Miniaturized High-Intensity Focused Ultrasound Device in Patients with Glaucoma: A Clinical Pilot Study

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PURPOSE. To evaluate the relative safety and potential efficacy of high-intensity focused ultrasound cyclocoagulation by a miniaturized annular device containing six piezoceramic transducers in patients with refractory glaucoma.

METHODS. This was a three-center prospective interventional pilot study. Twelve eyes of 12 patients with refractory glaucoma were sonified using a ring-shaped probe containing six miniaturized high-frequency transducers operating at 21 MHz. Ultrasonic biomicroscopy (UBM) and a complete ophthalmic examination were performed before the procedure and at 1 day, 1 week, 1 month, and 3 months after the procedure. Additional visits were performed 6 and 12 months after the procedure.

RESULTS. Intraocular pressure was significantly reduced ($P < 0.01$) from a mean preoperative value of 37.9 ± 10.7 mm Hg to a mean postoperative value of 27.3 ± 12.4, 25.2 ± 11.3, 25.2 ± 7.7, 24.8 ± 9.8, and 26.3 ± 5.1 mm Hg at 1 day, 1 week, 1 month, 3 months, and 6 months, respectively, and to a mean value of 24.7 ± 8.5 at the last follow-up visit. No major intraoperative or postoperative complications occurred. Minor postoperative corneal complications developed in four patients with previous corneal abnormalities: superficial punctate keratitis ($n = 3$) and central superficial corneal ulceration ($n = 1$). UBM showed cystic involution of the ciliary body in 9 of the 12 eyes and a suprachoroidal fluid space in 8 of the 12 eyes.

CONCLUSIONS. Ultrasonic circular cyclocoagulation using high-intensity focused ultrasound delivered by a circular miniaturized device containing six piezoceramic transducers seems to be an effective and well-tolerated method to reduce intraocular pressure in patients with refractory glaucoma. (Invest Ophthalmol Vis Sci. 2011;52:8747–8753) DOI:10.1167/iovs.11-8137

A variety of methods and energy sources have been used to destroy the ciliary processes and to reduce aqueous formation and intraocular pressure (IOP) in patients with difficult to control IOP and refractory glaucoma. Although recent methods such as transscleral diode laser have a relatively low rate of vision-threatening complications, the effect of the cyclo-destruction procedures is often not fully predictable; these methods are, therefore, still usually reserved for advanced glaucoma refractory to conventional treatments.1–6

Ultrasonic ablation of the ciliary body for treating glaucoma was extensively studied in the 1980s and early 1990s. Several animal studies and then clinical series have reported that high-intensity focused ultrasound (HIFU) is an effective method with favorable results in terms of IOP reduction.7–13 Maskin et al.12 achieved a 38.4% IOP reduction 8 months after HIFU cyclodestruction in 158 eyes with refractory glaucoma using a commercially available device (Therapeutic Ultrasound System Model; Sonocare Inc., Ridgewood, NJ). With the same device, Sterk et al.13 obtained a 42.2% IOP reduction 3 to 4 months after HIFU cyclodestruction in 44 eyes with refractory glaucoma. The specific advantage of HIFU is that the energy can be focused through nonoptically transparent media without uncontrolled energy absorption; thus potentially reducing the effects on the adjacent tissues. Similarly, energy deposition and tissue heating at the focus site do not depend on tissue pigmentation, which may vary greatly, particularly in the ciliary body. HIFU allows for a defined and adjustable tissue volume to be heated and treated at any depth or location within the eye. In the Sonocare device, the transducer was bulky and heavy (piezoceramic 80-mm diameter) and attached to an articulated arm that had to be positioned manually using an imaging probe. A fluid coupling bath of heated saline had to be set up by sticking a plastic sheet to the patient’s skin. Moreover, scleral thinning or perforation has been reported, probably caused by improper positioning of the transducer. Because of these severe complications, the use of HIFU for cyclodestruction was gradually abandoned in the mid 1990s.

