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Polymer Refilling of Presbyopic Human Lenses In Vitro Restores the Ability to Undergo Accommodative Changes

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Purpose. Because presbyopia is thought to be accompanied by increased lens sclerosis this study was conducted to investigate whether refilling the capsule of the presbyopic human lens with a soft polymer would restore the ability of the lens to undergo accommodative changes.

Methods. Accommodative forces were applied to natural and refilled lenses by circumferential stretching through the ciliary body and zonular complex. Nine natural lenses and 10 refilled lenses from donors ranging in age from 17 to 60 years were studied. Two refill polymers with a different Young's modulus were used. The lens power was measured by a scanning laser ray-tracing technique, and lens diameter and lens thickness were measured simultaneously while the tension on the zonules was increased stepwise by outward pull on the ciliary body.

Results. In the natural lenses the older lenses were not able to undergo power changes with stretching of the ciliary body, whereas in the refilled lenses, all lenses showed power changes comparable to young, natural lenses. The refilled human lenses had a higher lens power than the age-matched natural lenses. The Young's modulus of the polymers influenced the lens power change when measured with the ciliary body diameter increased by 4 mm.

Conclusions. Refilling presbyopic lenses with a soft polymer enabled restoration of lens power changes with mechanical stretching. Because sclerosis of the lens is an important factor in human presbyopia, refilling the lens during lens surgery for cataract could enable restoration of clear vision and accommodation in human presbyopia. (*Invest Ophthalmol Vis Sci.* 2003; 44:250–257) DOI:10.1167/iovs.02-0256

Accommodation is the ability of the human eye to change the optical power to focus images of far or near objects on the retina. The onset of presbyopia—that is, the decline of accommodative amplitude—usually occurs at approximately 45 years of age. At this point, most people require reading glasses. Today, attempts at surgical correction of presbyopia (with or without simultaneous cataract surgery) are receiving considerable attention,[1–7] yet the feasibility of restoring the accommodative capacity remains unclear.[8]

There are several structures in the human eye that contribute to the process of accommodation. Cramer[9] studied the lens Purkinje images and showed that accommodation is associated with an increase in anterior lens curvature. Helmholtz[10] showed that this increase in curvature is achieved by contraction of the ciliary muscle. His explanation of the accommodative mechanism is still generally accepted today.[11] According to his theory, contraction of the ciliary muscle releases the circumferential tension on the zonules, keeping the lens in suspension. The elasticity of the lens capsule and the lens nucleus and cortex enable the lens curvature to increase. During disaccommodation the tension of the zonular fibers, which insert into the ciliary body and choroid, increases, thus pulling the lens back into its disaccommodated, flattened state. All the structures involved in accommodation (lens capsule, lens nucleus and cortex, zonula, ciliary muscle, and choroid) show age-related changes that may explain the onset of presbyopia at the approximate age of 45 years. However, many investigators consider hardening of the lens nucleus and cortex to be an important factor. It seems to provide a logical explanation of presbyopia, because the lens changes its shape during accommodation. Pau and Kranz[12] described the simultaneous increase of lens sclerosis and decrease of accommodative ability. Fisher,[13] by placing lenses on a rapidly rotating table, demonstrated that older lenses are more resistant to deformation than younger lenses. Glasser and Campbell[14] established that older lenses, when exposed to equatorial stretching forces, show less change in focal length than younger lenses. If the lens nucleus and cortex are responsible for presbyopia, replacement of the hardened lens substance by a suitable soft, transparent polymer may restore the accommodative range. Such a replacement is certainly conceivable in combination with cataract surgery. Several investigators[15–19] have refilled the lens capsule in animal eyes. A number of publications[18,20–22] describe experiments to establish accommodative changes in young monkeys' eyes. Presbyopia tends to develop in these monkeys at 25 years of age.[23] Haefliger and Parel[24] found evidence of accommodative changes in response to intracameral pilocarpine treatment of presbyopic monkeys' eyes after refilling the lens capsule, which confirms that lens capsule refilling can restore accommodation. With their indirect lens change measurements, they indicated the limitations of their conclusion (they measured a decrease in anterior chamber depth instead of refractive changes). Although promising, these results pertaining to monkeys' eyes do not necessarily show that accommodation can be restored to the human lens by lens refilling. We therefore used a technique described by Glasser and Campbell[14] to study the effect of refilling the human lens in vitro on induced changes in focal length. A series of reference measurements were obtained in a set of human lenses in their natural state.

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MATERIALS AND METHODS

Human donor eyes (sometimes in pairs) were obtained from the Netherlands Ophthalmic Research Institute Corneabank. The donors' ages ranged between 17 and 60 years. In most cases, the corneas had been removed. The eyes were packed on ice for shipment from Amsterdam to Groningen and were stored at 4°C until they were used the same day, between 2 and 5 days after death.

The eyes were then randomly allocated to either a refill lens group or a natural lens group. Ten eyes underwent surgery to refill the lens capsular bag with a silicone polymer, and nine eyes were exempt from lens surgery. In all cases in which a pair of eyes originating from the same subject were obtained, one eye underwent lens-refilling surgery, and the other was used as a reference, without surgery. Single eyes were randomized—that is, they were allocated to either group, to obtain a comparable age distribution for both groups. Inclusion criteria stipulated eyes aged less than 60 years, because manual aspiration of the lens nucleus and the cortex of older, sclerotic lenses was too difficult.

