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● *Original Contribution*

DEVELOPMENT OF A MINIATURIZED HIFU DEVICE FOR GLAUCOMA TREATMENT WITH CONFORMAL COAGULATION OF THE CILIARY BODIES

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Abstract—This study examined the feasibility of high-intensity focused ultrasound (HIFU) for glaucoma treatment with conformal coagulation of the ciliary bodies (CB). A miniaturized high frequency (21 MHz) device was developed, based on the geometry of the eye and adapted to the anatomy of the rabbit eyeball. Six line-focus lesions were distributed along a circle and produced by six cylindrical transducers. To be conformal, the numerical model predicted an intensity of 6.9 W/cm^2, with exposure duration of 3 s ON (powered per sector). *In vivo* experiments were conducted on two rabbits. A significant intraocular pressure reduction was noted (–45% and –31%). Histology demonstrated conformal and homogeneous coagulation of the CB without side effects. (E-mail: thomas.charrel@inserm.fr)

Key Words: **High-intensity focused ultrasound, Ocular pathology, Glaucoma, Ciliary bodies, Conformal cyclocoagulation, Medical device, High frequency, Third harmonic.**

INTRODUCTION

Primary open-angle glaucoma (POAG) is a common chronic eye disease, particularly in elderly patients, potentially causing blindness (Weinreb et al. 2004). According to the World Health Organization, it is the second cause of blindness worldwide, with approximately 67 million patients affected (Quigley et al. 1996). This disease is an optical neuropathy generated by the progressive degeneration of the nerve fibers that converge on the optic nerve, resulting, functionally, in a decrease of the visual field and anatomically, in the excavation of the head of the optic nerve (optic disk). POAG is a multifactorial disease. The increase in intraocular pressure (IOP) is considered to be the main glaucoma-associated risk factor (Leske et al. 2003). Current glaucoma treatment, whatever the method, thus, consists of reducing intraocular pressure, which is the only risk factor that can be corrected (AGIS 2000).

The eye, an organ that can be likened to a sphere, is hermetically isolated from the external environment and from neighboring structures. The anterior segment, located between the lens and the cornea, is filled with a liquid called aqueous humor. This liquid is continuously produced by the ciliary bodies (CB), a circular organ located behind the iris. It is also continuously eliminated *via* the trabecular meshwork, located in front of the iris, in the iridocorneal angle. Under normal circumstances, the aqueous humor circulating between its production and removal sites is produced and removed in equal amounts, thus, ensuring equilibrium and constant pressure. In patients with abnormally high IOP and an open-angle, the increased IOP can be ascribed to reduced trabecular meshwork permeability (Llobet et al. 2003). As aqueous humor elimination is less efficient, and with constant production, the intraocular pressure increases in the anterior segment, propagating to the posterior segment, where the optic nerve is damaged.

Available treatments act either by reducing the production of aqueous humor or by facilitating its drainage. The first-line treatment is medical (pharmacologic) treatment (AAO 2000). There are approximately five therapeutic classes of medications with varied modes of action, generally administered topically. When this treatment is insufficient to stabilize the disease, surgical treatment must be considered (EGS 2003). Studies have

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determined the percentage of patients who fail to respond to medical treatment at between 30% and 50% (Rouland et al. 2005; Zhou et al. 2004). Surgical treatment consists in creating a small fistula through the sclera, thus, enabling the aqueous humor to flow from the inside of the eye under the conjunctiva (Cairns 1968; Roy and Mermoud 2006). The aqueous humor then drains through the conjunctiva, or into the veins, and the eye is, thus, decompressed. Surgical fistula creation is frequently aggressive, causing significant inflammation, which is a source of scarring and fibrosis and, therefore, of filtration failure (Daniels et al. 1998). Consequently, the long-term failure rate for filtering surgery is high (50% to 70%) (Edmunds et al. 2002; Nouri-Mahdavi 1995). Another therapeutic approach, consisting in partially destroying the CB processes, reduces the production of aqueous humor and, hence, the IOP. Currently, this procedure, called cyclodestruction, is generally performed using diode or Nd:Yag lasers *via* the transscleral route (De Roetth 1965; Kosoko et al. 1996; Schubert and Federman1989; Uram 1992; Vernon et al. 2006). Laser cyclodestruction is frequently effective, but poorly tolerated, as its selectivity for CB processes is low. Damage to adjacent tissues causes intraocular inflammation and serious complications, such as cataract or retinal detachment. Consequently, laser cyclodestruction is currently reserved for rare cases of highly advanced glaucoma.