We investigated the use of a miniaturized circular HIFU device to produce cyclocoagulation and developed a circular instrument with six miniaturized high-frequency transducers.4 The circular geometry of the device, located directly in contact with the eye, allows for constant and reproducible positioning in most eyes and reduces the procedure time and the risk for misplacement. High-frequency miniaturized transducers enable the creation of smaller focal zones that better target the treatment areas, particularly for small organs such as the ciliary body. The higher operating frequency of these transducers also allows for a steeper transition between the focal zone and the untreated area, thus reducing the risk for heating the neighboring healthy tissue.15,16 In a previous animal study performed with this device, we obtained significant IOP reduction in the eyes of 18 rabbits 4 weeks after HIFU cyclocoagulation, achieving a 55% drop in the initial IOP when the six sectors of the device were activated.17 Histologic examination showed...
segmental to annular coagulation necrosis of the ciliary processes, whereas the adjacent ocular tissues appeared undamaged. Clinical and histologic examinations showed limited ocular inflammation. Based on these results, the regulatory authorities allowed us to conduct a first clinical study with this new device in human patients with advanced refractory glaucoma. The objective of the present work was to report the methodology and results of the first pilot clinical study. Emphasis was placed on evaluating the safety of the procedure. We also evaluated the ability of the procedure to reduce IOP.

METHODS
This study was designed, conducted, and reported according to the World Glaucoma Association guidelines on the design and reporting of glaucoma surgical trials.18

HIFU Device
The HIFU device has been previously described in detail.14,17 A coupling cone made of polymer was placed in direct contact with the eye, which allowed good placement of the transducers in terms of centering and distance (Fig. 1). At the base of the coupling cone, a suction ring allowed the application of low-level vacuum and enabled the cone to maintain contact with the eye. A 30-mm diameter, 15-mm high ring containing six active piezoelectric elements was inserted in the upper part of the coupling cone. The cavity created between the eye, the cone, and the probe (4 mL) was filled through the central aperture of the device with room temperature saline solution (BSS, Alcon Inc., Fort Worth, TX). Each of the six transducers was a segment of a 10.2-mm radius cylinder with a 4.5-mm width and a 7-mm length (active surface area, approximately 35 mm²). The focal volume of each transducer has approximately an elliptic cylinder shape. The axial length of the focal zone is 1.2 mm (major section of the ellipse), the transverse focal width is 0.4 mm (minor section of the ellipse), and the lateral focal length is 3.5 mm (length of the elliptical cylinder) (Fig. 2). The six transducers were placed at regular intervals on the upper and inferior circumference of the ring, avoiding the nasal and temporal meridians, and were oriented to create a focal zone consisting of six regularly distributed elliptical cylinder-shaped volumes. Three device models with different ring diameters, equipped with the six transducers, were available. Depending on the diameter, the six elliptical cylinder-shaped volumes were centered on an 11.7-mm, 12.2-mm, or...
12.7 mm diameter circle. In each patient, the ring model whose focal zones actually matched the ciliary body was determined by ultrasound biomicroscopy (UBM) imaging of the anterior segment performed at baseline. The location of the focal zones was simulated using the UBM images, and the model that best targeted the ciliary body was chosen (Fig. 3). Most emmetropic patients were treated with the ring inducing six spots centered on a 12.2-mm diameter circle. The resonant frequency of the transducers was 7 MHz, and we operated it at its third harmonic (21 MHz). The ring was connected to a control module, which allowed each sector to be sequentially activated according to a program defined by the operator.

Clinical Study

Patients. We conducted this prospective pilot investigation in three university-affiliated glaucoma centers. The study followed the tenets of the Declaration of Helsinki and was conducted in conformity with the standards of ISO 14155 parts 1 and 2 (Clinical Investigation of Medical Devices for Human Subjects). The clinical trial was approved by an institutional review board (CPP Sud-Est III, Lyon, France) and the national health regulatory authority (registration number 2009-A01132-55, AFSSAPS, Saint-Denis, France). All patients provided both verbal and written informed consent. Inclusion criteria were men or women aged 18 years or older; ability and willingness to return for scheduled visits; diagnosis of refractory primary or secondary glaucoma with at least one previous incisional glaucoma surgery; average baseline IOP of 21 mm Hg or more while on maximally tolerated medical treatment; best-corrected visual acuity <20/60; and visual field defect with a minimum of one location in the paracentral region exhibiting repeatable abnormality at the P < 0.5% level in the study eye. Exclusion criteria were mental impairment conflicting with informed consent or
### Table 1. Demographic Characteristics of the 12 Patients