The eyes were inspected under a surgical microscope. Eyes in which the ciliary body had been damaged during removal of the cornea were excluded from study. The iris was removed with scissors. Lenses in the refilled-lens group underwent lens-refilling surgery and were subsequently mounted in a lens-stretching device. Lenses in the natural lens group were mounted in the lens-stretching device without lens-refilling surgery.

Lens Refilling: The Surgical Procedure

During lens refilling, the lens remained in its natural position in the eye. The anterior capsule of the lens was punctured with a 27-gauge needle. With appropriate forceps, a minicircular capsulorrhexis of 1 to 1.5 mm was created in the periphery of the lens. The lens substance was aspirated manually with an 18-gauge cannula connected to a 10-mL syringe by an extension tube. In older eyes, the aspiration process was more time-consuming, because of advanced sclerosis of the lens. A 2.7-mm diameter silicone plug was then inserted into the capsular bag to prevent polymer leakage during refilling. A two-component silicone polymer (A and B; Pharmacia, Groningen, The Netherlands) was mixed and was briefly exposed to a vacuum to remove any air bubbles. The polymer was then injected into the capsular bag with a 5-mL syringe with a 25-gauge cannula. Injection proceeded until the polymer began to leak past the capsular plug. Finally, the cannula was retracted, and the plug was manipulated into position to close the capsulorrhexis.

Silicone Polymers

Two different types of silicone polymers were used. The first one (Sil1) was injected into the first four eyes and attained a Young's modulus of 3.6 kPa after polymerizing for 22 minutes at 20°C. However, the Young's modulus increased continuously for several weeks, which ruled out this substance for future use as a lens refill material. A second type of silicone polymer (Sil2), developed later, exhibited a Young's modulus of 0.8 kPa after polymerizing for 70 minutes at 20°C. In this case, Young's modulus remained constant for 100 days. At 35°C, the final value was reached in 30 minutes. This material was injected into six eyes. For comparison, the Young's modulus of a 20-year-old human lens is approximately 1 kPa.[13] Both silicone types exhibited a refractive index of 1.428.

Mounting the Lens in the Stretching Device

To separate the lens, together with the anterior segment tissue, from the remainder of the eye, the ciliary body was separated from the anterior sclera by blunt dissection. The anterior sclera was cut away to expose the ciliary body and the anterior choroid. In the next step, a plastic ring with an inner diameter of 33 mm was placed around the exposed choroid. Twelve sutures (8-0 virgin silk) were knotted to the ciliary body and threaded through 12 holes that were radially drilled and evenly spaced around the ring (Fig. 1). The sutures were then immobilized by threading them through corresponding holes in a concentric outer ring, equipped with small plugs. The tension on the sutures was individually adjusted to make sure that the ciliary body remained unstretched but the sutures were not loose, either. After applying the sutures, a circumferential cut was made through the choroid in the region of the ora serrata to separate the anterior segment tissue from the posterior segment of the eye. The anterior segment tissue comprised the ciliary body and the ciliary muscle, the lens, and the zonular complex. This anterior segment tissue, with the lens still naturally suspended by the intact zonule, was then lifted off the globe, and remaining vitreous adhesions were cut. The outer plastic ring could be made to rotate around the inner ring, to simultaneously increase the tension of all the sutures. The amount of stretch correlated linearly with the rotation of the outer ring. The rings, together with the sutured ciliary body and lens, were mounted on a stepper motor that controlled the rotation of the outer ring. The entire arrangement was then submerged in a rectangular glass tank with a volume of 24 × 10 × 10 cm, filled with a saline solution consisting of 8 g/L NaCl, 0.4 g/L KCl, 1 g/L glucose, 2.38 g/L HEPES, and 0.1 g/L Na_2HPO_4.

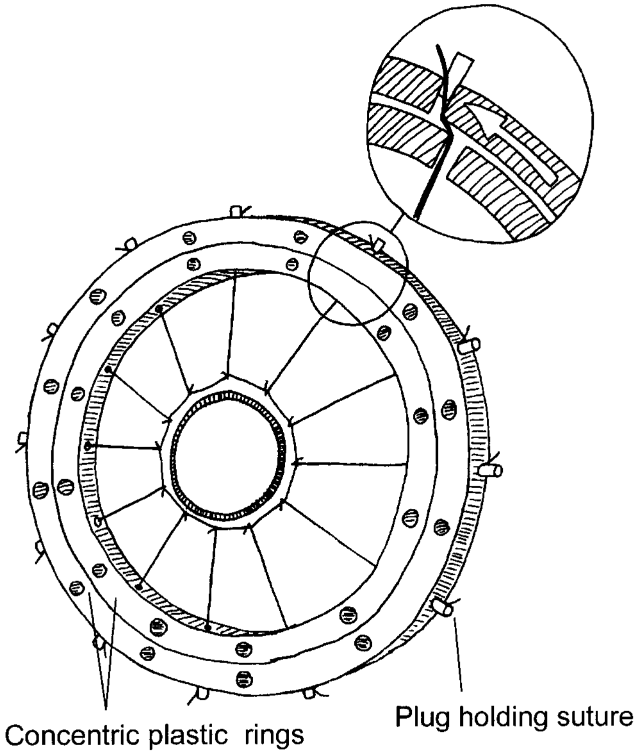

FIGURE 1. Two concentric plastic rings hold the lens-zonula-ciliary body specimen. An anterior segment of the eye is sutured and held at the center of the rings. Counter-rotation of the plastic rings tighten the sutures proportional to the angle of rotation. Holes drilled through the rings make it possible to attach them to a stepper motor to control the rotation of the rings.