Another research approach is ultrasonic coagulation of the CB using high-intensity focused ultrasound (HIFU). This strategy was studied in the 1980s and 1990s (Burgess et al. 1986; Coleman et al. 1985a, 1985b, 1986; Liu et al. 1994; Maskin et al. 1989; Polack et al. 1991; Silverman et al. 1991; Sterk et al. 1989; Valtot et al. 1989), leading to a commercially available device, the Sonocare Therapeutic Ultrasound System Model (Muratore 2005). Clinical series have shown this procedure to be effective in reducing the IOP. Sterk et al. (1989) achieved a 42.2% reduction in IOP 3 months after HIFU cyclodestruction in 44 eyes with refractory glaucoma. The specific advantage of HIFU compared with laser is that the energy can be focused through non-optically transparent media. Energy deposition is well controlled and side effects are significantly reduced. In the Sonocare procedure, the transducer used to produce HIFU treatment was a single spherical piezoceramic of 80 mm in diameter, focus at 170 mm in diameter and operated at 4.6 MHz (third harmonic). The coupling medium between transducer and eyeball required a bath of saline solution, heated to 37°C. The entire system was attached to an articulated arm and proper positioning was ensured by an imaging probe. Application of energy produced a single pinpoint lesion. The transducer was then moved to administer about six lesions. Despite safety and effectiveness, due to the complexity of the procedure, the use of HIFU for CB destruction was gradually abandoned in the mid 1990s.

The aim of the present work was to develop a new miniaturized device allowing safe, rapid and easy treatment of glaucoma using HIFU cyclocoagulation. To eliminate problems caused by the complexity of the procedure related to the Sonocare device, this new concept is based on a one-step, quick, accurate and easy procedure. This avoids the need to manipulate the device many times to treat the whole circumference of the eye and, for each step, the need to remove and replace the water bath, to measure the distance between the probe and the eye surface and to determine the position of the light spot showing the point where the ultrasound beam penetrates through the eye surface. The new device allows a one-step procedure that does not require measuring, imaging or replacing the system and which accurately and quickly allows the whole circumference to be treated. This new approach is based on the circular symmetry of the eyeball and the structure to treat (the CB). To be conformal to the CB, the device has circular focusing and does not exceed the dimensions of the eye. The circular geometry of the device should allow constant and reproducible positioning. To treat from 10% to 60% of the CB in increments of 10%, the device was divided into six separate cylindrical transducers to produce six line-focus beams. Furthermore, the probe was coupled to the eye by means of a truncated cone filled with saline solution (Fig. 1). Additionally, the coupling cone allowed aligning the device on the optical axis and positioning the focal areas on the CB. The coupling cone can be secured over the eyeball through a suction ring that ensures watertightness. This particular design allows treatment to be performed without moving the device, thus, reducing processing time and the risk of misalignment.

The prototype was designed using anatomical constraints (Werner 2006; Davis 1929) and numerical simulations (Curiel et al. 2004). A model of the rabbit eyeball was made for comparison with *in vivo* experiments. The numerical simulations allowed adjusting the operating frequency of the device and exposure conditions to limit thermal damage to the CB. The resulting prototype was fabricated, characterized acoustically and finally tested in heat-sensitive gel and *in vivo*.

MATERIALS AND METHODS

Anatomy and conformal device

The originality of this new therapeutic HIFU device is to be conformal to the CB. This organ can be approximated by a ring placed around the lens, 2 mm below the sclera and behind the iris. The assumption is that