<table>
<thead>
<tr>
<th>Age in years, mean ± SD (range)</th>
<th>54.7 ± 20.1 (25-84)</th>
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</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>3/9</td>
</tr>
<tr>
<td>Best-corrected visual acuity, mean Snellen (range)</td>
<td>20/1700 (20/200-1/3200)</td>
</tr>
<tr>
<td>Glaucoma type: no. eyes (%)</td>
<td>POAG: 5 (41.7)</td>
</tr>
<tr>
<td></td>
<td>Neovascular: 3 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Congenital: 2 (16.7)</td>
</tr>
<tr>
<td></td>
<td>PACG: 1 (8.3)</td>
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<tr>
<td></td>
<td>ICE syndrome: 1 (8.3)</td>
</tr>
<tr>
<td>Previous glaucoma surgery: no. procedures</td>
<td>Trabeculectomy: 26</td>
</tr>
<tr>
<td></td>
<td>Deep sclerectomy: 4</td>
</tr>
<tr>
<td></td>
<td>Diode cyclophotocoagulation: 3</td>
</tr>
<tr>
<td>Preoperative hypotensive therapies: no. patients</td>
<td>β-Blockers: 9/12</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin analogs: 9/12</td>
</tr>
<tr>
<td></td>
<td>Topic carbonic anhydrase inhibitors: 9/12</td>
</tr>
<tr>
<td></td>
<td>Systemic carbonic anhydrase inhibitors: 3/12</td>
</tr>
<tr>
<td></td>
<td>α2 Adrenergic agonists: 8/12</td>
</tr>
<tr>
<td></td>
<td>Myotics: 2/12</td>
</tr>
<tr>
<td>Follow-up in months, mean ± SD (range)</td>
<td>Group 1: 11.6 ± 1.5 (9-13)</td>
</tr>
<tr>
<td></td>
<td>Group 2: 4.0 ± 2.5 (1-9)</td>
</tr>
<tr>
<td></td>
<td>All patients: 6.5 ± 4.3 (1-13)</td>
</tr>
</tbody>
</table>

POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; ICE, iridocorneal endothelial.

follow-up; current use of any investigational drug or device; pregnancy; concomitant systemic medications that could affect IOP; diagnosis of normal tension glaucoma; history of refractive surgery, retinal detachment or ocular tumor; intraocular surgery or laser within the past month; and ocular infection in the past 2 weeks.

**Procedures.** Baseline evaluation included best-corrected visual acuity, slit lamp biomicroscopy with gonioscopy and mydriatic fundus examination, Goldmann applanation tonometry with three measurements, ultrasound pachymetry, visual field when applicable, and UBM. Refraction was performed using an autorefractometer (AR-360; Nidek Co., Gamagori, Japan), gonioscopy was performed using a Goldmann 3-mirror lens, ultrasound pachymetry was performed using an ophthalmic ultrasound system (OcuScan RxP; Alcon, Inc., Fort Worth, TX), visual field was performed using an automated diagnostic system (Humphrey Field Analyzer; 24–2 SITA-standard program; Carl Zeiss Meditec, Dublin, CA), and UBM with a 50-MHz probe (Aviso; Quantel Medical, Clermont-Ferrand, France). For UBM, patients were placed in the supine position for lid speculum and gel examination, and radial and transverse scans were obtained at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° meridians.

All HIFU procedures were performed by three authors (FA, EB, PD) under topical (n = 1), peribulbar (n = 1), or general (n = 10) anesthesia, depending on patient and physician preferences. The following parameters were used: suction ring, 70 mm Hg; operating frequency, 21 MHz; number of sectors activated, 6; acoustic power, 2 W; duration of each of the six shots, 3 seconds (group 1, patients 1–4) or 4 seconds (group 2, patients 5–12); time between each shot, 20 seconds. Postoperatively, patients were treated topically with tobramycin and dexamethasone (Tobradex; Alcon) in group 1 and flurbiprofen (Ocufen; Allergan, Irvine, CA) in group 2, three times a day for 2 weeks. Preoperative hypotensive medications were maintained unchanged throughout the course of the study, with no washout period before the baseline IOP measurements.