Measurement of Focal Length

A scanning laser instrument[14] was used to measure the focal length of the lens submerged in the saline solution. This solution was lightly clouded with coffee creamer to visualize a laser beam passing through the solution. The lens diameter was vertically scanned with a 5-mW HeNe laser beam (633 nm; model 1125; JDS Uniphase, Manteca, CA) with a diameter of 0.81 mm, by shifting the vertical position of a mirror on an X–Y stage (model UTM25PP1HL; Newport, Irvine, CA), driven by a computer-controlled stepper motor (model MM3300; Newport). This stepper motor allowed the laser beam to be moved and positioned

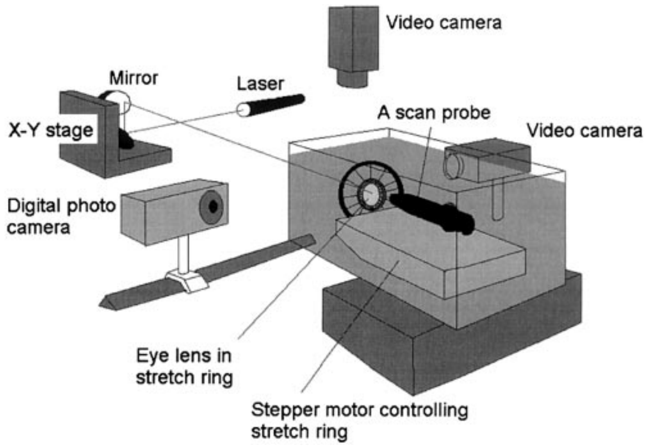

FIGURE 2. The experimental setup.

with an accuracy of approximately 12 μm. The horizontal beam entered the glass chamber and passed through the lens parallel to the optical axis. The horizontal and vertical displacement of the glass chamber could be adjusted manually to make the laser beam coincide with the optical axis of the lens. A video camera (model XC77; Sony Tokyo, Japan) viewed the glass chamber from above, and a second video camera observed the chamber from the side. The laser beam was clearly visible in the clouded saline solution. It was recorded by the two video cameras, and each image was displayed on a computer screen. A diagram demonstrating the experimental setup is shown in Figure 2. The incident and exiting pathways of the laser beam passing through the lens were digitized with image-processing software (Optimas, ver. 6.5; Media Cybernetics, Silver Spring, MD). This program calculated the positions of the incident and exiting pathways of the laser beam and the slopes of the beams. Whenever the slopes and the vertical displacements of the incident and the exiting beam were similar, the laser beam was deemed to coincide with the optical axis of the lens. During vertical lens scanning, one of the cameras recorded the incident and exiting laser beams in the vertical meridional plane. The recorded beam paths were reconstructed to calculate the lens power. The camera image was calibrated before the experiments by digitizing the laser beam in two positions, 10 mm apart, as positioned by the stepper motor. The distance of 10 mm between these two positions corresponded with 80 pixels. Each vertical lens scan covered a distance of 6 mm in 51 discrete steps, from 3 mm above the optical axis to 3 mm below the optical axis. Three images were digitized at each step. Two scans were initially performed across the vertical diameter of the lens, while the ciliary body and the zonule remained in the relaxed state, applying no substantial outward pulling force on the equator of the lens. The tissues were then incrementally stretched by rotating the outer plastic ring, thus increasing the outward pull of the sutures in five steps of 0.5 mm each. If necessary, the position of the tank was adjusted between scans to correct for the shift of the optical axis of the lens. In most cases, the ciliary body reached its yield point at a 5-mm total increase in diameter. To demonstrate the repeatability of the stretching procedure, we incrementally stretched the ciliary body diameter of one of the refilled lenses to 3 mm, released the strain in steps of 0.5 mm to return to 0 mm expansion, and then once more increased the tensile force until the ciliary body reached the point of yielding. During this experiment, we measured the lens power and the lens diameter.

Measurement of Lens Diameter

A digital camera (Coolpix 950; Nikon, Tokyo, Japan), installed on a sliding rail, traveled to a fixed position in front of the lens. Photographs were taken of the lens before and after each laser scan to assess the diameter of the lens under all conditions. The magnification of the image (pixels per millimeter) was calibrated by including a ruler scaled in millimeters and submerged in saline solution as a reference for the size of the lens.

Measurement of Lens Thickness

To measure changes in lens thickness as stretching increased, an ultrasound A-scan probe (A-5500; Sonomed, Lake Success, NY) was positioned approximately 2 cm behind the lens in the glass tank. To measure the lens thickness along the optical axis of the lens, the position of this probe was adjusted until maximum echographic signal peaks of the anterior and posterior side of the lens were obtained. Another image was recorded by the digital camera positioned in front of the lens. This image showed the fixation light of the A-scan probe behind the lens. The position of the probe was adjusted until it was well centered inside the lens. While the sutures were exposed to incrementally increasing tensile force, the thickness was measured at each step. For natural lenses a sound velocity of 1641 m/sec was used, whereas for silicone refilled lenses a sound velocity of 1066 m/sec was used. We established this sonic speed for the silicone material by measuring a 10-mm cylinder of material with calipers and also by A-scan at room temperature.

