardized data collection forms by either the investigator or trained technicians. Statistical analysis was performed using Excel (Microsoft, Inc, Seattle, Washington) and the Statistical Analysis System 6.07 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

STUDY 1. MULTIFOCAL CORNEAL EFFECTS AFTER CONDUCTIVE KERATOPLASTY

Preoperative Characteristics

Of the 37 patients studied, 14 were male and 23 were female. Although entry criteria per the protocol included patients 21 years of age or older, the mean age of patients treated in the study was 58 years (range, 50 to 68 years). The mean preoperative MRSE was +1.82 D (range, +0.75 to +3.25 D) and mean preoperative cycloplegic refraction spherical equivalent was +1.81 D (range, +0.50 to +3.50 D). The average preoperative manifest refractive astigmatism was 0.20 D (range, plano to 0.75 D).

Postoperative Characteristics

Mean postoperative refraction characteristics are summarized in Table 3. The mean 6-month postoperative MRSE in 72 CK eyes was –0.32 D. Postoperative eyes had, on average, 0.72 D of refractive astigmatism (ranging up to 2.25 D), whereas control eyes had mean preexisting astigmatism of 0.19 D. (See study 2 for an in-depth astigmatism analysis.)

TABLE 3. MULTIFOCALITY STUDY: POSTOPERATIVE REFRACTION CHARACTERISTICS AFTER CONDUCTIVE KERATOPLASTY FOR HYPEROPIA (n = 72)

	VALUE (D)		
CHARACTERISTIC	**RANGE**	**MEAN**	**SD**
Manifest refraction spherical equivalent	–2.25 to +1.50	–0.32	0.62
Cycloplegic refraction spherical equivalent	–2.00 to +2.00	–0.25	0.70
Manifest cylinder	Plano to 2.25	0.72	0.58

D = diopters; SD = standard deviation.

Distance Visual Acuity

The postoperative mean distance UCVA was 20/31 in the 72 CK eyes studied.

Figure 12 shows individual postoperative eyes as compared with control eyes of similar refractive error. As seen, for most CK eyes, postoperative UCVA compared with control eyes was better for equivalent MRSE. Of the 72 eyes treated, 45 eyes (63 %) fell below the trend lines, indicating that these eyes had a better UCVA than the control eyes with equivalent refraction. Six of eleven eyes (55%) with refractions of 1.00 D or more in magnitude had an uncorrected Snellen visual acuity of 20/40 or better. Similarly, when using the patients' cycloplegic refractions, postoperative eyes, in general, had better UCVA compared with controls. Of the treated eyes, 53 (74%) eyes had better vision than the residual cycloplegic refractive errors would predict (Figure 13). All eyes with residual hyperopia had better than predicted distance UCVA.

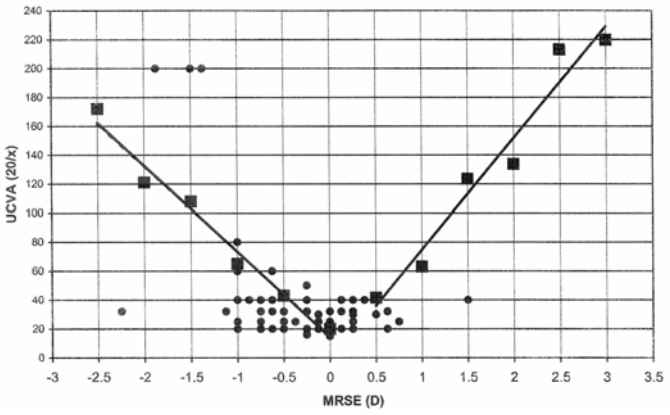

FIGURE 12

Multifocality study. Distance uncorrected visual acuity (UCVA) versus manifest refraction spherical equivalent (MRSE) of eyes after conductive keratopathy (CK) and untreated control eyes. Black squares indicate the mean UCVA of control eyes at the indicated level of refractive error. Black circles indicate postoperative CK subject data points. The black lines represent the best fit of the mean visual acuity points in control eyes.

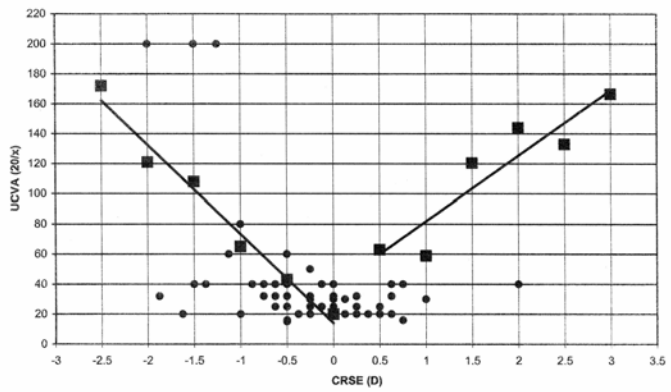

FIGURE 13

Multifocality study. Distance uncorrected visual acuity (UCVA) versus cycloplegic refraction spherical equivalent (CRSE) of eyes after conductive keratopathy (CK) and untreated control eyes. Black squares indicate the mean UCVA of control eyes at the indicated level of refractive error. Black circles indicate postoperative CK subject data points. The black lines represent the best fit of the mean visual acuity points in control eyes.

Near Visual Acuity

The mean near UCVA in the 72 CK eyes studied was 20/47, compared with a preoperative mean near UCVA of 20/253.

Figure 14 shows near UCVA of postoperative eyes as compared with control eyes of similar refractive error. As in the case of distance visual acuity, near UCVA compared with control eyes, generally, was better for an equivalent refractive error. Of the 72 eyes treated, 28 eyes had residual hyperopic refractive errors. Within this group, 23 (82%) had a better-than-predicted visual outcome for the residual refractive error. Similarly, using the patients' cycloplegic refractions, postoperative eyes, in general, had better near visual acuity compared with controls (Figure 15). Of the 32 eyes with residual hyperopia, 26 (81%) eyes had better vision than the residual cycloplegic refractive errors would predict.

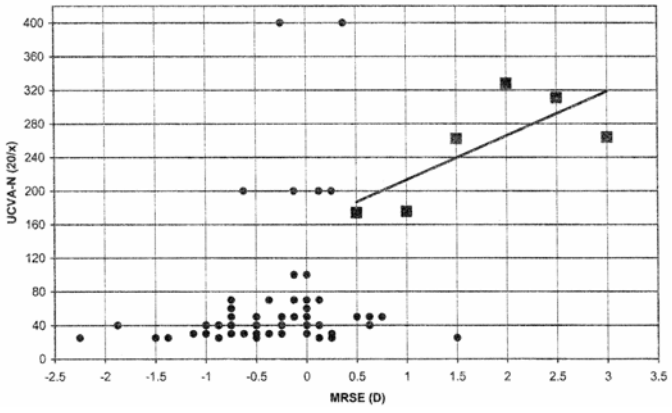

FIGURE 14

Multifocality study. Near uncorrected visual acuity (UCVA-N) versus manifest refraction spherical equivalent (MRSE) of eyes after conductive keratopathy (CK) and untreated control eyes. Black squares indicate the mean UCVA of control eyes at the indicated level of refractive error. Black circles indicate postoperative CK subject data points. The black line represents the best fit of the mean visual acuity points in control eyes.

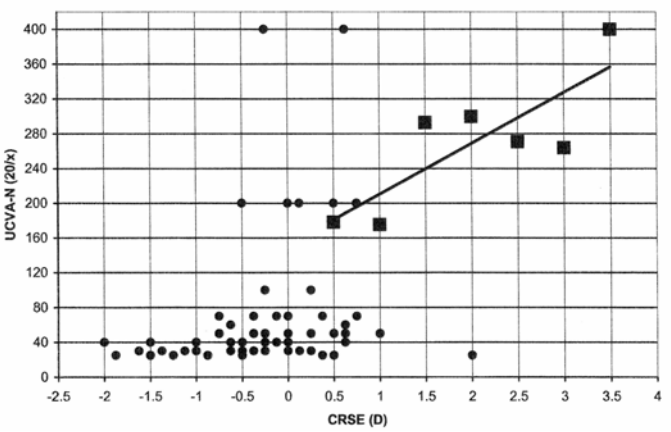

FIGURE 15

Multifocality study. Near uncorrected visual acuity (UCVA-N) versus cycloplegic refraction spherical equivalent (CRSE) of eyes after conductive keratopathy (CK) and untreated control eyes. Black squares indicate the mean UCVA of control eyes at the indicated level of refractive error. Black circles indicate postoperative CK subject data points. The black line represents the best fit of the mean visual acuity points in control eyes.

Eyes with residual myopic corrections generally had good near vision, but were not compared to control groups because improved near vision would be expected in overcorrected CK eyes. The average MRSE of this myopic group was –0.67 D (ranging up to –2.25

D), and the average cycloplegic spherical equivalent refraction was –0.72 D (ranging up to –2.00 D). The mean near UCVA in this group was 20/40.

Concurrent Distance and Near Visual Acuity

Concurrent distance and near visual acuities of individual eyes after CK are presented in Table 4**.** For example, 51% (37 of 72 eyes) had both distance visual acuity of 20/40 or better and near visual acuity of J3 or better**.**

STUDY 2. SURGICALLY INDUCED ASTIGMATISM AFTER CONDUCTIVE KERATOPLASTY

Preoperative Characteristics

Two hundred three eyes were in the study cohort. These represented the eyes from the Phase III group, which had data available at the 12-month follow-up examination. The mean preoperative manifest refraction astigmatism was 0.30 D (SD, 0.28; range, 0 to 0.75 D).

Absolute Change in Astigmatism

The absolute change in astigmatism 12 months after CK is shown in Table 5. Eighty-seven percent (177 eyes) were within ±0.75 D of their original astigmatism. Twelve percent (25 eyes) had an absolute induction of astigmatism of more than 0.75D. Seventeen percent (34 eyes) had less than their original astigmatism, 15% (31 eyes) had no change, and 70% (138 eyes) had more than their original astigmatism.

Vector Analysis of Change in Astigmatism

The mean vector of SIA was 0.23 D steepening at axis 175°, that is, a small average against-the-rule shift (Figure 16). This tendency toward an against-the-rule axis shift was statistically significant ($P < .001$) (Table 6). There was not a significant difference between eyes. The mean vector of SIA in right eyes was 0.27 D steepening at axis 178° and, in left eyes, was 0.18 D at axis 171°.

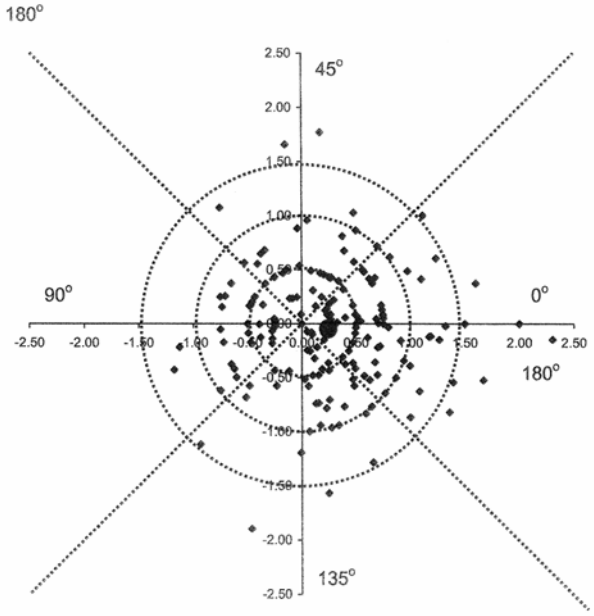

FIGURE 16

Astigmatism study. Double-angle scatterplot of vectoral induced astigmatism after conductive keratopathy at 1 year postoperatively. Dark circle is centroid of the data.

The mean vector magnitude of SIA was 0.66 ± 0.43 D. Fifteen percent (32 eyes) had more than 1.0 D of induced astigmatism as measured by vector analysis (Table 7). There was not a significant difference between eyes; the mean vector magnitude of SIA was 0.64 D ± 0.41 D in right eyes and 0.68 D ± 0.45 D in left eyes.

As shown in Table 8, there was no statistically significant relationship of vector analyzed SIA with number of CK spots.

TABLE 4. MULTIFOCALITY STUDY: CONCURRENT DISTANCE AND NEAR VISUAL ACUITY FOR EYES AFTER CONDUCTIVE KERATOPLASTY (CK) FOR HYPEROPIA (n = 72)

VISUAL ACUITY	POSTOPERATIVE CK
20/20 or better and J1 or better	2.8% (2)
20/20 or better and J2 or better	18.1% (13)
20/20 or better and J3 or better	19.4% (14)
20/25 or better and J3 or better	29.2% (21)
20/40 or better and J3 or better	51.4% (37)

TABLE 5. ASTIGMATISM STUDY: ABSOLUTE CHANGE IN ASTIGMATISM 12 MONTHS AFTER CONDUCTIVE KERATOPLASTY (n = 203)

CHANGE IN ASTIGMATISM (D)	% (n)
–0.76 to –1.25	0.5 (1)
–0.26 to –0.75	9.9 (20)
–0.25 to +0.25	36.0 (73)
+0.26 to +0.75	41.4 (84)
+0.76 to +1.25	8.4 (17)
+1.26 to +1.75	3.0 (6)
+1.76 to +2.25	1.0 (2)

D = diopters.

TABLE 6. ASTIGMATISM STUDY: AXIS SHIFT OF SURGICALLY INDUCED ASTIGMATISM 12 MONTHS AFTER CONDUCTIVE KERATOPLASTY

AXIS OF INDUCED ASTIGMATISM	% (n)
0^o to 22.5^o	42% (79)*
157.5^o to 180^o (ATR)	
22.5^o to 67.5^o	21% (39)
67.5^o to 112.5^o (WTR)	17% (32)
112.5^o to 157.5^o	20% (37)

ATR= induced against-the-rule astigmatism; WTR = induced with-the-rule astigmatism.
*$P < .001$.