**Follow-up.** Best-corrected visual acuity, slit lamp biomicroscopy with mydriatic fundus examination, and Goldmann applanation tonometry were performed postoperatively at 1 day, 1 week, 1 month, and 3 months. Ultrasound biomicroscopy was performed postoperatively at 1 week, 1 month, and 3 months. Additional similar visits were performed 6 and 12 months after the procedure. All IOP measurements were taken at the same time of day as the preoperative IOPs.

**End Points**

Main outcome measures were intraoperative or postoperative complications and IOP reduction. Surgical success was defined as an IOP reduction greater than 20% and an IOP greater than 5 mm Hg. Intraoperative and postoperative complications were classified as major or minor. Standardized tables defined in the World Glaucoma Association guidelines on the design and reporting of glaucoma surgical trials were used to classify and report the complications.\(^{18}\)

**Statistical Analysis**

Student’s t-test was used to compare means and percentages, and χ² tests were used for the analysis of dichotomous variables. Statistical significance was set at \( P < 0.05 \). Statistical software (SPSS version 17.0; SPSS, Inc., Chicago, IL) was used for data analysis.

**Results**

**Patients’ Characteristics**

Demographic data are summarized in Table 1. Twelve patients were enrolled and treated. All the treated patients had advanced glaucoma with low residual vision. All patients completed the planned visits. Mean follow-up time was 6.5 ± 4.3 months (group 1, 11.6 ± 1.5 months; group 2, 4.0 ± 2.5 months).

### Table 2. IOP at Baseline and during Follow-up in the Two Groups and in All Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Mean IOP (no. patients)</th>
<th>Relative IOP Reduction (%)</th>
<th>Group 2 Mean IOP (no. patients)</th>
<th>Relative IOP Reduction (%)</th>
<th>All Patients Mean IOP (no. patients)</th>
<th>Relative IOP Reduction (%)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>35.6 ± 2.5 (4)</td>
<td>NA</td>
<td>39.1 ± 13.2 (8)</td>
<td>NA</td>
<td>37.9 ± 10.7 (12)</td>
<td>NA</td>
</tr>
<tr>
<td>Day 1</td>
<td>27.9 ± 5.7 (4)</td>
<td>-22.0</td>
<td>26.9 ± 15.1 (8)</td>
<td>-33.8</td>
<td>27.5 ± 12.4 (12)</td>
<td>-29.8</td>
</tr>
<tr>
<td>Day 7</td>
<td>29.6 ± 4.9 (4)</td>
<td>-16.2</td>
<td>23.0 ± 13.1 (8)</td>
<td>-44.3</td>
<td>25.2 ± 11.3 (12)</td>
<td>-34.9</td>
</tr>
<tr>
<td>Month 1</td>
<td>27.3 ± 3.2 (4)</td>
<td>-22.8</td>
<td>24.2 ± 9.2 (8)</td>
<td>-38.2</td>
<td>25.2 ± 7.7 (12)</td>
<td>-33.1</td>
</tr>
<tr>
<td>Month 3</td>
<td>27.8 ± 9.0 (4)</td>
<td>-20.2</td>
<td>23.1 ± 10.6 (7)*</td>
<td>-44.5</td>
<td>24.8 ± 9.8 (11)*</td>
<td>-35.7</td>
</tr>
<tr>
<td>Month 6</td>
<td>27.0 ± 4.9 (4)</td>
<td>-23.5</td>
<td>25.4 ± 6.2 (5)*</td>
<td>-37.6</td>
<td>26.3 ± 5.1 (7)</td>
<td>-29.5</td>
</tr>
<tr>
<td>Month 12</td>
<td>28.0 ± 8.1 (4)</td>
<td>-20.1</td>
<td>23.0 ± 8.6 (8)</td>
<td>-40.8</td>
<td>24.7 ± 8.5 (12)</td>
<td>-33.9</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>28.0 ± 8.1 (4)</td>
<td>-20.1</td>
<td>23.0 ± 8.6 (8)</td>
<td>-40.8</td>
<td>24.7 ± 8.5 (12)</td>
<td>-33.9</td>
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</tbody>
</table>

All values are mean ± SD unless otherwise noted. NA, not applicable.