Analysis of the Data

Focal Length. The slope and the intercept data of the lens incident and exiting beams were stored in a computer data file and were analyzed. The focal length of the lens was calculated by computer (MatLab ver. 6.0; Natick, MA). The intersection points of both beams were calculated for each of the 51 incident and exiting beam pairs. Intersection points with coordinates in excess of 3 SD removed from the average intersection point were eliminated from the data set. A straight vertical line was fitted through the remaining points and was assumed to represent the principal plane of the lens. The optical axis of the lens was defined as the beam passing through the lens with the smallest slope difference between incident and exiting beam. The focal point of the lens was located by a fitting procedure. We calculated the angles between the exiting beams and the radii of a circle (centered on the optical axis) at the intersections of the light rays with the perimeter of the circle. In conjunction with the fitting procedure, the center of the circle was shifted along the optical axis until the squared sum of these angles reached its minimum. The position of the center of the circle then represented the focal point of the lens.

The distance between the principal plane and the center of the circle, by definition, was the focal length. Ten repeated measurements on a single lens, obtained sequentially after replacing the mounted lens in the glass chamber and performing a new scan with the laser beam, established a standard deviation of 0.27 D for the focal length.

Lens Diameter. The diameters of the individual lenses were determined from the digitized lens image by placing cursors on the edges of the lenses. The distance between the cursors in pixels was then converted to millimeters. Ten measurements of lens diameter, randomly performed on six lens images, yielded a standard deviation of 0.1 mm for the lens diameter.

RESULTS

All lenses were refilled successfully through a capsulorrhexis with a diameter of 1.5 mm or less. Qualitatively speaking, the capsular bags were fully refilled with silicone, leaving no noticeable intracapsular space for further refilling. The silicone did not leak from the capsule after refilling.

Figure 3 shows the change in lens power and lens diameter of one of the refilled lenses containing Sil 1 during expansion of the ciliary body diameter, during relaxation, and during repeated exposure to strain. It is obvious that the lens underwent changes that are reversible during the stress–relaxation cycles.

This discussion is limited to data pertaining to the increase in diameter of the ciliary body between 0 and 4 mm, because

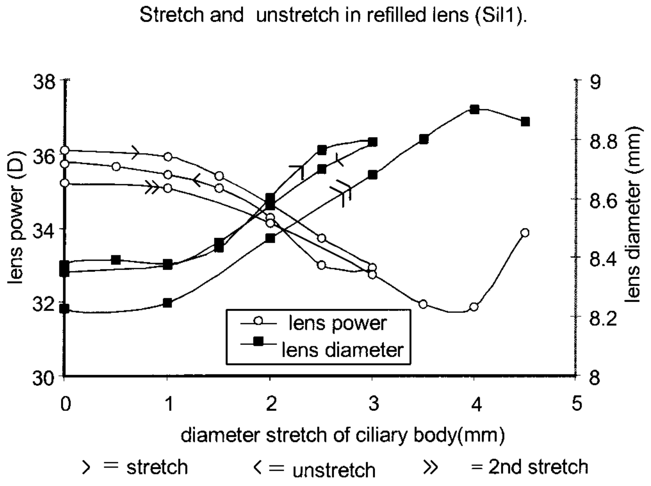

Figure 3. The change in lens power and lens diameter as a function of the stretching of the diameter of the ciliary body. Measurements were obtained as the tissue was stretched, relaxed, and stretched again. *Arrowheads*: direction of stretching. The decrease in lens diameter beyond 4-mm elongation indicates damage to the ciliary body.

the ciliary bodies investigated in this context usually ruptured when stretched 5 mm. The ciliary epithelium was pulled off the ciliary body. We did not observe any sutures tearing through the ciliary body.

Figure 4 shows the change in lens power in natural lenses at a 4-mm increase in ciliary body diameter as a function of age. Lenses obtained from donors aged 48 years and older did not show any change in lens power when exposed to tensile strain; however, the three younger lenses revealed a power change of 3.2 to 7 D. A linear fit of these data and the mean accommodative amplitude in human eyes, as measured by Duane,[25] is also shown. The in vivo results obtained by Duane resemble the fit through our data. All lenses refilled with silicone polymer showed a change in lens power as a result of stretching. The change in lens power in the refilled lenses varied between 3 and 9 D (Fig. 5A). A comparison between the induced power change in lenses refilled with Sil2 (−8 ± 1.5 D) and those refilled with Sil1 (−3.8 ± 0.65 D) at a 4-mm increase in ciliary body diameter showed a significant difference. Lenses refilled with Sil1 showed less change in power.

Figure 5B represents the change in lens power with an increase of the lens diameter of 7%. This agrees with the change in the natural lens diameter during accommodation in a human eye, as established by Wilson.[26] Lens power was determined from a linear fit to the change in lens power versus change in lens diameter. Some lenses in the Sil1 group and all natural lenses in eyes older than 45 years failed to attain a 7% increase in diameter. Measuring the change in lens power at a lens diameter increase of 7% revealed no significant differences between the Sil1- and Sil2-refilled lenses.

Figures 6 and 7 show the correlation between the change in lens power and lens diameter or lens thickness during the stretching of the ciliary body. The natural lenses of donors older than 45 years showed no change in power, although some of these lenses revealed an increasing lens diameter (Fig. 6A) and a decreasing lens thickness (Fig. 7A). All refilled lenses displayed a linear correlation of variation in thickness and diameter with change in lens power.

Table 1 presents a comparison between the properties of natural lenses and those of refilled lenses. In the relaxed state, the average lens power of refill lenses was significantly higher than that of natural lenses. Refilled lenses were thicker than natural lenses, and we were unable to detect a statistically significant difference in lens diameter between the refilled and natural lenses.