TABLE 7. ASTIGMATISM STUDY: VECTORAL MAGNITUDE OF SURGICALLY INDUCED ASTIGMATISM (SIA) 12 MONTHS AFTER CONDUCTIVE KERATOPLASTY

CHANGE IN SIA (D)	% (n)
≤0.50	46.3 (99)
0.51 to ≤1.0	37.9 (77)
1.1 to ≤1.5	11.3 (23)
1.6 to ≤2.0	3.9 (8)
2.1 to ≤2.5	0.5 (1)

D = diopters.

CK Optical Zone Centration and Surgically Induced Astigmatism

Centration Results. Of the 64 eyes, 32 were right eyes and 32 left eyes. Figure 17 shows a scatterplot of individual procedure decentrations. The mean decentration of the center of the optical zone from the pupil center was 0.49 mm (SD, 0.30 mm; range, 0.08 to 1.34 mm). Thirty-nine (61%) were decentered ≤0.50 mm or less, 20 (31%) >0.50 mm and 1.00 mm, and 5 (8%) >1.00 mm. The mean decentration from the corneal vertex was 0.39 (SD, 0.26 mm; range, 0.08 to 1.34 mm). Forty-nine of 64 eyes (77%) were decentered ≤0.50 mm, 13 (20%) were greater than 0.50 mm and 1.00 mm or less, two (3%) were greater than 1.00 mm, with no procedure decentered greater than 1.10 mm. On average, decentration from the pupil center was 0.11 mm greater than that from the corneal vertex, although not statistically significant.

TABLE 8: ASTIGMATISM STUDY: SURGICALLY INDUCED ASTIGMATISM (SIA) AND NUMBER OF CONDUCTIVE KERATOPLASTY SPOTS APPLIED

NO. OF SPOTS	SIA MAGNITUDE
8 (n = 8)	0.64 ± 0.40 D
16 (n = 90)	0.61 ± 0.46 D
24 (n = 73)	0.69 ± 0.42 D
32 (n = 32)	0.74 ± 0.38 D

D = diopters.

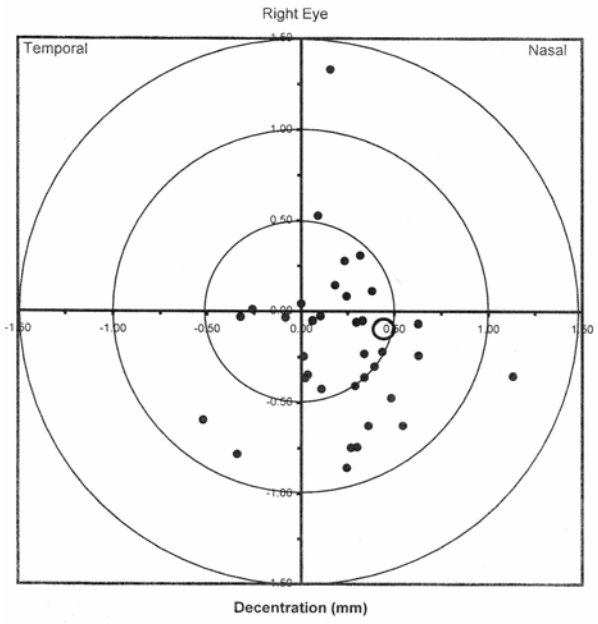

FIGURE 17A

Decentration from the pupil center in right eye. Each point represents the distance and angle of the center of the optical zone from the entrance pupil center. The mean decentration is 0.47 mm at 359° (open circles).

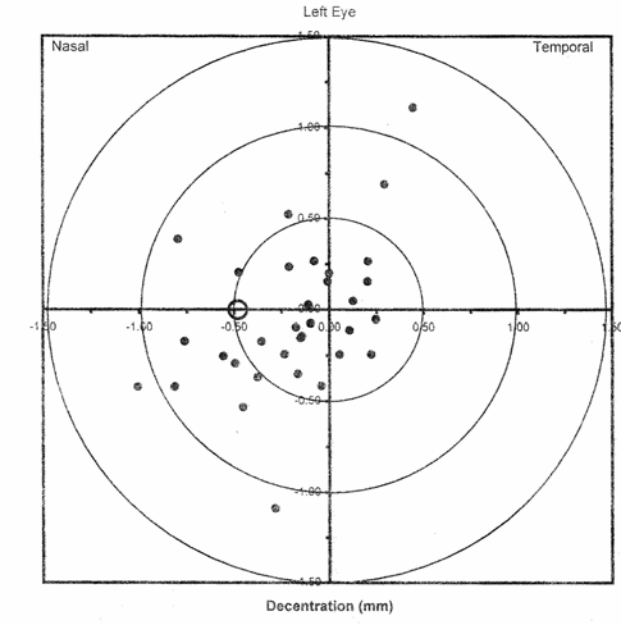

FIGURE 17B

Decentration from the pupil center in left eye. Each point represents the distance and angle of the center of the optical zone from the entrance pupil center. The mean decentration is 0.49 mm at 180° (open circles).

Mean decentration from the pupil center was located nasally in both right (0.47 mm, 358.8°) and left (0.49 mm, 180.3°) eyes. Mean decentration from the corneal vertex was 0.37 mm at 356.4° in right eyes and 0.41 mm at 180.6° in left eyes. To assess whether decentrations were random in directional orientation, the horizontal and vertical deviations were tested separately for statistical significance. Neither the mean horizontal nor vertical deviations for either right or left eyes were significantly different from zero, indicating that decentrations, indeed, were random in direction.

The amount of decentration was not correlated with attempted correction. Differences in decentration among groups stratified to number of spots applied were not statistically significant.

Association of Centration and Surgically Induced Astigmatism. Figures 18 and 19 show the relationship of SIA to CK optical zone topography decentration from the center of the pupil and the corneal vertex. As can be seen, there was no significant association between decentration and SIA for either. Indeed, the trend was for a negative relationship.

Clinical Effects of Induced Astigmatism

As seen in Table 9, the preoperative characteristics of the high induced astigmatism (≥1.0 D) group and low astigmatism group (<1.0 D) were similar, except for statistically significant baseline halo in the high astigmatism group.

Postoperatively, as expected, there was a statistically significant difference between groups in both sphere and cylinder ($P = .004$ and $P < .0001$, respectively) (Table 10). There was also a significant difference between groups in UCVA ($P = .0016$). The mean UCVA in high induced astigmatism groups was 20/33 compared with 20/27 in the low astigmatism group. With regard to safety outcomes, there was no difference in mean BSCVA or line change of BSCVA. In fact, no patients in the high astigmatism group lost 2 or more lines of BSCVA. Similarly, there was no difference between groups in the change in glare or halo index.

STUDY 3. HIGHER-ORDER OPTICAL ABERRATIONS AFTER CONDUCTIVE KERATOPLASTY AND HYPEROPIC LASIK

Preoperative Characteristics

CK Eyes. The mean preoperative MRSE was +1.98 (SD, 0.62) D. The preoperative MRSE ranged from 0.75 to 3.0 D. The mean preoperative cycloplegic spherical equivalent refraction was 1.95 (SD, 0.62) D. Of the 20 patients, four were male and 16 were female. The average age was 56.8 (SD, 4.7) years. The characteristics of the study population are shown in Table 2.

TABLE 9. ASTIGMATISM STUDY: BASELINE DATA FOR LOW VERSUS HIGH SURGICALLY INDUCED ASTIGMATISM GROUPS

OUTCOME	<1.0 D GROUP (n = 178)	≥1.0 D GROUP (n = 25)	*P* VALUE
Mean sphere (D)	+1.90	+2.00	.82
Mean cylinder (D)	–0.31	–0.22	.11
Mean UCVA	20/85	20/84	.87
Mean BSCVA	20/18	20/18	.44
Mean glare index*	0.29	0.57	.06
Mean halo index*	0.13	0.50	.007†

D = diopters; BSCVA = best spectacle-corrected visual acuity; UCVA = uncorrected visual acuity.
*On a scale of 0 to 4.
†Statistically significant.

LASIK Eyes. The mean preoperative MRSE was 1.90 (SD, 0.52) D. The preoperative MRSE ranged from 1.0 to 3.0 D. The mean preoperative cycloplegic spherical equivalent refraction was 1.89 (SD, 0.52) D. Of the 24 patients, 14 were male and 10 were female. The average age was 59.4 (SD, 6.7) years. The characteristics of the study population are shown in Table 2.

Surgically Induced Aberrations After CK

All Eyes Analysis. The RMS corneal wavefront error for third- to sixth-order aberrations increased significantly ($P < .002$) following surgery (Table 11). Mean preoperative wavefront error (RMS) was 0.034 µm (SD, 0.020). Mean postoperative wavefront error averaged 0.097 µm (SD, 0.077). Induced wavefront error ranged from +0.058 to –0.284 µm. Total RMS wavefront errors (third to sixth orders) are shown before and after treatment for individual eyes in Figure 20.

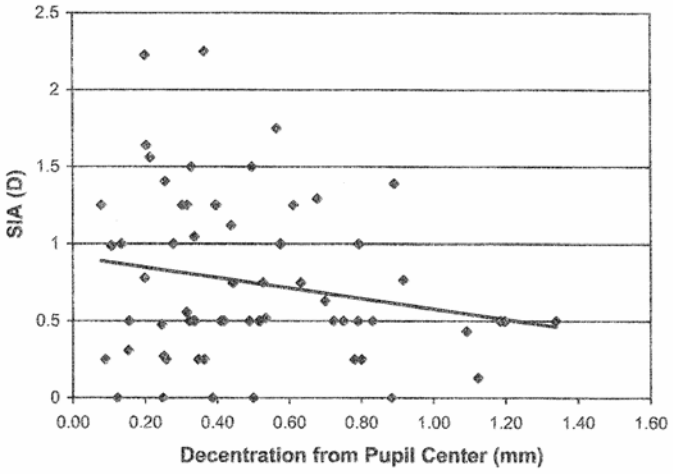

FIGURE 18

Astigmatism study. Surgically induced astigmatism (SIA) versus conductive keratopathy optical zone decentration from the pupil center. Best-fit line is shown.

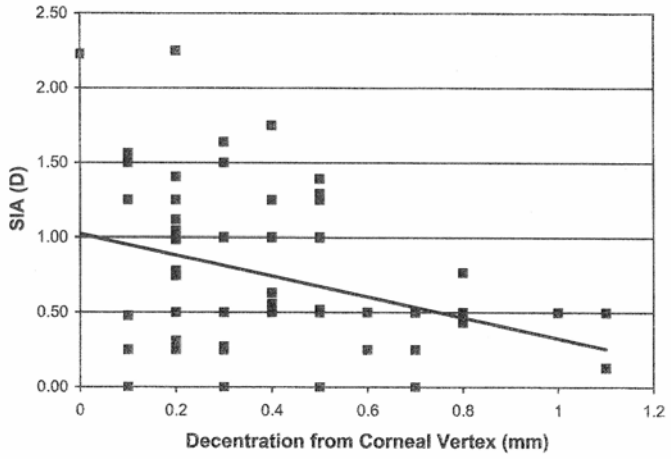

FIGURE 19

Astigmatism study. Surgically induced astigmatism (SIA) versus conductive keratopathy optical zone decentration from the corneal vertex. Best-fit line is shown.

A significant difference ($P < .002$) in spherical-like aberration (fourth and sixth orders) was found after CK (Figure 21). Mean preoperative spherical-like aberration RMS was 0.008 µm (SD, 0.006), and mean postoperative spherical-like aberration was 0.018 µm (SD, 0.014), a 2.25-fold increase. On average, the change in asphericity after CK was in the direction of a more prolate cornea (Figure 7). Independent analysis of the induced RMS error for the Z^{12} spherical aberration component alone failed to meet statistical significance.

TABLE 10. ASTIGMATISM STUDY: POSTOPERATIVE DATA FOR LOW VERSUS HIGH SURGICALLY INDUCED ASTIGMATISM GROUPS

OUTCOME	<1.0 D GROUP (n = 178)	≥1.0 D GROUP (n = 25)	*P* VALUE
Mean sphere (D)	+0.51	+1.10	.004†
Mean cylinder (D)	–0.56	–1.49	<.0001†
Mean UCVA	20/27	20/33	.0016†
Mean BSCVA	20/18	20/19	.39
Change in lines of BSCVA	+0.006	–0.08	.74
Change glare index*	0.21	0.39	.43
Change halo index*	0.43	0.29	.52

D = diopters; BSCVA = best spectacle-corrected visual acuity; UCVA = uncorrected visual acuity.
*On a scale of 0 to 4.
†Statistically significant

TABLE 11. CORNEAL WAVEFRONT HIGHER-ORDER ABERRATIONS BEFORE AND AFTER CONDUCTIVE KERATOPLASTY (CK) AND HYPEROPIC LASIK*

MEAN RMS (µm)	PRE-CK	POST-CK	PRE-LASIK	POST-LASIK
Total third to sixth	0.0346	0.0972*	0.0372	0.0772*
Spherical (fourth and sixth)	0.0077	0.0175*	0.0067	0.0083
Spherical (Z^{12})	0.0090	0.0100	0.0049	0.0026
Total coma (third and fifth)	0.0269	0.0797*	0.0305	0.0689*
Total coma (third and fifth) (right eyes)	0.0245	0.0767*	0.0272	0.0565
Total coma (third and fifth) (left eyes)	0.0293	0.0827*	0.0332	0.0789
Vertical coma (Z^7)	0.0113	0.0305*	0.0103	0.0183
Vertical coma (Z^7) (right eyes)	0.0129	0.0342	0.0101	0.0166
Vertical coma (Z^7) (left eyes)	0.0097	0.0268*	0.0104	0.0196
Horizontal coma (Z^8)	0.0554	0.0159*	0.0092	0.0245
Horizontal coma (Z^8) (right eyes)	0.0554	0.0190*	0.0069	0.0205
Horizontal coma (Z^8) (left eyes)	0.0554	0.0127*	0.0111	0.0276

RMS = root mean square.
*Statistically significant change ($P < .05$) in aberrations from preoperative to postoperative measurement.