* One patient withdrew from the study because of the trabeculectomy performed 1 month after the procedure.
Efficacy and Safety
No complications occurred during any of the procedures. Mean and relative intraocular pressure reductions of each group and of all patients are shown in Table 2. A scatter plot of postoperative versus preoperative pressure is shown in Figure 4. Surgical success (defined as IOP reduction 20% and IOP < 5 mm Hg) was achieved in 10 of 12 (83.3%) patients at the last follow-up visit. None of the patients encountered IOP spikes or major IOP increases in the early follow-up (IOP > baseline IOP + 10 mm Hg in the first 7 days). Because of the lack of IOP reduction in patient 7, we performed a trabeculectomy 1 month after the procedure (month 1 IOP, 26 mm Hg despite additional systemic carbonic anhydrase inhibitors and hypotensive agents). The eye of this patient was rather short (axial length, 22.0 mm); simulations based on UBM performed before the treatment showed that the focal zones could have only partially targeted the ciliary body.

No major intraoperative or postoperative complications occurred. Superficial punctate keratitis occurred in three patients and central superficial corneal ulceration in one patient. All had previous corneal conditions: corneal ulceration occurred in a patient with congenital glaucoma and moderate corneal edema, and superficial punctate keratitis occurred in patients with congenital glaucoma, iridocorneal endothelial syndrome, and neovascular glaucoma; all had mild to moderate corneal edema before treatment. All were successfully treated with artificial tears and vitamin A. Corneal ulceration was healed in 4 weeks, and superficial punctate keratitis was healed in 2, 4, and 6 weeks. Clinical examinations showed little or no signs of intraocular inflammation (Fig. 5). Visual acuity remained statistically unchanged (best-corrected visual acuity logMAR 1.935 before surgery and logMAR 1.942 at last follow-up; P > 0.1).

Ultrasound Biomicroscopy Imaging
UBM showed cystic involution of the ciliary body in 9 of the 12 eyes, with multiple hypoechoic ovoid cystic cavities ranging from 0.05 mm to 0.15 mm in diameter and hyporeflective suprachoroidal fluid space in 8 of the 12 eyes. Patients with hyporeflective suprachoroidal space had significantly lower IOP than those without visible suprachoroidal space (P < 0.01). Slit-lamp biomicroscopy photographs and UBM images of one treated eye at different time points are shown in Figures 5 and 6.

DISCUSSION
We developed a new miniaturized circular HIFU device for cycloocoagulation. We took advantage of recent breakthroughs in the field of HIFU technology and integrated high-frequency miniaturized transducers in a small device with a circular design, adapted to the geometry of the target organ. This design allows the device to be placed directly against the eye and not
to move during the procedure, thus enabling a one-step, quick, accurate, and reproducible treatment of the whole circumference. We investigated the safety and efficacy of this new device in a first clinical pilot study, reported in the present work. Ultrasonic circular cyclocoagulation using HIFU seems to be relatively safe and potentially effective in reducing IOP in patients with refractory glaucoma. We did not observe major complications during or after the procedure, and we achieved a mean IOP reduction of 35.7% three months after the treatment. IOP reduction was significantly greater in the group treated with the higher dose (44.5% vs. 20.2%). Ciliary body necrosis was confirmed in most cases by UBM.

The mechanisms of IOP reduction after HIFU treatment remain to be clarified. Many mechanisms have been advanced to explain IOP reduction after cyclodestruction or cyclophotocoagulation, including destruction of the pigmented and nonpigmented epithelium resulting in reduced aqueous production, ciliary body inflammation, enhanced uveoscleral outflow caused by changes in the ciliary body stroma and damage to the pars plana. In our study, clinical and UBM examinations did not show major intraocular inflammation or injury of the sclera. We, therefore, assume that the main mechanism for IOP reduction with this procedure was a decrease of aqueous production by the treated ciliary body. The cystic involution of the ciliary body showed by UBM supports this suggestion. These results are consistent with those of a previous animal study in which histologic examinations showed localized and circumferentially distributed coagulation necrosis of the ciliary body without damage to the adjacent ocular structures or intraocular inflammation. Similarly, we observed hypoechoic suprachoroidal space in 8 of the 12 patients. This may indicate increased uveoscleral outflow through the supraciliary and suprachoroidal space.