In vivo, disaccommodated lenses are stretched by the zonules. Thus, we also compared natural lenses with refilled lenses in the stretched condition. At a 4-mm increase in ciliary body diameter, the lens power was the only parameter to show

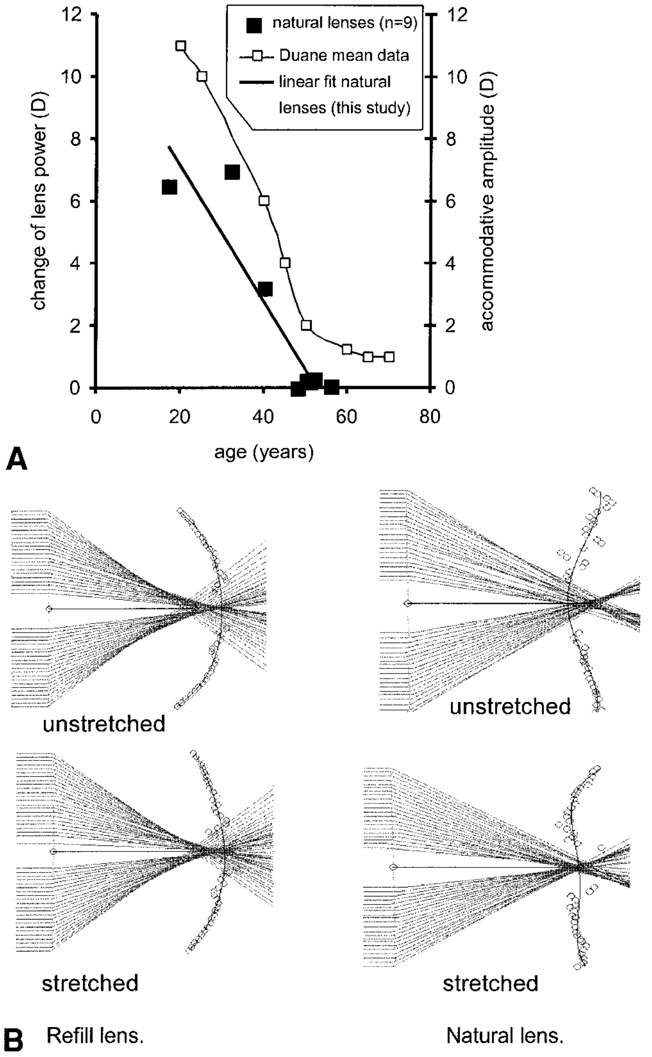

Figure 4. (**A**) Comparison of the amplitude of accommodation as measured by Duane, with changes in lens power as measured in this study, in natural lenses at 4 mm ciliary body elongation. Duane's measurements are subjective measures of the accommodative amplitude, whereas our data are isolated changes in lens power. Both sets of data exhibit a similar age-related decrease in amplitude. Subjective measurements are hampered by depth-of-focus effects, possibly explaining to a certain extent the larger accommodative amplitudes revealed by these data. Data adapted from Duane A. Studies in monocular and binocular accommodation with their clinical application. *Am J Ophthalmol.* 1922;5:865–877. (**B**) Reconstruction of a single scan of one refilled and one natural human lens in the relaxed and the stretched states, when the ciliary body diameter showed a 4-mm elongation. *Vertical line*: primary plane of the lens; *circles*: horizontal position, where each exiting beam intersects with the optical axis, and the vertical position, where the incident beam meets the lens. A fourth-order polynomial was fitted through these points to show the pattern of spherical aberration. The refilled lens shows positive spherical aberration, which was slightly reduced in the stretched condition. The natural lens showed negative spherical aberration, which was slightly reduced in the stretched condition.