Coma-like (third and fifth orders) aberrations increased significantly after CK ($P = .0001$) (Figure 22). Mean coma-like wavefront error in CK eyes averaged 0.027 µm (SD 0.019) preoperatively, and 0.080 µm (SD, 0.074) postoperatively. Similarly, vertical (Z^7) coma showed a significant 2.8-fold increase after surgery, from 0.011 to 0.031 µm. Conversely, the horizontal coma (Z^8) wavefront error showed a statistically significant decrease ($P < .0001$). Horizontal coma RMS was 0.055 µm (SD, 0.054) and 0.016 µm (SD, 0.018) before and after surgery, respectively, representing a 3.4-fold reduction.

Right and Left Eye Analysis. Independent analysis of right eyes and left eyes before and after CK also showed significant increases in total third- to sixth-order aberrations (right: $P = .003$; left: $P = .004$) following surgery. Mean preoperative RMS was 0.033 µm (SD, 0.023) and 0.037 µm (SD, 0.018) for right and left eyes, respectively. Postoperative wavefront errors averaged 0.095 µm (SD, 0.071) for right eyes and 0.099 µm (SD, 0.083) for left eyes. For right eyes, wavefront error change ranged from +0.014 to –0.2685 µm. For left eyes, the RMS change ranged from +0.058 to –0.284 µm.

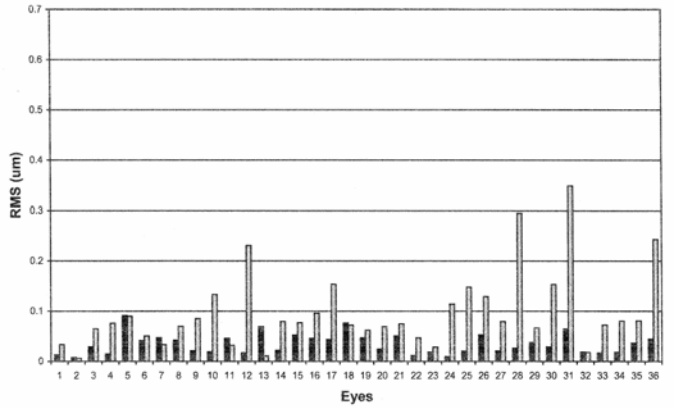

FIGURE 20

Wavefront study. Root mean square (RMS) wavefront error for total third- to sixth-order aberrations before (black bars) and after (gray bars) conductive keratopathy surgery for individual eyes. Data are sorted by increasing preoperative spherical equivalent refraction from left to right.

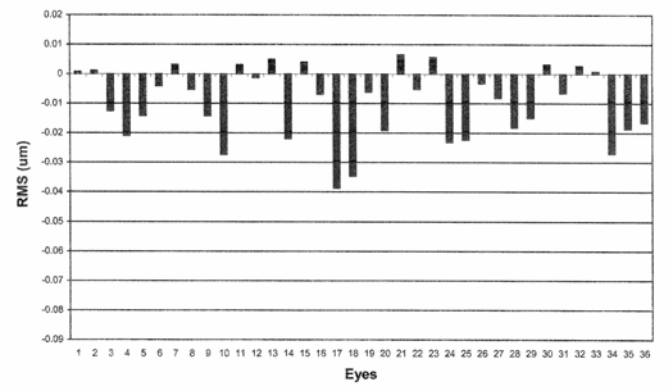

FIGURE 21

Wavefront study. Change in root mean square (RMS) wavefront error for spherical-like aberrations (fourth and sixth order) after CK surgery. Data are sorted left to right by increasing treatment.

In the analysis of spherical-like aberrations, CK eyes measured significantly more negative spherical-like aberrations postoperatively compared to preoperative values (right: $P = .003$; left: $P = .004$). Mean preoperative spherical-like aberration RMS was 0.008 μm (SD, 0.006) and increased to 0.018 μm (SD, 0.014) postoperatively for right eyes. In left eyes, mean preoperative RMS for spherical-like aberrations was 0.007 μm (SD, 0.003) and increased to 0.017 μm (SD, 0.012) postoperatively. Mean changes in spherical-like aberrations were 0.010 μm for right eyes and 0.009 μm in left eyes in the direction of a more prolate cornea profile.

Consistent with the all eyes analysis of CK-treated eyes, statistical significance was found when analyzing coma-like aberrations before and after surgery in right ($P = .01$) and left ($P = .008$) eyes. Mean coma RMS changed from 0.025 μm (SD, 0.022) and 0.029 μm (SD, 0.017) before surgery to 0.077 μm (SD, 0.070) and 0.083 μm (SD, 0.079) after treatment in right and left eyes, respectively. Vertical coma (Z^7) in right eyes failed to meet significance, whereas left eyes demonstrated a significance increase ($P = .043$). Independent assessment of horizontal (Z^8) coma showed a significant decrease in RMS wavefront error in right ($P = .002$) and left ($P = .02$) eyes after treatment.

A summary of induced spherical and coma RMS errors for CK treated eyes is shown in Table 11.

Surgically Induced Aberrations After Hyperopic LASIK

All Eyes Analysis. As for CK, the RMS corneal wavefront error for third- to sixth-order aberrations increased significantly ($P < .04$) after hyperopic LASIK. Mean preoperative wavefront error (RMS) was 0.037 μm (SD, 0.025); postoperative wavefront errors averaged 0.077 μm (SD, 0.114). Induced wavefront error ranged from +0.067 to –0.658 μm. Total RMS wavefront errors (third to sixth orders) for individual eyes are shown before and after treatment in Figure 23.

Unlike CK, analysis of spherical-like aberration (fourth and sixth orders) did not show a statistically significant difference comparing preoperative to postoperative values (Figure 24). Mean preoperative spherical-like aberration RMS was 0.007 μm (SD, 0.032), and mean postoperative spherical-like aberration was 0.008 μm (SD, 0.014). As seen in Figure 24, the small mean change was a result of individual eyes variably changing in a prolate or oblate direction. As for CK, separate analysis of the induced RMS error for Z^{12} spherical aberration failed to meet statistical significance.

As for CK, coma-like (third and fifth order) aberrations increased significantly after hyperopic LASIK ($P = .04$) (Figure 25). Mean coma-like wavefront error averaged 0.031 μm (SD, 0.024) preoperatively and 0.069 μm (SD, 0.109) postoperatively, a 2.22-fold increase. However, individual vertical coma (Z^7) and horizontal coma (Z^8) measurements failed to meet statistical significance.

Right and Left Eye Analysis. Independent analysis of both right eyes and left eyes before and after hyperopic LASIK did not show a statistically significant difference in total third- to sixth-order aberrations. Mean preoperative wavefront RMS was 0.032 μm (SD, 0.026) and 0.041 μm (SD, 0.024) for right and left eyes, respectively. Postoperative wavefront errors averaged 0.066 μm (SD, 0.065) for right eyes and 0.086 μm (SD, 0.143) for left eyes.

Unlike CK, stratified analysis of spherical-like aberrations for both right and left eyes did not show a statistically significant difference before and after surgery. Similarly, preoperative and postoperative coma-like aberrations were not significantly different, and independent analysis of vertical (Z^7) and horizontal (Z^8) coma also showed no significant difference.

A summary of induced spherical and coma RMS errors for LASIK-treated eyes is shown in Table 11.

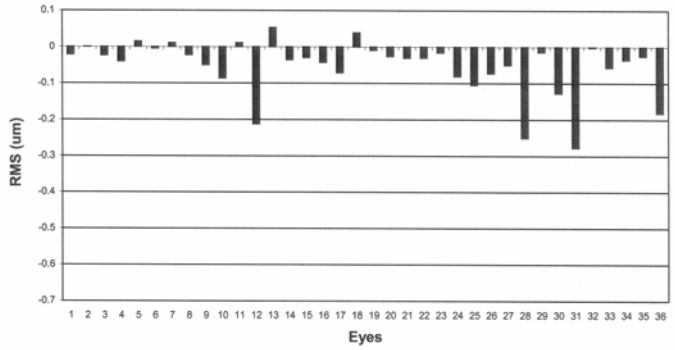

FIGURE 22

Wavefront study. Change in root mean square (RMS) wavefront error for coma-like aberrations (third and fifth order) after conductive keratopathy surgery. Data sorted left to right by increasing treatment.

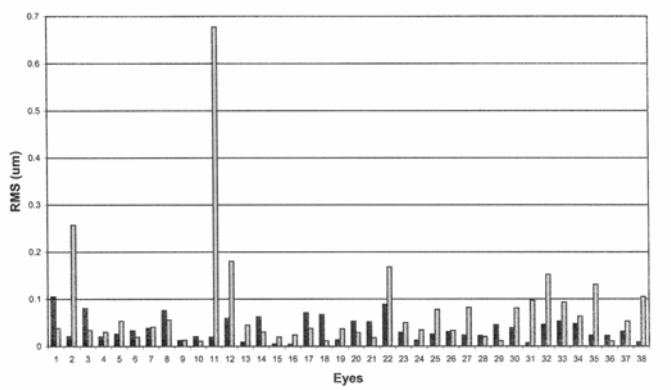

FIGURE 23

Wavefront study. Root mean square (RMS) wavefront error for total third- to sixth-order aberrations before (black bars) and after (gray bars) hyperopic LASIK for individual eyes. Data are sorted by increasing preoperative spherical equivalent refraction from left to right.

Comparison of CK and LASIK Wavefront Aberrations

In the analysis of surgically induced total wavefront aberration (third to sixth order), the difference between CK and LASIK was not statistically significant, either for the total eye or separate eye cohorts. The mean change in RMS error was –0.063 µm (SD, 0.077) for CK eyes and –0.040 µm (SD, 0.117) for LASIK eyes (Table 12).

TABLE 12. COMPARISON OF PREOPERATIVE TO POSTOPERATIVE CORNEAL WAVEFRONT HIGHER-ORDER ABERRATIONS IN CONDUCTIVE KERATOPLASTY (CK) VERSUS HYPEROPIC LASIK*

DIFFERENCE (PRE MINUS POST) RMS (µm)	CK	LASIK
Third to sixth (all eyes)	–0.0626	–0.0400
Third to sixth (right eyes)	–0.0624	–0.0341
Third to sixth (left eyes)	–0.0628	–0.0448
Spherical (fourth and sixth) (all eyes)*	–0.0099	–0.0016*
Spherical (Z^{12})*	–0.0006	0.0023*
Total coma (third and fifth)	–0.0528	–0.0384
Total coma (third and fifth) (right eyes)	–0.0522	–0.0292
Total coma (third and fifth) (left eyes)	–0.0534	–0.0458
Vertical coma (Z^7) (all eyes)	–0.0192	–0.0152
Vertical coma (Z^7) (right eyes)	–0.0213	–0.0136
Vertical coma (Z^7) (left eyes)	–0.0171	–0.0165
Horizontal coma (Z^8) (all eyes)	–0.0108	–0.0124
Horizontal coma (Z^8) (right eyes)	–0.0191	–0.0054
Horizontal coma (Z^8) (left eyes)	–0.0025	–0.0180

RMS = root mean square.
*Statistically significant change ($P < .05$) in aberrations from preoperative to postoperative measurement.

Of note, spherical-like aberrations were significantly more negative (more prolate) in CK compared with LASIK eyes ($P = .009$). Induced spherical-like aberrations were –0.010 µm (SD, 0.012) and –0.002 µm (SD, 0.014) for CK and LASIK eyes, respectively. Similarly, for the spherical aberration term (Z^{12}) alone, comparison of CK- and LASIK-induced wavefront error was significantly different ($P < .02$); on average, LASIK procedures induced relatively more positive (Z^{12}) spherical aberration compared with CK. The induced spherical wavefront error (Z^{12}) was –0.0006 µm (SD, 0.031) for CK eyes and 0.002 µm (SD, 0.005) for LASIK eyes.

Surgically induced coma-like aberrations failed to meet statistically significant differences in comparison of CK and LASIK eyes. Individual assessment of vertical and horizontal coma for all eyes also showed no difference between CK and LASIK. Similarly, the right and left eye analysis of vertical and horizontal coma showed no difference.

A summary of induced spherical and coma RMS errors for CK compared with hyperopic LASIK treated eyes is shown in Table 12.

STUDY 4. MULTICENTER STUDY OF PRESBYOPIA CORRECTION USING CONDUCTIVE KERATOPLASTY

Baseline Patient and Operative Data

In this study, results are presented of a consistent cohort of patients seen through the 12-month follow-up visit. This cohort consisted of 126 eyes of 106 patients (Table 13). Of the 106 patients, 86 were treated in one eye only for monovision and 20 were treated in both eyes, the dominant for correction of hyperopia and the nondominant for monovision. Thus, a total of 106 eyes were treated for near and 20 were treated for distance. Forty-five (42%) were male and 62 (58%) were female. Average age was 52.8 years (range, 45 to 70 years).

TABLE 13. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: COHORT BASELINE DATA

VARIABLE	VALUE
No. of patients studied	106
No. of eyes	126
No. of eyes treated for near vision	106
No. of eyes treated for distance vision	20
Male: female ratio	42% (45): 58% (62)
Mean age (years)	52.8 (range, 45 to 70)
Preoperative MRSE in eyes treated for near vision	
Mean	+0.39
SD	0.46
Range	–0.75 to +1.25 D
Preoperative MRSE in eyes treated for distance vision	
Mean	+1.03
SD	0.30
Range	+0.75 to +1.75 D

D = diopters; MRSE = manifest refraction spherical equivalent; SD = standard deviation.

The average manifest preoperative spherical equivalent of the 106 eyes in which monovision was attempted was +0.39 D (SD, 0.46; range, –0.75 to +1.25). For these eyes, a mean of 22.5 CK spots were applied (SD, 6.8) for an attempted correction of approximately 2.0 D on average. The average manifest spherical equivalent of the 20 eyes in which improved distance vision was attempted was +1.03 D (SD, 0.30; range, +0.75 to +1.75). For these eyes, a mean of 13.4 CK spots were applied (SD, 4.9) for an attempted correction of approximately 1.1 D on average. Fourteen eyes (11%) underwent retreatment. Of these, 12 retreatments were in eyes treated for near (11% of near eyes) and two were in eyes treated for distance (10% of distance eyes).