We did not observe any major intraoperative or postoperative complications after HIFU cyclocoagulation. In particular, no eyes developed severe hypotony or phthisis, which are some of the most serious adverse effects of the currently available cyclodestructive methods. Clinical examinations did not show significant intraocular inflammation, and no persistent uveitis occurred during the follow-up. This could explain why none of the patients encountered IOP spikes or major IOP increase in the early follow-up and could also explain why none of the patients reported ocular pain after the procedure or during the follow-up, except the patient who had a corneal ulceration. Similarly, no specific complications of the Sonocare method, such as conjunctival burns, corneoscleral burns, or scleral thinning, occurred. These results regarding tolerability are consistent with those of a previous animal study, which showed localized and reproducible coagulation necrosis of the ciliary processes without histologic or clinical damages to the adjacent ocular structures and without signs of intraocular inflammation. The demarcations between treated

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**FIGURE 6.** 50-MHz UBM before (left) and 1 month after (right) ultrasonic circular cyclocoagulation in a pseudophakic patient with refractory primary open-angle glaucoma. (A) Radial 90° meridian section. (B) Radial 145° meridian section. (C) Transverse section centered on the 90° meridian. Note the cystic involution of the treated ciliary body and the hyporeflective suprachoroidal fluid space.
and untreated areas were very sharp, and the localization of the lesions was constant with approximately 75% to 90% of the length of the ciliary processes treated. The high operating frequency (21 MHz) and geometry of the transducers also explain that we obtained localized focal zones, with very sharp demarcations between the treated and untreated areas, thereby reducing the risk for treating the surrounding healthy tissue. The higher the focusing and frequency of a therapeutic ultrasound beam are, the lower the energy deposition on tissue in front of and behind the focal zone and the smaller and sharper the focal zone. In this study, we determined the geometry of the ring containing the six piezoelectric elements whose focal zones actually matched the ciliary body by means of UBM. Because the coupling cone was placed in direct contact with the eye and was fixed by means of a vacuum suction ring, we can assume that the procedure effectively treated the ciliary body as simulated on the UBM images and no other surrounding structures.

We report here the first clinical series of patients treated with HIFU coagulation of the ciliary body using this new device. Therefore, our first concern was to evaluate the safety of the device on a relatively low number of patients. To this end, the first patients were treated using conservative power and time shot parameters. Because we did not have any complications during or after the procedure in the first four patients, the regulatory authorities allowed us to increase the dose by increasing the duration of each shot. Therefore, all 12 patients were not treated using the same parameters. This may be one bias of the present study because it may make it more difficult to interpret the measured IOP decrease and may reduce the significance of the results in each subgroup. Similarly, the inclusion criteria of this first clinical study were stringent. Most patients included had previously undergone numerous filtering surgeries or diode laser cyclodestructive procedures and had limited residual visual acuity up to light perception. For these reasons and because our first concern was to evaluate the safety of the procedure, the surgical success criteria we chose—IOP reduction greater than 20% three months after the procedure—may be considered not very stringent.

One concern regarding glaucoma surgery or cyclodestructive procedures is long-term IOP reduction. This pilot study, designed with safety as the main outcome, has a limited duration of follow-up. A multicenter study evaluating the long-term efficacy and safety of this procedure in patients with less advanced glaucoma is in progress. Similarly, further prospective randomized clinical trials will compare the efficacy and safety of this method with conventional cyclodestructive procedures or filtering surgery.

In summary, this first clinical study shows that ultrasonic coagulation of the ciliary body using high-intensity focused ultrasound delivered by miniaturized high-frequency transducers seems to be an effective method of reducing IOP in patients with refractory glaucoma. The procedure seems to be safer than other cyclodestructive procedures.

References