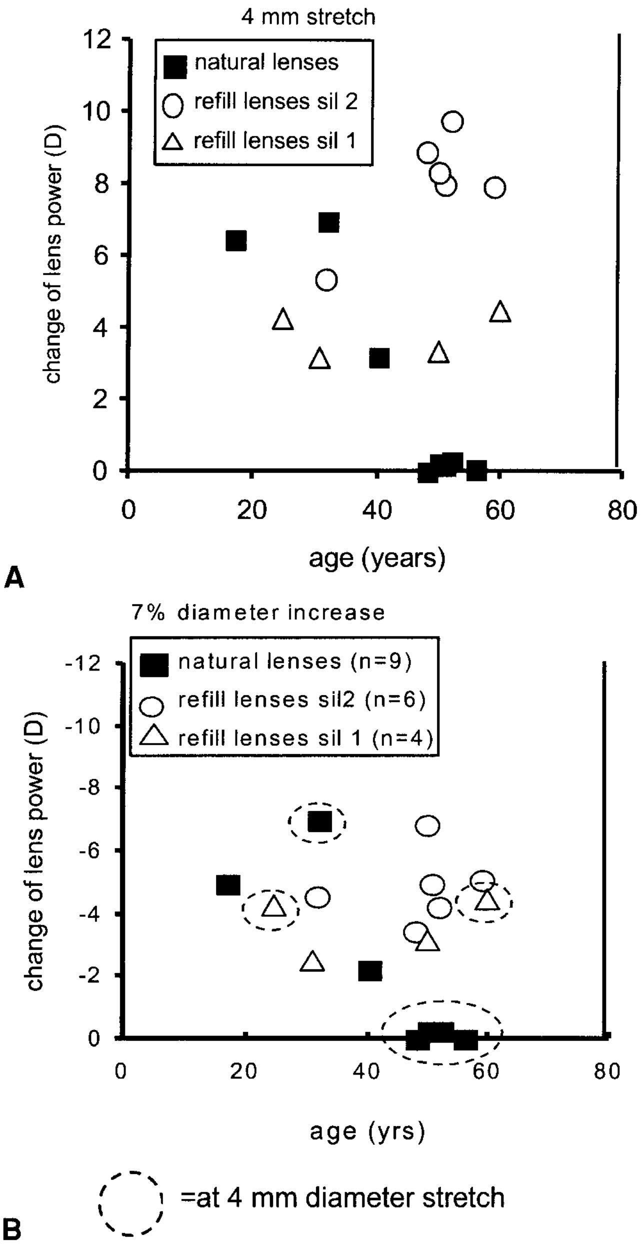

Figure 5. (**A**) Change in lens power versus age in three groups of lenses. The results were measured at a 4-mm elongation of ciliary body diameter. The lens power changed less drastically in older lenses, whereas the refilled lenses invariably exhibited a more noticeable change in lens power in the same age groups. Lenses refilled with Sil2 showed a more drastic change in lens power than those refilled with Sil1. (**B**) Change in lens power versus age in natural lenses and in lenses refilled with Sil1 and Sil2 measured at a 7% increase in diameter, based on data from Wilson.[26] Not all lenses showed a 7% change in diameter. *Dashed circles*: data points of lenses that failed to reach this stretched condition. These represent the change in lens power at a 4-mm increase in the diameter of the ciliary body.

any significant difference, whereas lens diameter and thickness remain largely identical (Table 1).

A scanning laser ray-tracing technique was used to determine the lens' optical power. This also enabled us to visualize spherical aberrations. In most refilled lenses, spherical aberration was positive, whereas natural lenses commonly showed negative spherical aberration. Stretching the refilled lenses decreased the degree of spherical aberration, but it did not change the sign. Spherical aberration in natural lenses did not change much with stretching. In some lenses, irregular aberrations precluded reliable measurement of spherical aberration, and therefore we did not quantify this parameter. Figure 4A shows some typical examples of spherical aberration in a natural and a refilled lens.

DISCUSSION

This study primarily revealed that refilled human lenses, in contrast to natural lenses, showed no age-related decline of lens power when exposed to circumferential tensile forces.

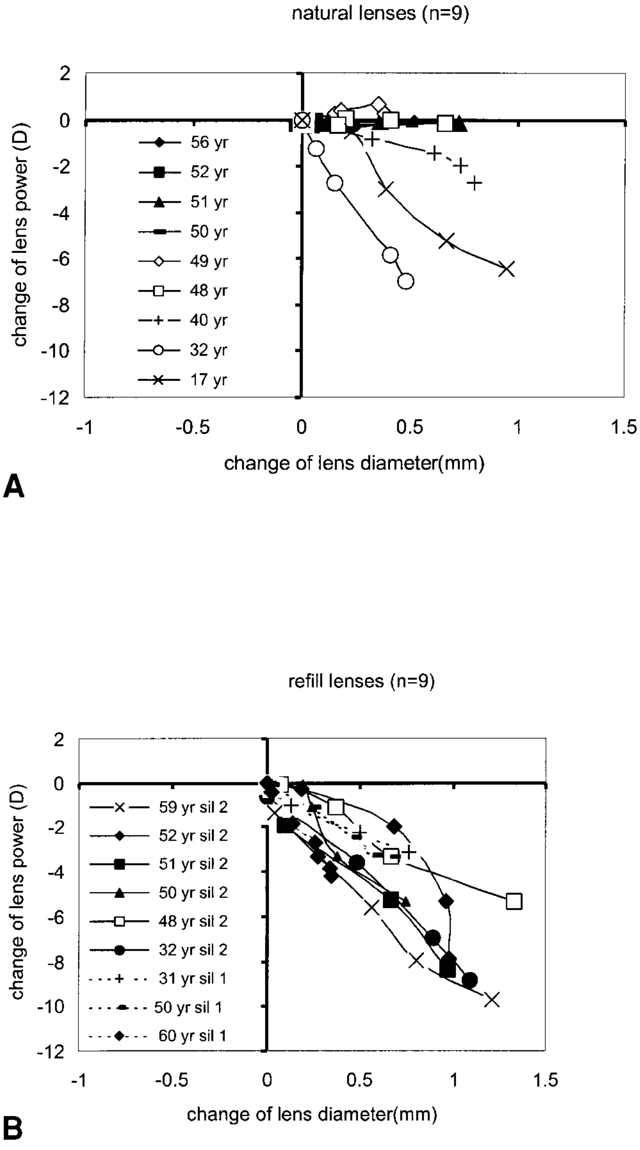

Figure 6. (**A**) Change in lens power versus change in lens diameter of natural lenses at different ages ($n = 9$). Older lenses showed a less drastic change in power. Some lenses increased in diameter, but showed no change in lens power. Some of the photographs taken for lens diameter measurements demonstrate that in these cases the capsule was pulled off the lens. (**B**) Change in lens power versus change in lens diameter of refilled lenses ($n = 9$). All lenses, regardless of age, show an increasing change in lens power with increasing lens diameter. The relation between lens power and lens diameter seemed to be identical in Sil1- and Sil2-filled lenses; however, Sil1-filled lenses had a more narrow dynamic range.