Uncorrected Near Visual Acuity

Uncorrected near visual acuity data are presented in Tables 14 and 15 and Figures 26 and 27. Measuring just the eye treated for near, preoperatively, 0% were J1 or better and 5% (five eyes) were J3 or better. Postoperatively at 3 months, 46% (49 eyes) were J1 or better and 75% (80 eyes) were J3 or better. Postoperatively at 1 year, 35% (37 eyes) were J1 or better and 77% were J3 (82 eyes) or better. Measuring binocular near visual acuity, preoperatively 1% (one patient) was J1 or better and 12% (13 patients) were J3 or better. Postoperatively at 3 months, 47% (50 patients) were J1 or better and 72% (76 patients) were J3 or better. Postoperatively at 1 year, 42% (45 patients) were J1 or better and 80% (85 patients) were J3 or better.

Uncorrected Distance Visual Acuity

Uncorrected distance visual acuity data are presented in Tables 16 and 17 and Figures 28 and 29. Measuring just the eye treated for near, preoperatively 52% (55 eyes) were 20/20 or better and 94% (100 eyes) were 20/40 or better. Postoperatively at 3 months, 27% (29 eyes) were 20/20 or better and 69% (73 eyes) were 20/40 or better. Postoperatively at 1 year, 43% (46 eyes) were 20/20 or better and 92% (98 eyes) were 20/40 or better. Measuring binocular distance visual acuity, preoperatively 84% (89 patients) were 20/20 or better and 99% (105 patients) were 20/40 or better. Postoperatively at 3 months, 94% (100 patients) were 20/20 or better and 100% (106 patients) were 20/40 or better. Postoperatively at 1 year, 96% (102 patients) were 20/20 or better and 100% (106 patients) were 20/40 or better.

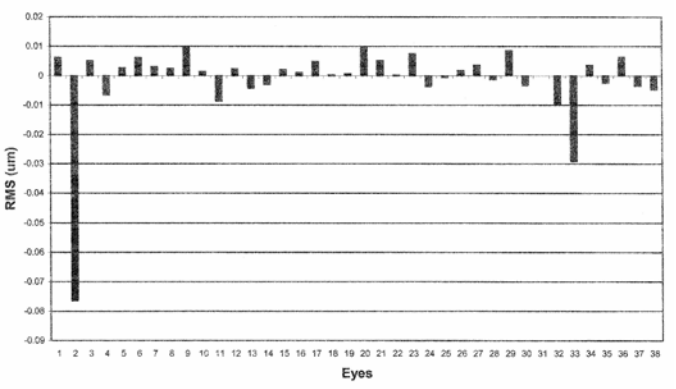

FIGURE 24

Wavefront study. Change in root mean square (RMS) wavefront error for spherical-like aberrations (fourth and sixth order) after hyperopic LASIK. Data are sorted left to right by increasing treatment.

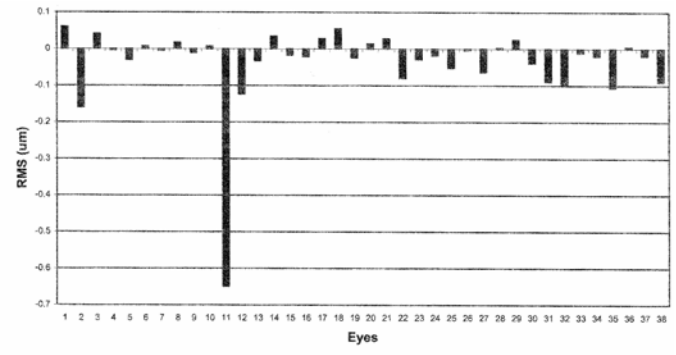

FIGURE 25

Wavefront study. Change in root mean square (RMS) wavefront error for coma-like aberrations (third and fifth order) after hyperopic LASIK. Data are sorted left to right by increasing treatment.

TABLE 14. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: UNCORRECTED VISUAL ACUITY (UCVA) AT NEAR FOR EYES TREATED FOR NEAR VISION (n = 106)

NEAR UCVA	PREOPERATIVE	3 MONTHS	1 YEAR
J1+	—	18.9% (20)	9.4% (10)
J1	—	27.4% (29)	25.5% (27)
J2	0.9% (1)	19.8% (21)	29.2% (31)
J3	3.8% (4)	9.4% (10)	13.2% (14)
J5	8.5% (9)	16.0% (17)	12.3% (13)
J7	17.0% (18)	4.7% (5)	6.6% (7)
J10	29.2% (31)	2.8% (3)	2.8% (3)
J16	35.0% (37)	0.9% (1)	0.9% (1)
<J16	5.7% (6)	—	—

Concurrent Distance and Near Visual Acuity

Concurrent binocular distance and near visual acuity is presented in Table 18. For example, preoperatively, 10.4% (11 patients) were both 20/20 or better at distance and J3 or better at near. At 1 year postoperatively, 78.3% (83 patients) had both good distance and good near visual acuity.

Although this study was concerned with monovision correction and thus binocular outcomes in general, concurrent distance and near visual acuity for individual eyes treated for near vision is presented in Table 19. For example, preoperatively, only 3.8% (4 eyes) were both 20/20 or better at distance and J3 or better at near. At 1 year postoperatively, 24.5% (26 eyes) had 20/20 or better at distance and J3 or better at near. Of note, at 1 year, 66.0% (70 eyes) of eyes treated for near vision had both 20/40 or better at distance and J3 or better at near.

Postoperative Refraction

Spherical Equivalent. Table 20 presents the postoperative MRSE in eyes treated for near vision. The mean preoperative refraction was +0.39 D (SD, 0.46 D). The mean spherical equivalent refraction was –1.01 D (SD, 0.69 D) and –0.68 D (SD, 0.58 D), respectively, at 3 months and 1 year postoperatively.

Astigmatism. The average postoperative astigmatism was 0.51 D (SD, 0.46 D). The range was 0 to 2.0 D.

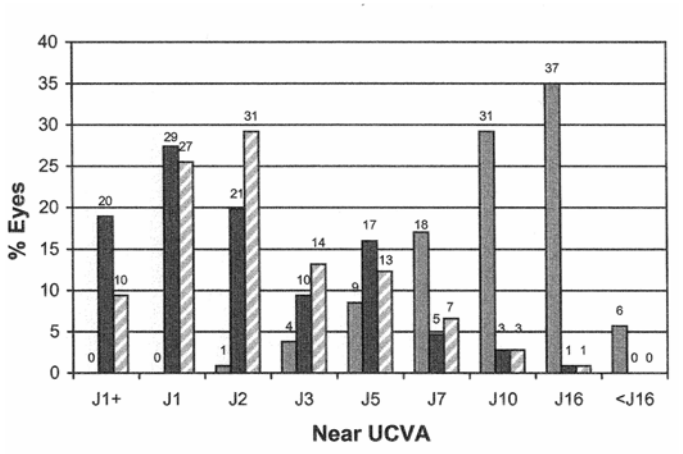

FIGURE 26

Presbyopia study. Uncorrected visual acuity (UCVA) at near for eyes treated for near vision (n = 106). Gray = preoperative; black = 3-month follow-up; cross-hatched = 1 year follow-up.

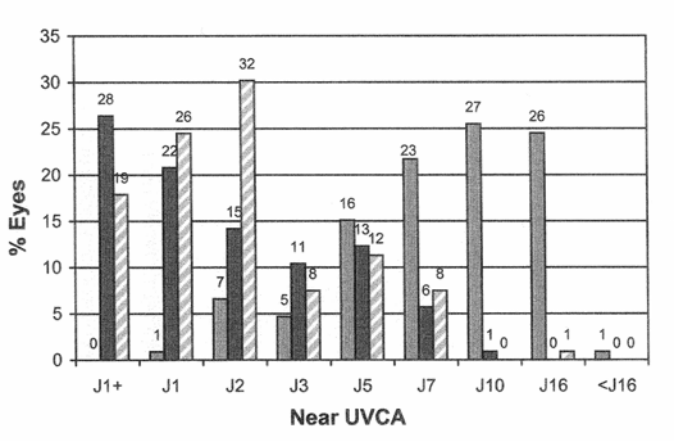

FIGURE 27

Presbyopia study. Binocular uncorrected visual acuity (UCVA) at near after conductive keratopathy (n = 106). Gray = preoperative; black = 3-month follow-up; cross-hatched = 1-year follow-up.

TABLE 15. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: BINOCULAR UNCORRECTED VISUAL ACUITY (UCVA) AT NEAR (n = 106)

NEAR UCVA	PREOPERATIVE	3 MONTHS	1 YEAR
J1+	—	26.4% (28)	17.9% (19)
J1	0.9% (1)	20.8% (22)	24.5% (26)
J2	6.6% (7)	14.2% (15)	30.2% (32)
J3	4.7% (5)	10.4% (11)	7.5% (8)
J5	15.1% (16)	12.3% (13)	11.3% (12)
J7	21.7% (23)	5.7% (6)	7.5% (8)
J10	25.5% (27)	0.9% (1)	—
J16	24.5% (26)	—	0.9% (1)
<J16	0.9% (1)	—	—

Loss of Spectacle-Corrected Visual Acuity

As seen in Table 21, at 3 months postoperatively, 3.7% (four eyes) had lost 2 or more lines of spectacle-corrected near visual acuity (three eyes with 2 lines loss and one eye with 3 lines loss) and 0.9% (one eye) had lost 2 lines of distance acuity. At 12 months, loss of near corrected acuity had improved; only 0.9% (one eye) had lost 2 lines at near and, similarly, 0.9% (one eye) had lost 2 lines at distance. Moreover, 1.8% (two eyes) had gained 2 or more lines at near.

Table 22 presents changes in binocular spectacle-corrected visual acuity. At 3 months postoperatively, no patients had lost 2 or more lines of spectacle-corrected near visual acuity and 0.9% (one patient) had lost 2 lines of distance acuity. A gain in corrected visual acuity of 2 lines was seen in 2.8% (three patients) at near and 3.8% (four patients) at distance. At 12 months, 0.9% (one patient) had lost 2 lines at near and no patients had lost 2 or more lines at distance. A gain in corrected visual acuity of 2 lines was seen in 3.8% (four patients) at near and 6.6% (seven patients) at distance.

Subjective Patient Responses to Questionnaire

Patient Satisfaction. Ninety-seven patients in the study cohort had data available at the 12-month follow-up visit. On a subjective scale of 1 to 5 (very dissatisfied to very satisfied), 0% (0 patients) were very dissatisfied, 5% (5) were dissatisfied, 11% (11) were neutral, 32% (31) were satisfied, and 52% (50) were very satisfied (Figure 30).

Possible associations of characteristics related to the patient having either a neutral or a dissatisfied response were tested. Preoperative characteristics included gender, age, and binocular (hyperopia correction one eye, monovision correction one eye) versus monocular (monovision correction only) treatment plan. There was no statistically significant association of patient gender (n = 43:54, M:F) with subjective satisfaction (P = .29). With regard to patient age, the average of the cohort analyzed was 52.5 years (SD,

4.54) with a median of 52 years. Comparing patients stratified to ≤52 years (n = 56) and >52 years (n = 41) with subjective satisfaction, there was no statistically significant association of age with satisfaction (*P* = .33). Of the 97 patients, 19 were treated bilaterally and 78 were treated unilaterally; there was no statistically significant difference in satisfaction between the groups (*P* = .43).

TABLE 16. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: UNCORRECTED VISUAL ACUITY (UCVA) AT DISTANCE FOR EYES TREATED FOR NEAR VISION (n = 106)

UCVA AT DISTANCE	PREOPERATIVE	3 MONTHS	1 YEAR
≥20/20	51.9% (55)	27.4% (29)	43.4% (46)
20/25 to 20/40	42.5% (45)	42.0% (44)	49.1% (52)
20/50 to 20/80	5.7% (6)	20.8% (22)	4.7% (5)
20/100 to 20/200	—	10.4% (11)	2.8% (3)
<20/200	—	—	—

TABLE 17. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: BINOCULAR UNCORRECTED VISUAL ACUITY (UVCA) AT DISTANCE (n = 106)

UCVA AT DISTANCE	PREOPERATIVE	3 MONTHS	1 YEAR
≥20/20	84.0% (89)	94.3% (100)	96.2% (102)
20/25 to 20/40	15.1% (16)	5.7% (6)	3.8% (4)
20/50 to 20/80	0.9% (1)	—	—
20/100 to 20/200	—	—	—
<20/200	—	—	—

Postoperative characteristics tested as possible associations with subjective patient satisfaction included monocular and binocular near UCVA, monocular and binocular distance UCVA, subjective grading of postoperative depth perception, and preoperative to postoperative change in subjective depth perception quality. With regard to near UCVA, there was a statistically significant association of patient satisfaction with near UCVA of J3 or better in the eye corrected for monovision (*P* = .001); those patients who could not see J3 or better unaided after the procedure were more likely to be dissatisfied or neutral. In particular, eight of 16 patients (50.0%) who were neutral or dissatisfied with the procedure could not see J3 or better after surgery compared with 14 of 81 satisfied patients (17.3%). The association of binocular near vision of J3 or better with patient satisfaction was not statistically significant (*P* = .15). With regard to distance UCVA, there was no statistically significant association of patient satisfaction with either monocular distance visual acuity of 20/40 or better in the monovision eye (*P* = .50) or binocular distance visual acuity (where no patients were worse than 20/40).

General data regarding subjectively perceived depth perception are presented below. However, with regard to patient satisfaction with the CK procedure, there was a statistically significant association of patient satisfaction with subjectively good postoperative depth perception (grades 4 or 5) (*P* = .038). Of 82 patients with both satisfaction and quality of depth perception data, seven of 11 (63.6%) who were neutral or dissatisfied with the procedure ranked their depth perception as 1, 2, or 3 compared with 22 (30.9%) of 71 satisfied patients with similarly low depth perception rankings. There was no statistically significant association of patient satisfaction with change in depth perception from the preoperative level, however (*P* = .059).

Quality of Vision. Ninety-seven patients in the study cohort had data available at the 12-month follow-up visit. On a subjective scale of 0 to 4 (no improvement to extreme improvement), 3% (three patients) had no improvement, 8% (seven) had slight improvement, 12% (12) had moderate improvement, 39% (38) had marked improvement, and 38% (37) had extreme improvement (Figure 31). Similar to the patient satisfaction outcome, there was a statistically significant association of good subjective quality of vision (ranking 3 or 4) with near visual acuity of J3 or better (*P* < .001) as well as with subjectively good postoperative depth perception (grades 4 or 5) (*P* < .001). Again similar to the satisfaction analysis, there was no statistically significant association of subjective quality of vision with either distance UCVA in the monovision eye (*P* = .23) or binocular distance visual acuity of 20/40 or better.

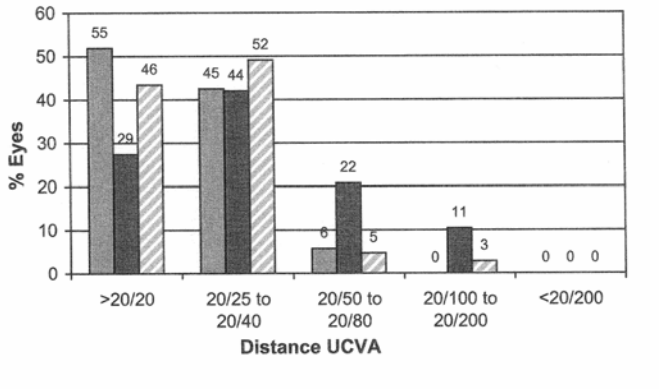

FIGURE 28

Presbyopia study. Uncorrected visual acuity (UCVA) at distance for eyes treated for near vision (n = 106). Gray = preoperative; black = 3-month follow-up; cross-hatched = 1-year follow-up.

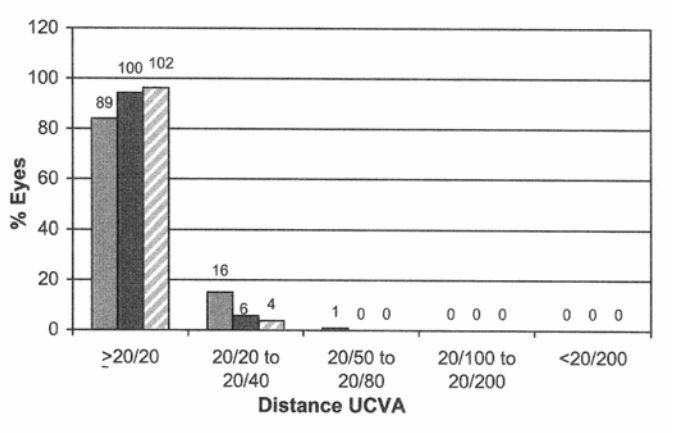

FIGURE 29

Presbyopia study. Binocular uncorrected visual acuity (UCVA) at distance after conductive keratopathy (n = 106). Gray = preoperative; black = 3-month follow-up; cross-hatched = 1-year follow-up.

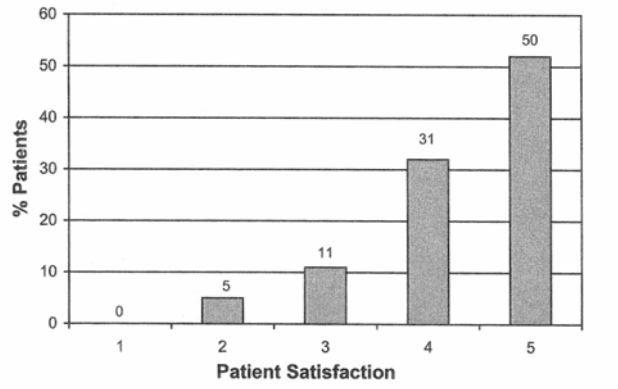

FIGURE 30

Presbyopia study. Patient ranking of satisfaction 1 year after conductive keratopathy for presbyopia. Scale = 1 (very dissatisfied) to 5 (very satisfied).

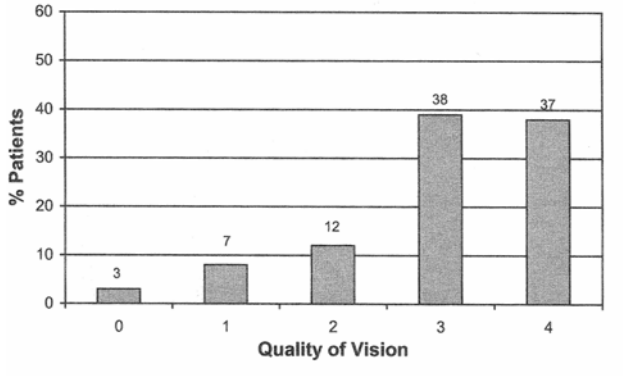

FIGURE 31

Presbyopia study. Patient ranking of quality of vision 1 year after conductive keratopathy for presbyopia. Scale = 0 (no improvement) to 4 (extreme improvement).

Depth Perception. Eighty-two patients had data available both preoperatively and postoperatively regarding perceived quality of depth perception. Table 23 and Figure 32 summarize the results. Before surgery, 52% (43 patients) graded their depth perception as very good or excellent and, after surgery, 65% (53 patients) ranked it as very good or excellent. Similarly, 6% (five patients) ranked their depth perception as fair or poor both before and after CK.

Analyzing change in perceived depth perception in individuals, 1% (one patient) worsened by 3 units, 2% (two) worsened by 2 units, and 18% (15) worsened by 1 unit. There was no change in 30% (25 patients). Twenty-two percent (18) improved by 1 unit and 12% (10) improved by 2 units.

Subjective Comparison of Preoperative and Postoperative Near, Intermediate, and Distance Vision. Thirty-nine patients in the study cohort had data available at the 12-month follow-up visit. Data are presented in Figure 33.

- Near vision: On a subjective scale of 1 to 5 (significantly worse to significantly better), 0% (0 patients) were significantly worse, 5% (2) were worse, 10% (4) were the same, 33% (13) were better, and 51% (20) were significantly better.
- Intermediate vision: 0% (0) were significantly worse, 5% (2) were worse, 33% (13) were the same, 49% (19) were better, and 13% (5) were significantly better.
- Distance vision: 3% (1) were significantly worse, 8% (3) were worse, 59% (23) were the same, 18% (7) were better, and 13% (5) were significantly better.

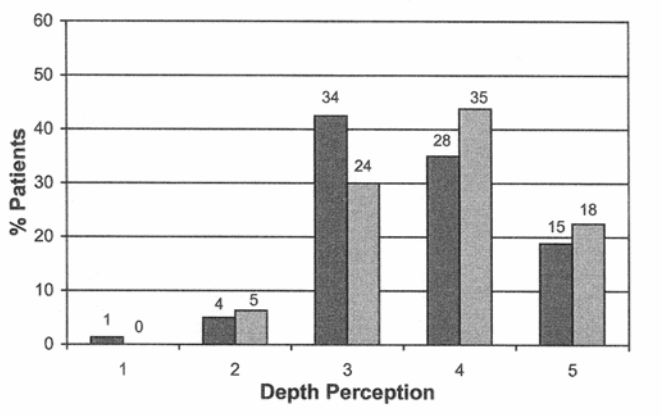

FIGURE 32

Presbyopia study. Subjective quality of depth perception before and after conductive keratopathy for presbyopia. Scale is graded from 1 to 5, indicating incrementally poor to excellent quality of depth perception. Black = preoperative; gray = postoperative.

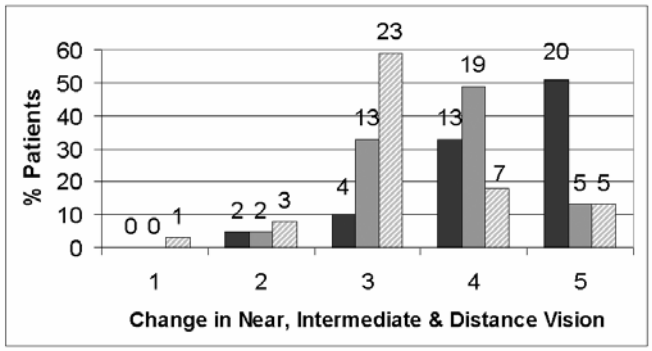

FIGURE 33

Presbyopia study. Subjective comparison of preoperative and postoperative (1 year) near, intermediate, and distance vision. Scale = 1 (significantly worse) to 5 (significantly better). Black = near vision; gray = intermediate vision; cross-hatched = distance vision.

Ability to Perform Visual Tasks. Figure 34 shows the proportion of patients able to see without glasses for a number of tasks before and after surgery. Thirty-nine patients in the study cohort had data available at the 12-month follow-up visit for all tasks except for ability to see street signs, see books on a shelf, or read a newspaper, where 38 patients had data, and knitting, sewing, and performing crafts, where 37 patients had data.

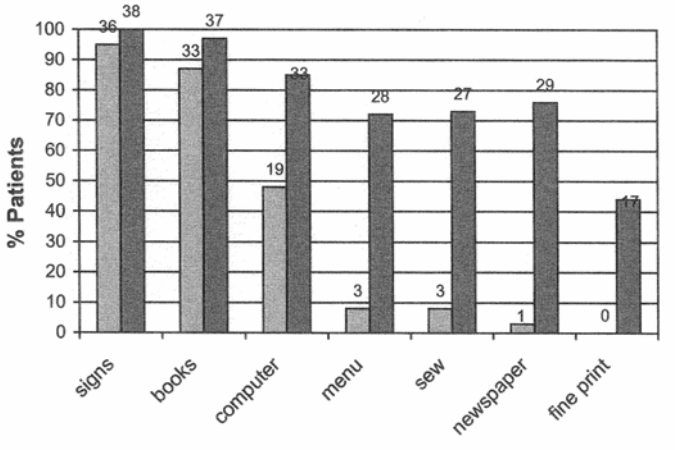

FIGURE 34

Presbyopia study. Ability to perform visual tasks before and 1 year after conductive keratopathy.

Before surgery, 95% (36 patients) were able to see street signs without glasses, and 100% (38) could after surgery. Eighty-seven percent (33 patients) could see books on a shelf before CK, and 97% (37) could do so afterwards. Forty-nine percent (19) were able to see their computer screen preoperatively, whereas 85% (33) could postoperatively. Before surgery, only 8% (3) could see a menu, compared with 72% (28) who were able to after surgery. Similarly, 8% (3) could knit, sew, or perform crafts before CK, whereas 73% (27) could do so postoperatively. Only 3% (1 patient) could read a newspaper without glasses before surgery, and 76% (29) could after surgery. Finally, 0% (no patients) could read fine print preoperatively, and 44% (17) could read fine print after CK.

TABLE 18. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: BINOCULAR CONCURRENT DISTANCE AND NEAR VISUAL ACUITY (n = 106)

VISUAL ACUITY	PREOPERATIVE	3 MONTHS	1 YEAR
20/20 or better and J1 or better	0.9% (1)	51.9% (55)	39.6% (42)
20/20 or better and J2 or better	6.6% (7)	67.9% (72)	70.1% (75)
20/20 or better and J3 or better	10.4% (11)	75.5 % (80)	78.3% (83)
20/25 or better and J3 or better	10.4% (11)	81.1% (86)	79.2% (84)
20/40 or better and J3 or better	10.4% (11)	81.1% (86)	79.2% (84)

TABLE 19. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: CONCURRENT DISTANCE AND NEAR VISUAL ACUITY FOR EYES TREATED FOR NEAR VISION (n = 106)

VISUAL ACUITY	PREOPERATIVE	3 MONTHS	1 YEAR
20/20 or better and J1 or better	—	6.6% (7)	3.8% (4)
20/20 or better and J2 or better	—	11.3% (12)	13.2% (14)
20/20 or better and J3 or better	3.8% (4)	13.2% (14)	24.5% (26)
20/25 or better and J3 or better	3.8% (4)	25.5% (27)	39.6% (42)
20/40 or better and J3 or better	4.7% (5)	46.2% (49)	66.0% (70)

TABLE 20. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: POSTOPERATIVE MANIFEST REFRACTION SPHERICAL EQUIVALENT (MRSE) IN EYES TREATED FOR NEAR VISION (n = 106)

MRSE	PREOPERATIVE	3 MONTHS	12 MONTHS
–2.75 to –2.26 D	—	3.8% (4)	—
–2.25 to –1.76 D	—	7.5% (8)	0.9% (1)
–1.75 to –1.26 D	—	18.9% (20)	8.5% (9)
–1.25 to –0.76 D	—	28.3% (30)	31.1% (33)
–0.75 to –0.26 D	4.7% (5)	23.6% (25)	33.0% (35)
–0.25 to +0.24 D	31.1% (33)	11.3% (12)	19.8% (21)
+0.25 to +0.74 D	34.9% (37)	4.7% (5)	1.9% (2)
+0.75 to +1.24	23.6% (25)	1.9% (2)	4.7% (5)
+1.25 to +1.74	5.7% (6)	—	—

TABLE 21. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: CHANGE IN SPECTACLE-CORRECTED VISUAL ACUITY IN EYES TREATED FOR NEAR VISION (n = 106)

	3 MONTHS		12 MONTHS	
LINES OF CHANGE	NEAR	DISTANCE	NEAR	DISTANCE
+3	—	—	0.9% (1)	—
+2	—	0.9% (1)	0.9% (1)	3.8% (4)
+1	7.5% (8)	17.9% (19)	12.2% (13)	30.2% (32)
0	78.3% (83)	57.5% (61)	78.3% (83)	56.6% (60)
–1	9.4% (11)	22.6% (24)	6.6% (7)	8.5% (9)
–2	2.8% (3)	0.9% (1)	—	0.9% (1)
–3	0.9% (1)	—	0.9% (1)	—

TABLE 22. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: CHANGE IN SPECTACLE-CORRECTED VISUAL ACUITY MEASURED BINOCULARLY (n = 106)

LINES OF CHANGE	3 MONTHS		12 MONTHS	
	NEAR	DISTANCE	NEAR	DISTANCE
+3	—	—	—	—
+2	2.8% (3)	3.8% (4)	3.8% (4)	6.6% (7)
+1	7.5% (8)	28.3% (30)	8.5% (9)	25.5% (27)
0	85.8% (91)	51.9% (55)	84.0% (89)	56.6% (60)
–1	3.8% (4)	15.1% (16)	2.8% (3)	11.3% (12)
–2	—	0.9% (1)	0.9% (1)	—
–3	—	—	—	—

TABLE 23. CONDUCTIVE KERATOPLASTY PRESBYOPIA STUDY: QUALITY OF DEPTH PERCEPTION (n = 82)

SUBJECTIVE RANKING*	PREOPERATIVELY % (n)	POSTOPERATIVELY % (n)
1	1.2 (1)	0.0 (0)
2	4.9 (4)	6.1 (5)
3	41.5 (34)	29.3 (24)
4	34.1 (28)	42.7 (35)
5	18.3 (15)	22.0 (18)

*On a scale of 1 (poor) to 5 (excellent).