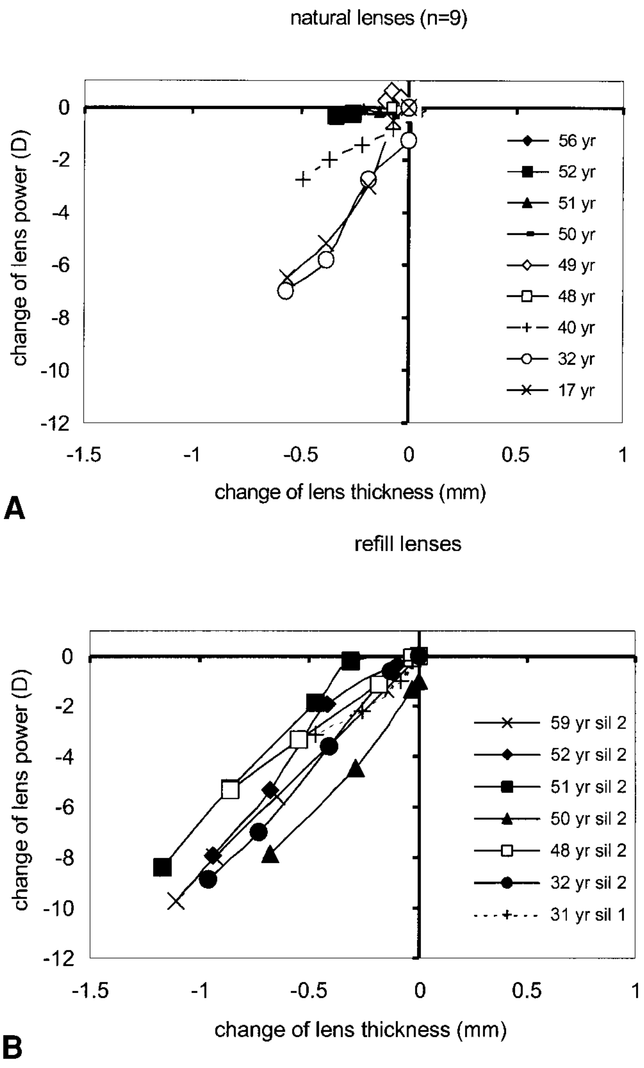

FIGURE 7. (**A**) Change in lens power versus change in lens thickness of natural lenses ($n = 9$). Older lenses were characterized by lack of variation in lens power, although they reveal minor changes in lens thickness. This may be explained by assuming that older lenses possess a firm lens nucleus that determines the lens power and is not affected by stretching. This nucleus would be surrounded by a thin, softer cortical layer, which becomes thinner if stretched by tensile forces. (**B**) Change in lens power versus change in lens thickness of refilled lenses ($n = 7$). All lenses showed a change in lens power when the lens thickness changed. Measurements of thickness were performed on only one lens refilled with Sil1.

Glasser and Campbell,[14] using a similar experimental setup and studying 27 natural lenses from donors between 10 and 87 years of age, demonstrated that the ability of the natural human lens to undergo lens power variation with stretching decreases with age. Having reached the age of 58 years, none of the lenses revealed any change in focal length while being stretched. Our findings, pertaining to a smaller group of natural lenses, confirm these results. Our refilled lenses, however, showed the ability to undergo changes in lens power comparable to those of the youngest natural lenses.

To demonstrate this principle, we had to assess the properties of the refilled lenses with considerable accuracy. To our knowledge, no quantitative data on human lens refilling have previously been published. Parel et al.[19] refilled human capsular bags, but reported no further data on these human lenses. Nishi et al.[27] published quantitative data on refilled porcine lenses and concluded that a porcine lens refilling of 60% by volume yields the highest accommodative amplitude when exposed to circumferential tensile forces. Porcine lenses, however, are known for their lack of accommodation, and they are more spherically shaped than human lenses. Thus, we cannot say with any certainty whether their findings also apply to human lenses. Other publications focused on the properties of refilled monkeys' lenses.[20–22] Most of these in vivo experiments involved young monkeys. Accommodative amplitudes exhibited by monkeys' eyes with a refilled lens were usually less than those of eyes with a natural lens. Haefliger et al.,[24] studying monkeys with presbyopia, demonstrated that the anterior chamber depth in eyes with a refilled lens changed more drastically than the anterior chamber depth of eyes with a natural lens. This confirms that refilling a monkey's lens may restore the accommodative power of the monkey's eye. The authors supported this claim by measuring the decrease in anterior chamber depth. However, they did not publish any additional data pertaining to the change in lens power, the refraction of the eye, or changing lens parameters, such as thickness and diameter. Axial displacement of the lens may contribute to the reported change in anterior chamber depth. In our experiments, during simulated in vitro accommodation of natural and refilled human lenses, we monitored several lens parameters that are known to change during in vivo accommodation of natural lenses.

The donor lenses investigated in this context may have undergone postmortem changes that affected their accommodative behavior. However, optical transparency of the lenses remained good during the experiments, as reported by Glasser and Campbell.[14] Weale[28] reported similar findings and found no significant change in lens power in adult eyes during the postmortem period up to 5 days. Our experiments revealed an age-related decline of accommodative amplitude, similar to that in in vivo measurements.[25] These findings suggest that the accommodative ability of the donor lenses is not lost after death, at least not during the first few days.