TABLE 24. SURGICALLY INDUCED ASTIGMATISM: COMPARISON OF CONDUCTIVE KERATOPLASTY (CK) TO PUBLISHED STUDIES

INVESTIGATORS	STUDY	≥1.0 D ASTIGMATISM
Current study	CK for hyperopia	12%
Hersh et al[6]	PRK (1.5 to 6.0 D)	4%
Hersh et al[117]	LASIK (6 to 15 D)	12%
	PRK (6 to 15 D)	22%
Yi et al[118]	Hyperopic PRK (+0.50 to +4.25 D)	0%
	Myopic PRK (–2.25 to –6.5 D)	24%
Kapadia et al[119]	PRK (–1.0 to –7.0 D)	Approximately 7%
Twa et al[120]	ICRS	4%

D = diopters; ICRS = intracorneal ring segments; LASIK = laser in situ keratomileusis; PRK = photorefractive keratectomy.

TABLE 25. CONDUCTIVE KERATOPLASTY (CK) PROCEDURE DECENTRATION: COMPARISON TO PUBLISHED STUDIES

PUBLISHED STUDY	PROCEDURE	OD R (mm)	OD Ø (°)	OS R (mm)	OS Ø (°)	OD AND OS R (mm)	% IN 0 TO .50-mm GROUP
Current study	CK	0.47	359°	0.49	180°	0.49	61
Schwartz-Goldstein et al[80]	PRK	0.42	332°	0.49	234°	0.46	64
Cantera et al[122]	PRK	—	—	—	—	—	70
Cavanaugh et al[123]	PRK	0.40	185°	0.46	198°	0.40	71
Lin et al[124]	PRK	0.36	—	0.20	—	—	85
Wilson et al[125]	PRK	—	—	—	—	0.78	18

Ø = average meridian of decentration in degrees; PRK = photorefractive keratectomy; R = decentration in millimeters.

DISCUSSION

To date, there have been only three studies of the clinical results of CK published in the peer-reviewed literature.[67,69,70] All of these have assessed the same multicenter clinical trial of the procedure for the correction of hyperopia and have presented basic outcomes. Otherwise, little is known about CK.

In this thesis, an attempt is made to analyze the corneal optics of CK in an effort to gain an understanding of their effects on clinical results, for both hyperopia and presbyopia correction. In this pursuit, the possibility of corneal multifocality, in general, is assessed, with specific regard to SIA and higher-order aberrations.

In exploring such a broad range of CK outcomes in a series of studies, this thesis does suffer from the presentation of results from different, noncomparable patient groups. Studies 1, 2, and 3 all consist of patients from a single prospective clinical trial. However, in study 3, the hyperopic LASIK patient group is taken from a different cohort, which, although age and refraction matched on average, was treated noncontemporaneously and analyzed retrospectively. Similarly, study 4 on presbyopia correction, though prospective, examines an entirely different patient population.

Therefore, it is important that the reader keep these problems in study design in mind when drawing conclusions from the data presented herein. Despite these shortcomings, however, this thesis should elucidate various aspects of the postoperative optics and, thus, the clinical results of the CK procedure.

THE CONDUCTIVE KERATOPLASTY PROCEDURE

Efforts at corneal reshaping via thermal collagen shrinkage generally have met with disappointing results over the last century. Though generally safe, most modalities have been unpredictable in effect and unstable in duration. Although the purpose of this thesis is not to evaluate the general safety, efficacy, and stability of CK, there are unique attributes of the CK surgical strategy that may militate toward a more efficacious result and should be considered.

The magnitude and quality of collagen shrinkage are a function of temperature and time.[99] As discussed in the "Introduction," collagen contraction occurs at temperatures of approximately 50° to 70°C, secondary to the breaking of intramolecular hydrogen bonds, with maximal shrinkage at the higher temperature range.[100] Above this, breaking of intermolecular covalent bonds causes frank tissue destruction.[29] In the CK procedure, time is controlled at 0.6 seconds per application. More important, CK effectuates the temperature increase indirectly through the electrical resistance of the tissue. As a consequence of this mechanism, the increased impedance in areas of collagen denaturation may serve to autoregulate and thus homogenize the increase in temperature, because current naturally will flow to remaining areas of less resistance. Therefore, the CK methodology may afford greater heating control than previous attempts at thermokeratoplasty, both laser and nonlaser, which may be confounded by anterior-posterior temperature gradient effects, tissue hydration variation, and progressive tissue shrinkage during the application.[59]

In addition, corneal biomechanics suggests that homogeneous collagen contracture throughout the greater depth of the cornea in CK may result in a more profound, predictable, and stable result.[101] The laser thermokeratoplasty procedures, as a result of surface application and attenuated effect deeper in the cornea, produce a conical shrinkage architecture, broad anteriorly and dissipating posteriorly.[55,58-60,102] In analogy to a shallow corneal suture, this could result in unpredictable and unstable topography changes.[30] Conductive keratoplasty, in contradistinction, by virtue both of deep probe penetration, with consequent radial and anterior-posterior symmetric effects and of the aforementioned tendency of spatial autoregulation of the current, results in a relatively deep, symmetric, and homogeneous collagen shrinkage architecture. Moreover, although speculative, the stromal lamellar architecture, which is more orthogonal and with less interposition of lamellae posteriorly,[23] possibly could make posterior lamellar shrinkage more efficacious and

predictable.

Although perhaps the most promising thermokeratoplasty procedure to date because of these attributes, whether this collagen shrinkage methodology and unique histologic profile lead to a biomechanical procedure with results substantially better than other thermokeratoplasty techniques awaits further results of long-term clinical investigations. In this thesis, as well as past clinical trials,[67] general efficacy data are good. However, there is evidence of mild regression on average, the clinical implications of which, as yet, are unclear. For instance, in the presbyopia clinical trial herein (study 4), the mean spherical equivalent refraction was –1.01 D at 3 months, shifting 0.33 D in the hyperopic direction over the subsequent 9 months to –0.68 D at 1 year follow-up. This is consistent with stability data from the Phase III trial of CK for hyperopia,[67] where there was an average regression of 0.11 D from postoperative months 6 to 9 and a similar regression of 0.11 D from months 9 to 12 as well. Further studies should elucidate the long-term efficacy of primary CK as well as retreatments.

THE OPTICS OF CONDUCTIVE KERATOPLASTY AND IMPLICATIONS FOR PRESBYOPIA CORRECTION

Multifocality

The findings in this study suggest that many patients following CK have better Snellen visual acuity at distance and at near than might be expected from their residual refractive error. A number of reasons potentially may contribute to this result. By geometric optics, simply correcting a hyperopic eye at the corneal plane instead of the spectacle plane will decrease the necessary accommodation because of lens effectivity, and thus improve near vision in the presbyopic hyperope. For instance, 3.27 D of accommodation is required for a +5 D hyperope to focus at 33 cm when corrected at the spectacle plane. This decreases to 2.90 D when the hyperopia is corrected at the corneal plane. For lower degrees of hyperopia, this difference is less. Lens effectivity alone, therefore, will contribute only a small portion toward presbyopia improvement after CK.

One explanation that may more fully account for the findings is the postoperative production of a multifocal cornea, as generally suggested by previous investigations demonstrating and defining multifocal topography patterns after other types of refractive surgery.[74,103-109] Nonuniformity of the corneal optical surface after CK may create clinical *focal nearpoint areas* or, conversely, *focal areas of emmetropia* that allow the patient to achieve better visual acuity than the refraction may predict, at both near and distance (Figure 10). For instance, in the cohort of hyperopic eyes treated for emmetropia, 51% could see 20/40 or better and J3 or better concurrently despite both presbyopia and a nearly emmetropic refractive error (mean = –0.32 D). Furthermore, as seen in the clinical trial of monovision CK treatment for presbyopia, it is possible that multifocality enhances the effect of mild monovision while preserving distance Snellen acuity in the near eye. For example, two thirds of eyes treated for near vision in the presbyopia trial could see concurrently 20/40 or better at distance and J3 or better at near. This was despite the fact that with respect to near vision, the average postoperative refraction was only –0.68 D myopic and only 9% were more myopic than –1.25 D, and that with respect to distance vision, only 54% were within 0.75 D of emmetropia. Therefore, for both distance and near visual acuity, despite a confounding refractive error, a clear near and distance *signal* (which, indeed, may comprise only a small percentage of the incoming light rays) may be discerned amid a sea of optical *noise* resulting from the nonfocused light rays; thus, focus of at least a small portion of the incoming light may be achieved with, consequently, good visual acuity.

In this way, although the eye's refraction is determined by some average of the entire bundle of rays proceeding through the treatment zone overlying the entrance pupil,[110] focal areas of relative corneal flatness or steepness (or, perhaps more quantitatively, a particular profile of optical aberrations, as will be discussed) may support better distance and near Snellen visual acuity, at least as measured by high-contrast visual acuity charts. Effects on low-contrast visual acuity and contrast sensitivity were not addressed in this study. However, the Phase III report of CK[67] found no change in mesopic contrast sensitivity 6 months after surgery using the Optec 1600X, both with and without a glare source. These findings notwithstanding, it might be expected, in general, that such measures would suffer in the setting of a multifocal cornea.[111-113] Moreover, multifocality likely contributes to adverse clinical optical sequelae of subjective glare and halo effects as well as monocular diplopia and multiplopia.[81,90,95]

The findings of study eyes in comparison to myopic control eyes may be skewed by the fact that study patients had, on average, 0.7 D of refractive astigmatism, whereas myopic control patients were corrected for any preexisting astigmatism. Indeed, potentially important implications of SIA will be discussed below. Nevertheless, the average UCVA of 20/121 in our –2.0 D control patients is similar to the results of Santos and coworkers[108] in the Prospective Evaluation of Radial Keratotomy Study; these investigators found a mean UCVA of 20/125 in 56 unoperated eyes with refractive errors of –2.0 to –2.5 D and an average astigmatism of 0.54 D. Thus, our control group visual acuity findings are similar to the results presented in previously published investigations.

Surgically Induced Astigmatism

Having demonstrated a putative multifocal-like effect after CK, the next part of this thesis sought to elucidate the general implications of astigmatism in clinical outcomes after CK, in general, as well as in presbyopia correction. Thus, the goal here was to quantitate rigorously the SIA after CK, its potential causes, and clinical consequences.

Study Design. This study was done as a cohort substudy of the Phase III multicenter clinical trial of CK for the correction of hyperopia. No retreatments were allowed, so the data assess the SIA of CK without additional intraoperative or postoperative treatment.

Many investigators have stressed the importance of vector analysis when analyzing SIA.[77,79,114-116] Such a methodology is essential to properly assess the actual change in corneal cylinder caused by surgery. There are caveats in clinical interpretation of induced vectoral changes in astigmatism that warrant consideration, however. The mean induced astigmatism derived from vector

analysis gives the centroid of the individual induced astigmatism data. The closer the mean is to zero, the less is the general tendency to induce astigmatism at a specific axis. However, because the data are derived from coordinates that are positive or negative signed functions, in order to quantitate the actual magnitude of induced astigmatism, the absolute values of the Cartesian coordinates need to be used in the vector algorithm.

From a clinical viewpoint, however, the derived values for average magnitude of induced astigmatism may be misleading. First, both increases and decreases in absolute astigmatism are considered induced astigmatism. For instance, 10.4% of eyes after CK had an actual decrease in astigmatism. The vector methodology, however, considers these decreases in astigmatism to be induced astigmatism. Therefore, patients who are clinically improved are presented as having SIA. Second, a small axis change causes a large shift in vectoral induced astigmatism. For example, a preoperative astigmatism measurement of -1.00 D $\times$ 165° and a postoperative astigmatism measurement of -1.00 D $\times$ 180° calculates to an induced astigmatism of 0.52 $\times$ 128°. Although such differences likely fall within measurement error after laser refractive surgery, they will consistently add to the calculated vectoral magnitude change. These two factors—the consideration of an improved magnitude of manifest astigmatism as an induction of astigmatism and measurement error—thus maximize the value of surgically induced magnitude of astigmatism, perhaps leading to a specious interpretation of its clinical significance. Therefore, although vector analysis is the accurate and meaningful method to report induced astigmatism, it is also important to assess the patient's actual refractive circumstance after surgery in order to determine the clinical impact of this astigmatism.

Induced Astigmatism After CK. Twelve percent of eyes after CK had an absolute increase in refractive astigmatism of greater than 0.75 D. Sixteen percent had a vectoral magnitude of SIA of greater than 1.0 D. These findings are consistent with other studies of a variety of refractive surgery procedures[6,117-120] (Table 24). Regarding the angle of induced cylinder, there was a statistically significant tendency, though mild in magnitude, toward against-the-rule astigmatism. Speculatively, this may be due, in part, to the influence of corneal microarchitecture on the biomechanical response, somewhat analogous to putative effects of lamellar flap retraction on induced astigmatism and aberration profile in LASIK.[121] There were no significant associations of SIA with the eye (right or left) treated, the number of CK spots, or procedure decentration.

Clinical Effects of SIA After CK. When analyzing SIA after refractive surgery, it is important to ascertain any negative clinical consequences that may result. As expected, since refraction is other than plano with induced cylinder, there was a statistically significant decrease in distance UCVA in the higher-induced cylinder group compared with the group with lower-induced cylinder (Table 10). However, uncorrected distance acuity was still markedly improved, averaging 20/33 (compared with 20/27 in the low astigmatism group). The influence of SIA on near vision will be discussed shortly.

Of note, there was no association of SIA with poor clinical outcomes of loss of BSCVA or induced night glare or halo.

CK Centration. As a substudy, the accuracy of CK centration was analyzed because decentration might be expected to have deleterious refractive and clinical consequences. The CK procedure is centered on the entrance pupil, the generally accepted approach in corneal refractive surgical procedures.[71] Average decentration from the entrance pupil was 0.49 mm. This is comparable to previously published studies of other refractive surgery procedures (Table 25).[80,122-125] There was no correlation of decentration with the number of CK spots applied. This might be expected, because the surgeon applies the inner 6-mm annulus of spots first, thus substantially defining the procedure centration at that point. The subsequent addition of more peripheral spots likely does not have a significant effect on the ultimate decentration of the procedure.

Mean decentration was located nasally in both eyes, although this was not a significant finding. Centration of refractive surgery procedures in general may be complicated by the fact that the pupil does not dilate and constrict symmetrically. The geometric center of the entrance pupil has been shown to shift by as much as 0.4 mm to 0.7 mm at the extremes of pupil diameters, although the extent of this effect is not likely to be greater than 0.2 mm.[126,127] Moreover, there tends to be a nasal shift with miosis. Thus, even if a procedure is centered correctly on the entrance pupil at the time of surgery, if performed in a lighting situation different from that when the topography map is taken, the optical zone may be off-center on the map. Since the CK procedure is generally performed under the bright light of the operating microscope, it might be expected that this miosis would cause an average tendency for nasal decentration from the pupil center existing in natural light circumstances or in low illumination.

Although not statistically significant, the decentration from the corneal vertex was less than from the pupil center, a paradoxical finding because the goal was to center the procedure on the pupil. Unlike laser refractive surgical procedures, the biomechanical strategy of CK could be implicated in this finding. As noted in the "Introduction," a single CK spot will tend to move the corneal apex away from the application.[32] Although speculative, when placed in an eight-spot annulus, it is thus possible that the procedure tends to center the apex within the CK ring. Further investigation of the corneal biomechanics of CK should elucidate the actual topographic effects.

Astigmatism and Multifocality. The general notion of multifocality can be expanded and described quantitatively by the concept of lower- and higher-order optical aberrations. It is first important to consider that better-than-expected near and distance acuity (based on refractive error) after CK could result, in part, simply from postoperative astigmatism, a lower second-order aberration. Induced cylinder could leave the patient with an expanded interval of Sturm, and hence a greater depth of field. As described by Sawusch and Guyton[128] in a theoretical model, a certain degree of astigmatism, indeed, may be useful. Although never producing a crisp focus, it may produce a situation of pseudoaccommodation, improving nearpoint function in the presbyopic patient without substantial loss of distance acuity. These investigators, calculating cross-sectional area of Sturm's conoid on the retina in a schematic eye, found that the optimal depth of focus was obtained when the plus cylindrical component of the refraction equaled negative sphere – 0.25 D; that is,

plus cylinder = –(sphere) –0.25, when the spherical equivalent is –0.25 D or less. Their model indicated that the least amount of summated blur, when measuring object distances from 0.5 to 6 meters, occurred at refractions of –0.25–0.75 and –0.25–0.50, followed by –0.25–1.50 and –0.25–2.50. Clinically, in pseudophakic patients, these refractions led to distance visual acuities of 0.67, 0.67, 0.29, and 0.29, respectively, and near visual acuities of 0.80, 0.67, 0.80, and 0.67, respectively.

These results are consistent with the findings herein. For instance, study 1 of multifocality found that 51% of eyes had concurrent uncorrected distance and near vision of 20/40 or better and J3 or better, respectively, after CK for hyperopia. Study 2 of induced astigmatism found that 54% had more than 0.25 D increased astigmatism. Although the patient cohorts are not identical, this does suggest that postoperative astigmatism could play a role in effecting an enhanced depth of field. Similarly, in study 4, in which a myopic refraction was targeted for monovision, the mean postoperative spherical equivalent refraction was found to be –0.68 D and the mean astigmatism was 0.51 D. Here, 66% of eyes had concurrent uncorrected distance and near vision of 20/40 or better and J3 or better, respectively, a finding consistent with Sawusch and Guyton.[128]

The orientation of astigmatism may also be important with regard to near vision. With-the-rule astigmatism may be better tolerated, because the vertical strokes of letters are more important for recognition when reading letters such as b, d, h, t, p, y. Furthermore, there is less space between letters on a line than between lines. In such circumstances, it is most useful to have a better focus in the vertical meridian, as is produced by with-the-rule astigmatism.[129] In study 2, however, there was a tendency for CK to shift the axis against-the-rule on average, a finding which, theoretically, would not be optimal for reading vision.

Wavefront Aberrations and Multifocality

As already seen, most patients following CK enjoy better visual acuity at distance and at near than might be expected from their residual refractive error, and thus far have posited optical effectivity, multifocality, and induced astigmatism as possible factors contributing to this finding. To extend this analysis of CK optics, study 3 investigated wavefront-derived higher-order aberrations induced by the procedure.

The field of wavefront analysis and the detection and quantification of higher-order aberrations have recently become topics of great interest. Most work to date has been directed at the diagnosis of adverse postsurgical optical sequelae.[90,94,95,113] It has been well established that myopic excimer laser surgery increases higher-order aberrations.[82-85,88-94,96] Although less work has been directed at changes in the aberration profile following hyperopic surgery, research by one group suggests that hyperopic LASIK introduces more dramatic changes in higher-order aberrations compared with myopic treatments.[86] To date, there are no published studies of wavefront aberrations after CK.

Changes in Higher-Order Aberration Profile After CK. Significant increases in higher-order aberrations were found after CK in this study. Composite fourth- to sixth-order aberrations through a 4.0-mm pupil more than doubled. This is similar in magnitude to values previously reported following hyperopic PRK.[86,130] In comparison to laser procedures for myopia, total cornea aberrations have been reported to have increased on average 1.7-fold with a 3-mm pupil by Oshika and coworkers,[82] and up to 3.72-fold using a 6.5-mm pupil by Marcos.[94] (In assessing wavefront data, it should be noted that varying pupil sizes used for aberration measurements complicate comparison among studies, because changes in pupil size over which the wavefront is measured will significantly impact the magnitude of individual aberrations.[81,82,84,85])

Analysis of specific aberrations composing the composite wavefront showed that spherical aberrations (including fourth and sixth order) were significantly increased after CK. Important from the clinical viewpoint and with respect to multifocality and improved nearpoint acuity, this change in asphericity was in the direction of a more prolate corneal contour (Figure 21). This might be expected, intuitively, on the basis of the biomechanical topographic changes induced by CK (Figure 7) as discussed previously; that is, midperipheral flattening over and proximal to the CK applications with central steepening. Analysis of the fourth-order spherical aberration component (Z^{12}) alone showed no statistically significant change, however.

In addition to the composite spherical aberration, total coma (third and sixth order) was significantly increased after CK. Since they may have different clinical effects, vertical coma and horizontal coma were analyzed separately. Vertical coma showed a significant increase, whereas horizontal coma showed a significant decrease. The cause of this is less apparent than for spherical aberration. As speculated for induced astigmatism, perhaps the meridional corneal microarchitecture influences biomechanical reshaping induced by collagen shrinkage.

Comparison of Changes in Higher-Order Aberration Profile: CK Versus Hyperopic LASIK. For myopic LASIK procedures, changes in the aberration profile most notably have been increases in spherical aberration. The contour of the cornea has been shown, both in clinical and in theoretical work, to change from a prolate shape to a more oblate conformation after myopic excimer laser procedures.[88,131-133] This asphericity change and induction of a more oblate corneal profile have been implicated in a less-than-optimal image quality.[134] In hyperopic LASIK, ablation of the tissue more peripherally compared with myopic treatments might be expected to have a reverse effect on corneal asphericity, causing the cornea to become more prolate. Indeed, an accentuated prolate profile following hyperopic LASIK treatment has been described.[135]

Significant increases in higher-order aberrations were found after hyperopic LASIK in this study. Composite fourth- to sixth-order aberrations through a 4.0-mm pupil more than doubled. However, there were no significant average changes in either the composite spherical aberrations (fourth and sixth order) or spherical aberration (Z^{12}) alone. As can be seen in Figure 24, this is likely because some eyes changed in the prolate direction and others became more oblate. Thus, in comparison to CK, in which most eyes become more prolate, the directional change in spherical aberration after hyperopic LASIK was less predictable. One reason for this is a potential splinting and masking effect of the LASIK flap; that is, the flap may not perfectly conform to the ablation profile and, thus,

alter the desired optical architecture.[136] Indeed, flap dynamics may introduce aberrations entirely unrelated to the ablation.[121]

As in CK, total coma was increased in hyperopic LASIK. However, unlike in CK, parsing total coma into its vertical and horizontal components showed no statistically significant difference for either vertical or horizontal coma.

In the direct statistical comparison of the two procedures, there was no difference in induction of total higher-order aberrations. Thus, neither procedure, on average, would be expected to induce fewer aberrations in toto. It was confirmed that induction of spherical aberration, both composite fourth- and sixth-order as well as fourth-order Z^{12} alone, was significantly different comparing the CK and hyperopic LASIK cohorts. CK induced more consistent negative spherical aberration (prolateness) than hyperopic LASIK. Although changes in coma were significant in CK, there was no difference in coma induction comparing the two procedures directly.

Again, it should be stressed that the analyses of higher-order aberrations after CK and LASIK in this thesis were performed retrospectively on distinct patient groups, and procedures were not contemporaneously performed. Thus, these results need to be assessed and interpreted with this drawback in study design in mind.

Higher-Order Aberrations and Corneal Multifocality After CK. As discussed, the general concept of multifocality can be thought of as an amalgam of (1) differential refractive errors over the optical zone, secondary to an inhomogeneous corneal topography[74,105,137-141]; (2) postoperative astigmatism; and (3) higher-order optical aberrations. Higher-order aberrations, historically, have been considered clinically problematic. The consequent "static" in the visual system can decrease the *signal-to-noise* ratio and potentially result in visual sequelae such as glare and halo. Indeed, the current effort in laser refractive surgery is to minimize such postoperative aberrations.

However, there is evidence that shows that some aberrations in the visual system may actually improve visual function.[142] For instance, the natural negative asphericity of the native cornea counteracts the inherent positive spherical aberration of the lens.[143,144] Moreover, and with greater implications for presbyopia management, there is the possibility that some aberrations increase depth of field or produce a multifocal effect. In this study, increased spherical aberration and vertical coma were found as statistically significant features after CK. One might conjecture from a clinical vantage point that these aberrations render the postoperative cornea analogous to a multifocal contact lens. The central steepening with midperipheral flattening could be thought of as a center-surround "bull's-eye" multifocal, with greater power centrally to effect better reading vision and better distance vision from the peripheral optical zone. Similarly, the increased vertical coma could be thought of as a bifocal with upper and lower segments devoted to different foci. Though intriguing, further investigation is necessary to elucidate these putative effects.

MONOVISION CORRECTION OF PRESBYOPIA

Background

The concept of correcting one eye for distance and the fellow eye for near gained acceptance and utilization for the treatment of presbyopia historically with the advent and development of contact lenses. Eyeglasses did not allow clinicians to use this strategy for presbyopic correction because of the induction of prism with changes in versions. The average distance that the eye traverses across spectacle bifocal lenses when going from distance fixation to nearpoint fixation is 8 mm. If the distance lens powers are equal, no vertical prism is induced. Otherwise, the difference in distance power in D between right and left lenses along the vertical meridian, when multiplied by this distance in centimeters, equals induced vertical imbalance in prism diopters. For instance, if a single-vision eyeglass prescription is prepared (for example, OD plano, OS +2.50), this refractive disparity will result in two prism diopters of binocular imbalance. This may be tolerable horizontally but will be intolerable vertically. With correction at the corneal plane with contact lenses or corneal refractive surgery, however, the induction of prism is minimized, since the optical center moves with the eye.

Monovision can be achieved by applying an add to an emmetropic eye, or by overcorrection of hyperopia or undercorrection of myopia in one eye. In general, the use of the dominant eye for the distance correction, with the reading prescription worn on the nondominant eye, is recommended. This generally assumes that corrected visual acuity is roughly equivalent in both eyes. Where a modest visual deficit exists and the patient is still acceptable for monovision, the better eye may be selected for distance. Similarly, visual asymmetries may suggest changes in this rule; when seeking the most comfortable distant/nearpoint arrangement, some patients prefer reversing distant and nearpoint eyes. For instance, it has been suggested that the less myopic or more hyperopic eye should be corrected for near vision, because by the optical principle of effectivity, as has been discussed, correction of hyperopia at the corneal plane will call for less accommodative effort, whereas correction of myopia at the corneal plane will require more accommodation.[145]

The dominant eye is usually determined by sighting tests (for example, hole-in-card at arm's length), handedness, and observation. The nondominant eye generally is selected to receive the add. However, trial contact lens fitting with analysis of patient response should be used as a final basis for selection of the nearpoint eye.

When looking for related phenomena that might lend support to the concept of monovision, one might observe the once common use of the monocle, and most clinicians have encountered the unilateral myope who does not accept glasses.[146] Similarly, the transient suppression accomplished by persons using monocular optical instruments (microscopes, telescopes) demonstrates the commonality of this capability.