The technique of mechanical stretching of the lens to simulate accommodation, of course, can never precisely reflect the natural accommodation process in the human eye. The lens, after all, is placed in a saline solution, thus eliminating the influence of pressure in the anterior chamber or vitreous on

TABLE 1. Average Lens Diameter, Lens Thickness, and Lens Power

	Unstretched Lenses			Stretched Lenses		
	Diameter (mm)	**Thickness (mm)**	**Power (D)**	**Diameter (mm)**	**Thickness (mm)**	**Power (D)**
Natural lenses ($n = 9$)	9.5 ± 0.5	4.2 ± 0.5	22.7 ± 2.4	10.0 ± 0.6	4.0 ± 0.6	20.8 ± 5.3
Refilled lenses ($n = 10$)	9.0 ± 1.0	5.0 ± 0.2	31.7 ± 2.7	9.8 ± 1.1	4.3 ± 0.8	25.3 ± 4.0
Difference	0.5	0.8*	9.0*	0.2	0.3	4.5*

* Significant in two-tailed Student's t-test $P < 0.001$.

the lens.[29] The zonular tensile vector lies in the lens equatorial plane, whereas the natural lens is exposed to a certain posteriorly oriented tensile force, due to the orientation of the zonules.[30] We consider it unlikely, however, that these influences had a substantial effect on our quantitative results. The sutures might have ruptured the ciliary body during the experiments, which may have reduced the tensile force on the zonules; however, this was not observed during the experiments. Figure 3 shows that there was an upper limit to the stretchability of the ciliary body, which could not expand more than 4 mm. Beyond this, the lens diameter did not increase any more, which indicates that the connection between the ciliary body and the ciliary epithelium was damaged at this point. While the tissue was stretched, relaxed, and then stretched again, the lens diameter underwent comparable changes, at least within the accuracy of the measurements. This shows that stretching from 0 to 4 mm caused no structural damage to the tissue. In general, little is known about the zonular forces acting on the lens during disaccommodation of the natural human ciliary muscle. The increasing lens diameter with stretching observed in younger natural lenses (maximum increase in a lens of a 17-year-old donor; this value of 0.95 mm corresponds to a 10% increase in diameter) is comparable to the 7% increase in lens diameter with disaccommodation exhibited by a 27-year-old human subject, as reported by Wilson.[26] Thus, we may conclude that our experiments reveal a physiological change, expressed by a variation in lens diameter. The zonular pull on the lenses was not excessive.

This study shows that it is possible to refill the human capsular bag with a silicone polymer without risking leakage of the refill material. Parel et al.[19] published experiments involving human eyes, in which a precured low-temperature vulcanizing silicone was used. The precured state of their material should have prevented leakage from the capsular bag; however, some leakage occurred, regardless.[21] Precured materials must be used within a limited time and are therefore deemed unsuitable for future use as lens refill materials. Besides, precuring may also introduce optical and mechanical inhomogeneities in the lenses. Injecting an uncured material and using a plug to prevent leakage may circumvent these disadvantages. Nishi et al.[31] also experimented with a capsular plug when refilling rabbit, pig[27] and monkey lenses,[22] but not in conjunction with human lenses.

Surgical techniques must be improved before this type of surgery can be performed in humans. In our study, surgical access to the lenses in the donor eyes was facilitated by removing the cornea and the iris, which, of course, is not an option in lens surgery in humans. Besides, removal of the lens contents by vacuum-aspiration techniques was very time consuming. Laser phacoemulsification may make it possible to remove the lens substance through small capsular openings. New instrumentation used to create a small capsulorrhexis in the lens periphery may also contribute to the success of this surgical technique.[32]

In this study, we also found that the refilled lenses exhibited a significantly greater lens power than the natural lenses. This was true both in the stretched and the relaxed state. The lens power of the natural and the refilled lenses must be compared in the stretched state (Table 1), which represents the disaccommodated state (i.e., the human eye at rest).

In our refilling experiments we attempted to fill up the capsular bag completely. If emmetropic refraction is to be achieved by this approach involving refilling of the capsular bag in vivo, then intraoperative refraction measuring techniques during lens refilling should be developed for this type of surgery.

Because the refractive index of the refill material (1.428) is similar to the equivalent refractive index of the human lens,[33] the enhanced lens power exhibited by refilled lenses may be attributable to steeper surface curvatures. In terms of lens thickness, however, there was no significant difference between the refilled group and the natural lens group. It is possible that natural lenses have some inherent shape that the polymer-refilled lens does not have, resulting in flatter surface curvatures at a similar degree of capsular filling. Glasser and Campbell[14] measured negative spherical aberration in young natural human lenses, which became positive in older lenses, both in the relaxed state and the stretched state. Our refilled lenses usually revealed either positive or zero, but never negative, spherical aberration. Absence of negative spherical aberration in the refill lens group may have enhanced the mean lens power, because according to our analysis all rays contribute to the calculation of lens power. A less complete degree of lens filling or refill material with a lower refractive index could result in the refilled lenses' exhibiting the same lens power as natural lenses. Because we did not measure the lens volume, we cannot tell whether our lenses were insufficiently filled or even contained too much filling material.

Sil1, with its higher Young's modulus, allowed a less noticeable change in lens power with stretching than the Sil2 polymer, with its lower Young's modulus. Sil2 seemed to attain better restoration of good accommodative ability. Haefliger et al.[21] used a material with an elastic Young's modulus of 1 kPa in owl monkeys and recorded accommodative amplitudes of 11 D. This compares well with the Sil2 value of 0.87 kPa. Nishi and Nishi[22] provide no information about the Young's modulus of the filling material, but their material allowed accommodative changes of 4.5 D in monkeys.

To summarize this discussion, lens refilling restored the ability of the human lens to undergo changes in lens power during equatorial stretching. These results confirm the idea that sclerosis of the lens substance is an important factor in human presbyopia and suggest that refilling the lens capsule with a soft material may be a good technique for restoring accommodation in patients who undergo cataract surgery.

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