Despite frequent success, concern still remains about the effect that monovision, with its implicit iatrogenic anisometropia, has on binocular visual acuity, contrast sensitivity, peripheral vision, visual field width, and binocular depth of focus. Whereas binocular contrast sensitivity does show a significant reduction in some studies, the other aspects of binocular vision generally reveal a minimal effect. Jain and colleagues,[147] in a review of monovision, reported that as the nearpoint add increases and, thus, monocular defocus increases, binocular contrast sensitivity decreases. This may make monovision less suited for fine detailed work of a concentrated and

extended nature. Clinically, such situations are frequently resolved by an overglass focusing the distance eye for the nearpoint. These investigators also reported that monovision causes no significant effect on peripheral visual acuity or visual fields. In other work, reporting on a monocular reading study done on 16 adults, Knehr[148] noted that monocular reading time, fixation frequency, and regression frequency did not differ significantly from binocular. Additionally, he found that vergence movements found in binocular eye-movement records retained their characteristic form and approximate magnitude in monocular reading.

Among other reservations and questions prompted by the monovision model is the introduction of unwanted aniseikonia. For instance, if a patient is corrected with a +4.0 contact lens in one eye and +6.50 in the other, image magnification will be 1.1% and 1.2%, respectively. However, this difference is substantially within the tolerance limit of 5% overall for binocular fusion.[149]

Adaptation

Successful monovision requires cortical adaptation and suppression by the patient. Some investigators favor younger patients with lower add powers, because with greater anisometropia, patients may experience imbalance and disorientation during the first few days of a monovision trial.[146] Although lower add powers may constitute a lesser impediment to binocularity at the outset of monovision adaptation, it does not foreclose monovision for more advanced presbyopes. Numerous anecdotal reports speak to the efficacy of large add powers still allowing patients comfortable adaptation and successful use of the system. Indeed, Schor and coworkers[150] suggest that higher add powers actually facilitate suppression by increasing the amount of anisometropia. Bier[151] has noted that patients with monovision may take a month or two to adapt, but thereafter are often free of symptoms without visual imbalance or undue loss of spatial perception. He also suggests prescribing a distance correction lens for the reading eye in some cases where the patient requires optimal distance vision for long periods of time. Similarly, as discussed earlier, converting the distance eye to a nearpoint prescription during periods of long-term concentrated close visual work often is subjectively appreciated by the patient.

The paramount attribute necessary to make a functional adaptation to contact lens monovision is *inter*ocular central suppression. This is in contradistinction to *intra*ocular suppression, which presumably allows one to make productive use of a multiplicity of images such as found in many iterations of current bifocal contact lenses and intraocular lenses. Interocular suppression allows one to choose between using the right or left eye image and to ignore the opposite. Conversely, intraocular suppression refers to suppressing portions of a potentially confusing single image. The patient with monovision CK, for instance, may require components of both interocular and intraocular suppression as a result of anisometropia and multifocality, respectively.

Hom[152] has investigated personality traits that are more conducive to adapting to monovision, citing traits such as "adaptability, holistic bent, optimism, superego strength, conscientiousness, persevering, determined, moralistic, cooperative, realistic, hopeful, and duty-bound." Opposite traits are listed as "self-pity, emotionally dependent, and fickleness." In the same study, he noted that under scotopic conditions, the suppression of blur becomes less effective, accounting for night driving visual problems. Indeed, a significant number of patients report glare under these conditions. In other work, Schor and colleagues[153] report 33% of monovision patients experience night driving glare. They suggest that interocular suppression of blur is most effective under photopic viewing conditions, but that anisometropic blur is not as readily suppressed under mesopic and scotopic luminance conditions. Therefore, patients may see a large, out-of-focus headlight image in the near eye and a much smaller, clearer, image in the distance eye. Supporting this hypothesis is the work of Helmholtz,[154] in which he noted that the perceived size of bright, high-contrast objects on a dark background is exaggerated in comparison to the reverse contrast condition, that is, dark on bright. Although this has not yet been studied, it is possible that CK monovision, with possibly less anisometropia and less loss of distance visual acuity than contact lens monovision, could thus lead to relatively better night visual function as compared with contact lens monovision.

Jain and coworkers[147] reported that, in general, interocular suppression is greater for small nearpoint additions in unadapted cases (1 or 2 days). However, suppression of the blurred eye at near ultimately is enhanced by increasing the amount of anisometropia. Blur suppression increased in 50% of patients after 2 months of adaptation when the dominant eye was corrected for distance. It increased only 28%, however, in patients where the nondominant eye was assigned to distant sight. Therefore, the surgeon should be cautioned against contact lens trials with monovision that are too brief, since there seems to be better suppression after a longer period of adaptation. In addition, these data might encourage higher adds, especially on the nondominant eye, with consequent better suppression.

General Results With Monovision

Notwithstanding the theoretical obstacles to successful monovision, many sources are in agreement that with proper selection, the majority of patients can achieve success. Jain and colleagues[147] report that a review of the contact lens literature showed a mean monovision contact lens success rate of 76%. They found that patients who were dissatisfied with monovision had strong sighting preferences, significant reduction in stereoacuity, minimal interocular suppression, and large esophoric shifts. In particular, factors that influence monovision success were noted to be:

1. Dominant eye: Visual input via the dominant eye produces a greater cortical response than that from the nondominant eye. Thus, the success rate in monovision generally is improved with the distance correction on the dominant eye.
2. Interocular suppression of blur: In successful monovision wearers, the interocular suppression of blur was approximately two orders of magnitude greater than in unsuccessful monovision wearers.
3. Age distribution: There were no significant differences in age distribution observed between successful and unsuccessful monovision wearers.
4. Stereoacuity: Unsuccessful monovision patients demonstrated a greater reduction in stereopsis compared with successful patients by a factor of 50 to 62 arc seconds.

5. Phorias: An esophoric shift was noted to be somewhat greater in unsuccessful monovision patients. (In speculating on a cause for this esophoric shift, one is tempted to regard the suppression phenomenon as a form of occlusion of the suppressed eye, thus vitiating the central fusional control over the phorias.)

These investigators further report that patient satisfaction after monovision laser refractive surgery ranges from 72% to 81%. (In comparison, in study 4 of CK monovision, 84% of patients were either satisfied or very satisfied with their outcome.) The inference was that these patients were able to accomplish at least the minimal degrees of interocular suppression to make monovision usable.

Other Considerations

Surgically accomplished monovision, optically, is qualitatively different from contact lens monovision, as seen in the studies herein. It has been the goal of this thesis to define the optical properties unique to the post-CK cornea. As previously discussed, after CK surgery, myriad multifocalities may be introduced over and above the refractive monovision modality; the newly reformed cornea is not simply the original cornea with a different power. Moreover, changes in astigmatism and the corneal aberration profile may enhance CK monovision correction, leading to a greater depth of field with less frank refractive anisometropia. How these affect one's suppression capabilities and ultimate acceptance has yet to be fully examined, however. This notwithstanding, the results of subjective patient questionnaires in this study suggest general patient acceptance of the CK monovision result.

Given the unique optical architecture of the cornea after refractive surgery, in general, and CK, in particular, although a contact lens trial of monovision may be considered somewhat of a predictor of postoperative success, this may not properly mimick the surgical outcome. The postoperative cornea has a new cluster of higher-order aberrations, which taken together with the refractive alterations, may diminish or magnify postoperative monovision adaptation in comparison to simple contact lens correction.

PRESBYOPIA CORRECTION WITH MONOVISION CONDUCTIVE KERATOPLASTY

Having now looked at the postoperative corneal optics of CK and having reviewed some of the historic success with monovision, it is interesting to assess the clinical results of presbyopia correction with monovision CK.

Study Design

This multicenter clinical trial utilized the same CK procedure and nomogram as studies 1 through 3 did in analyzing CK optics. The only difference was that retreatments were allowed in the monovision study. Eleven percent of eyes did undergo retreatment. This should be considered when comparing the different studies presented.

OUTCOMES

Visual Acuity. In the monovision eyes, 76% and 77% saw J3 or better at near at 3- and 12-month follow-up, respectively. Forty-six percent and 35% saw J1 or better at 3 and 12 months, respectively. The slight loss in acute near vision can be explained by the change in mean postoperative refraction from –1.01 D to –0.68 D from 3 to 12 months; thus, some of the refractive monovision correction was lost over time. This is consistent with previous reports of CK refractive stability.[67] Perhaps more important in a study such as this is the binocular setting, because the patient's goal is to have good functional near vision without correction. Thus, the impact of the distance eye on near function warrants consideration. Here, 72% and 80% saw J3 or better at 3 and 12 months, respectively, and 47% and 42% were J1 or better. Curiously, despite loss of refractive monovision correction, more patients actually met the J3 or better window at 1 year, speculatively as a result of cortical adaptation to their monovision binocularity over time.

Another outcome indicating a successful monovision result is maintenance of good distance visual function. Binocularly, all patients were 20/40 or better at both time points. All were 20/20 or better at 1 year, and 94% were 20/20 or better at 3 months. Furthermore, only one patient lost 2 or more lines of BSCVA in the treated eye; 9% lost 1 line. Loss of spectacle-corrected visual acuity after CK presumably is caused by irregular induced astigmatism, since no corneal opacity or ocular surface abnormality was seen.

Perhaps the best indication of a successful monovision CK result is the likelihood of a patient achieving good uncorrected distance and near visual acuity, concurrently, because the patients' goal is to improve near vision without compromising distance vision function. Looking at this, 81% and 79% of patients were both 20/40 or better at distance and J3 or better at near, at 3 and 12 months, respectively.

It also is interesting to note that 93% of eyes treated for near vision actually retained 20/40 or better distance acuity. Similarly, 66% of these eyes could see both 20/40 or better at distance and J3 or better at near, concurrently. By comparison, in study 1, where patients were treated for hyperopia with an emmetropic, not near vision, goal, 51% concurrently could see 20/40 or better at distance and J3 or better at near. Thus, the similarity of findings in these two studies would seem to support the concept of multifocality in the post-CK cornea.

Patient Satisfaction and Subjective Visual Function. Patient satisfaction and unaided visual function are of utmost importance in an elective procedure such as monovision CK. Eighty-four percent of patients were satisfied or very satisfied with the outcome of the procedure, a rate similar to the report by Jain and colleagues[147] of a 76% success rate with monovision contact lenses. Importantly, patient satisfaction was associated with near UCVA of J3 or better in the monovision eye, a statistically significant outcome. This finding suggests that the foremost criterion for success in the monovision-CK procedure is good uncorrected postoperative near visual acuity.

There was no association of patient satisfaction with gender, age, monocular versus binocular treatment, or loss of distance visual

acuity in the treated eye to less than 20/40. This last finding is curious and suggests that patients undergoing monovision CK may be willing to lose some distance visual acuity in the treated eye if they gain good reading vision. To some extent, however, this notion is belied by the finding that lack of satisfaction with the procedure was associated with lower subjective grades of postoperative depth perception. Therefore, it may not be the loss of distance acuity per se, but the subjective perception of impaired binocularity that decreases patient satisfaction. These findings, too, are supported by Jain and colleagues,[147] who in reviewing monovision in general found that unsuccessful monovision patients demonstrated a greater reduction in stereopsis compared with successful patients. In interpreting these outcomes, moreover, it is important to note that all patients in this study had tried monovision contact lenses with success. Those who were intolerant did not undergo surgery. Therefore, the cohort undergoing surgery potentially was biased, excluding those who a priori demonstrated inability to accept the decrease in distance vision function implicit in monovision. Without this exclusion criterion, it is likely that overall satisfaction rates would be less. Although, as discussed earlier, contact lens monovision may not accurately reflect the optics of the postoperative monovision CK situation, these findings do suggest the continued benefit of a preoperative monovision contact lens trial in an effort to exclude patients who may not be able to tolerate distance vision compromise. Certainly, further studies directed at quantitatively assessing binocular function and stereopsis before and after CK would help both to elucidate the clinical outcome of CK and to further identify those patients who may not be good candidates

An assessment of everyday tasks suggests relatively good functional results after CK monovision. Subjective data on near, intermediate, and distance vision similarly were encouraging. Near vision was better or significantly better in 84%, again similar to the patient satisfaction rate. With regard to intermediate vision, 73% improved and 5% worsened. For distance vision, where one would expect the least subjectively positive results, 34% actually improved whereas 11% worsened; 77% remained the same. Again, the impact of the low degree of anisometropia and possible corneal multifocality (for all the reasons discussed) must be considered in assessing these results. Both possibly could influence cortical adaptation to monovision, as well as the actual need and/or ability to suppress blurred images both interocularly and intraocularly.

CONCLUSION

It has been the goal of this thesis to define the corneal optics resulting from CK. In addition, the implications of these findings to CK clinical results, in general, and to presbyopia correction, in particular, have been addressed.

As demonstrated, optical factors that may militate toward improved near vision function after CK include (1) accommodative implications of effectivity when hyperopia is corrected at the corneal plane, (2) corneal multifocality in general, (3) surgically induced corneal astigmatism, and (4) higher-order optical aberrations, particularly changes in spherical aberration (with a more prolate contour after CK) and vertical coma. However, the corneal optics after CK are complex and the optical predictability of the procedure remains to be assessed. Concepts of multifocality and the implications thereof, although beginning to be elucidated, remain as yet not fully defined.

The clinical trial of monovision CK demonstrated encouraging outcomes. Near visual function improved without loss of distance function in many patients, possibly potentiated by the changes in corneal optics described. However, a perceived loss of binocularity and depth perception may lead to patient dissatisfaction. The successful CK monovision patient, thus, appears to be one who achieves good near UCVA, but without loss of good distance binocular function. It remains for future clinical and basic investigation to further define optical and visual function after CK, and to better guide the surgeon, preoperatively, to those patients who may not achieve the desired outcome.

ACKNOWLEDGMENTS

The author would like to acknowledge the following individuals for their assistance: Kristen Fry, OD, Donald Hersh, OD, and the Conductive Keratoplasty Investigators Group (Penny Asbell, MD, Jonathan Davidorf, MD, Daniel S. Durrie, MD, David Hardten, MD, Richard Lindstrom, MD, Robert K. Maloney, MD, Edward E. Manche, MD, Marguerite B. McDonald, MD, Louis Nichamin, MD), who contributed data from the multicenter clinical trials discussed in this thesis.

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